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Health Technology Assessment Department

Health Technology Assessment Report on Synthetic and Biologic DMARDs Used in the Treatment of Rheumatoid Arthritis

ANKARA, 2019

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1. PREFACE

Health Technology Assessment (HTA) is an comprehensive assessment and interpretation of the technologies used in health services and within the definition of health technology; drugs, medical devices, medical treatment methods, surgical techniques, health care systems and similar applications.

Evaluation of health technology is primarily done in terms of clinical effectiveness and patient safety; Then, economic analysis, organizational ethics, patient, social and legal aspects are evaluated and finalized with a report. Scientific evidence is taken into consideration in all stages of the HTA, to which multiple stakeholders and experts contribute and which are carried out in a transparent process.

Article 12 (1) of the Decree Law No. 663 on the Organization and Duties of the Federal Ministry of Health and its subsidiaries mandates proper establishment of the efficacy and effectiveness of all diagnostic, protective, promotive, therapeutic and rehabilitative methods used in Turkey. As per this mandate the General Directorate of Health Research (SAGEM) is tasked to carry out assessments on economic impacts, to conduct and develop evidence-based medical practices and clinical guidelines, and to carry out activities to develop and disseminate clinical guidelines at the national level. However, this responsibility of HTAs was subsequently transferred from SAGEM to Health Services General Directorate (SHGM) on 26th November 2017. Subsequently all the staff, processes and HTA related business and transactions continue under SHGM.

The Health Technology Assessment Department in Turkey is located within the SHGM offices. The main policy of the SHGM is to design and implement health technology evaluation processes, review and encourage the use of new or ignored clinical technologies in a reasonable and equal manner, to reduce the use of financially unsustainable health technologies in health services. The present HTA study was undertaken to collect and review global evidence on most effective combination therapies of newer biological and traditional synthetic DMARDs. The HTA project / study on the current use, definition and technical characteristics, safety and clinical effectiveness, costs and economic evaluation was carried out in this framework and finalized as HTA report.

Rheumatoid arthritis (RA) is a disease with high public health burden and significant societal costs, often needing aggressive management to reduce the patient suffering and complications that are often the bony joints. Research shows that the total direct and indirect annual costs of treating RA patients was estimated to be about 19.5 billion Turkish Liras RA in Turkey . It is therefore of vital economic importance to determine the most effective treatment option(s) and to contribute to the sustainability of resources allocated to healthcare services by reducing the financial loss to the minimum level possible.

Disease-modifying anti-rheumatoid drugs (DMARDs) have been the main treatment choice in RA. New knowledge about the pathophysiological mechanism of the disease has impressively grown leading to improvements in the treatment of RA. The current pharmacological treatment options include the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), as the latest addition. The treating physicians have a choice of using these drugs as monotherapy or in different combinations, which is often decided based on a variety of factors related to the patient. Evidence available from scientific studies strongly favour the early start of treatment with csDMARDs. Improvement in clinical outcomes was shown by treatment with a combination of csDMARDs as compared to monotherapy. There was not much significant difference in the clinical efficacy between bDMARDs and, it is seen that tumor necrosis factor inhibitors appeared to have better safety profile than other bDMARDs. The combination of methotrexate with biologic after the failure of csDMARDs (monotherapy and combination) yielded better clinical outcomes as compared to bDMARDs monotherapies. MTX was the most prescribed csDMARDs. An overwhelming majority of patients in Turkey were on csDMARDs (about 91%) and less than 10% of patients were on bDMARDs. The present study was undertaken to research further by using the evidence from scientific studies as well in order to make a deep assessment.

1.1. References

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2. ABBREVIATIONS

Abbreviation	Description
ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
ADR	Adverse drug reaction
AMSTAR	A measurement tool to assess the methodological quality of systematic reviews
AS	Visual Analog Scale
ICSR	Separate Case Safety Notifications
DMARDs	Disease-Modifying Antirheumatoid Drugs
bDMARDs	Biological DMARDs
CBA	Cost Benefit Analysis
CCA	Cost Consequence Analysis
CEA	Cost Effectiveness Analysis
CIA	Cost Identification Analysis
CMA	Cost Minimization Analysis
CUA	Cost Utility Analysis
CRP	C-Reactive Protein
csDMARDs	Conventional Synthetic DMARDs
CZP	Certolizumab Pegol
DALY	Disability Adjusted Life Years
DAS28	Disease Activity Score 28
DMARDs	Disease-Modifying Antirheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EUnetHTA	European Network for Health Technology Assessment
GOL	Golimumab
HAQ	Health Assessment Questionnaire

HCQ	Hydroxychloroquine
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessments
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
JAK	Janus kinase
LEF	Leflunomide
LYG	Life Years Gained
MAHs	Marketing Authorization Holders
MTX	Methotrexate
PBO	Placebo
PvCPs	Pharmacovigilance Contact Points
QALY	Quality Adjusted Life Year
RA	Rheumatoid arthritis
RCTs	Randomized Control Trials
RTX	Rituximab
SB	Republic of Turkey Ministry of Health
SF 36	Short Form (36)
SGK	Republic of Turkey Social Security Institution
SHGM	Health Services General Directorate
SJC	Swollen Joint Count Of 28 Joints
SSZ	Sulfasalazine
SUT	Healthcare Implementation Communique
TCZ	Tocilizumab
TLAR	Turkish League Against Rheumatism
TNF	Tumor Necrosis Factor
TOFA	Tofacitinib
TUFAM	Turkish Pharmacovigilance Center
TUKMOS	Board of Specialty in Medicine
tsDMARD	Targeted Synthetic DMARDs

WHO	World Health Organization

3. EXECUTIVE SUMMARY

This report provides comprehensive evaluation worldwide and in Turkey for rheumatoid arthritis (RA) drugs used in treatment (conventional synthetic and biological disease modifying anti-rheumatoid drugs -DMARDs) method with 9 HTA size (health problem and current use of technology, description and current use of technology, safety, clinical effectiveness, costs and economics evaluation, ethical perspectives, organizational aspects, patient and social aspects and legal aspects) and findings of discussions with experts on the current policies, practices and key gaps in treatment of RA in Turkey.

The inclusion of all methods of HTA for RA also meant plan, design, and implementation of observational and experimental studies locally to review the current evidence on the various health technologies applicable for RA. After review of the current data available and the additional resources needed for the actual implementation of the epidemiological studies in RA, it was decided to first conduct a systematic review the current body of evidence on HTAs in RA. This was to be done by a review of published global and Turkish literature. The systematic review was to be followed by consultations with local experts on RA within Turkey. These consultations can then shed more light on the gaps present in the published literature and thereby make suitable and locally relevant recommendations.

RA is a disease with high public health burden and significant societal costs, often needing aggressive management to reduce the patient suffering and complications that are often in the bony joints.

Research shows that the mean annual direct cost was of treatment per patient was EUR 4,954 (median, EUR 1,805), whereas the mean annual indirect cost was EUR 2,802 per patient (median, EUR 608). When these direct and indirect costs are extrapolated to the total number of patients with RA (0.5% of adult population) in Turkey and in Turkish liras, it is estimated that an annual amount of approx..19.5 billion Turkish Liras was spent on management of RA in Turkey in 2016 (1).

In our study, we have attempted to estimate the direct costs of medications for RA patients after adjusting the treatment compliance and the approaximate number of patients actually receiving treatment for RA. Accoridngly, we find that the total annual direct costs for medications for all

RA patients was approximately 458 million TL (approximately 70 million Euro) and the average annual direct costs for medications for per RA patient was approximately 2480 TL (approximately 390 Euro). Details of these calculations are available in the subsequent sections.

It is therefore of vital economic importance to determine the most effective treatment option(s) and to contribute to the sustainability of resources allocated to healthcare services by reducing the financial loss to the minimum level possible.

DMARDs have been the key approach / cornerstone of treatment in RA. New knowledge about the pathophysiological mechanism of the disease has impressively grown leading to improvements in the treatment of RA. The current pharmacological treatment options include the conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), as the latest addition. The treating physicians have a choice of using these drugs as monotherapy or in different combinations, which is often decided based on a variety of factors related to the patient.

Rheumatologists in Turkey were practicing in accordance with the both ACR and EULAR guidelines the most common international guidelines followed globally. MTX was the most prescribed csDMARDs for both mono and combo treatment protocols. Combination of csDMARDs was the initial treatment option for the early resistant and advanced RA including a short trial of low dose corticosteroids. Subsequent addition of bDMARDs was determined by several factors. Most important factors influencing choice of treatment included any pre-existing morbidities, the intensity of disease activity of RA, the current functional status of the patient and compliance to drugs by patients due to adverse effects. The first choice of bDMARDs was TNF-inhibitors to be started in combination with the csDMARDs.

Currently, early treatment of RA with csDMARDs is fully reimbursed in Turkey with proper documentation of disease progression. Disease activity scores for 28 joints (DAS28) is the key indicator to assess the response to the treatment. Treatments are usually changed either by additional of a second csDMARD or combination with a short trial of corticosteroid before starting with a TNF-inhibitor. Addition of a bDMARD also needs to be documented well by the relevant specialist for the treatment to be fully reimbursed by the government funded insurance system.

Traditionally, these DMARDs were referred to as synthetic DMARDs comprising of drugs such as methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine, D-penicillamine, and

leflunomide. These were often effective in short-term but fraught with several adverse drug reactions and frequent relapse of the clinical disease. Several newer medications collectively known as biologic DMARDs or simply referred to as biologics have demonstrated better clinical efficacy over their synthetic counterparts in the management of RA. However, biologics come at a very high economic cost and also have a lesser safety profile. For this reason, arrangements should be done for focusing this subject. Therefore, they need to be carefully evaluated for their clinical as well as cost-effectiveness over the traditional DMARDs.

Patients on bDMARDs compared with patients on csDMARDs had a higher risk of serious infections (Adjusted Hazard Ratio (aHR) 1.1 to 1.8)—without differences across bDMARDs—a higher risk of tuberculosis (aHR 2.7 to 12.5), but no increased risk of infection by herpes zoster. Hazard ratio is the chance of an adverse event occurring in the treatment arm divided by the chance of the event occurring in the control arm, or vice versa, in a clinical trial. It is the most commonly used indicator to compare the safety parameters of 2 treatments. These are usually depicted using Kaplan–Meier survival curves.

Patients on bDMARDs did not have an increased risk of malignancies in general. However, there was a slightly increase risk for certain type of skin cancers called melanomas (aHR 1.5). The findings from the systematic review and the interviews with the local experts in Turkey confirm the known safety pattern of csDMARDs and bDMARDs, including both tumour necrosis factor-α inhibitor (Anti-TNF) and non-Anti-TNF, for the treatment of RA.

Disease activity scores across 28 joints (DAS28) was the main indicator for measuring the clinical effectiveness of treatment in RA.

Compared with patients receiving bDMARDs for <3 months, those receiving bDMARDs for ≥3 months exhibited significantly lower DAS28 scores ($p < 0.0001$), and a significantly higher proportion of patients who received bDMARDs for ≥12 months achieved the treatment goal (remission or low disease activity, 62.5 % vs. 18.3 %, $p < 0.0001$). Patients receiving combination therapy with csDMARDs exhibited lower DAS28 scores than patients receiving bDMARD monotherapy (4.3 vs. 4.8, $p = 0.011$).

Cost-effectiveness is a key measure being looked for comparative effectiveness of two or more medications during health technology assessments (HTA). Such measures often need further contextualization to a country or region by considering the prevailing socio-economic conditions

such as per capita GDP, local affordability thresholds or willingness to pay (WTP) to be used effectively by the country's regulators and payers.

Clearly when compared on economic parameters alone, csDMARDs were most cost-effective than bDMARDs. However, as can be seen from the earlier sections, bDMARDs (mainly adalimumab, etanercept, infliximab, and tocilizumab) combined with csDMARDs are showing better overall and long-term clinical outcomes than when treated with csDMARD monotherapies. Evidence available from the published literature on bDMARDs demonstrate patients achieving faster remission and low disease activity scores when the treatment is initiated early in the disease. These have been discussed in detail in the later sections.

In a review published in Annals of Rheumatic Diseases 2017, it was noted that switching to biologics before a trial of combination therapy of csDMARDs was not cost effective in RA (2). These studies have been listed in the reference section. Studies explored the cost-effectiveness of the addition of Anti-TNF for the treatment of methotrexate naïve patients. These were infliximab, adalimumab, golimumab, etanercept and certolizumab. The incremental cost of bDMARDs after the inadequate response to csDMARDs, was shown to be high in most of the studies. The drugs from Anti-TNF category listed above were not considered to be cost-effective options if used earlier in the course of RA, as compared to non-Anti-TNF drugs such as abatacept, tocilizumab, or tofacitinib. Therefore, it was noted in studies that Anti-TNF group of drugs were more cost-effective when used in later stages of RA .

The main indicators evaluated by HTA agencies across the world when comparing between csDMARDS and bDMARDs for cost-effectiveness were the incremental cost-effectiveness ratio and the cost per Quality Adjusted Life Year (QALY) gained.

While, bDMARDs appear to have higher cost per QALY gained than the thresholds set by many HTA agencies around the World for interventions to be cost-effective. These thresholds are set on the basis of the per-capita GDP and the country's 'willingness-to-pay' against the national economic burden of RA.

In Turkey, the current usage of bDMARDs including the biosimilars is approved and fully reimbursable under the government funded health insurance schemes. However, there are many preconditions to prescription of bDMARDs including extensive documentation by the treating

specialist and higher thresholds set for disease activity scores to denote failure of treatment with csDMARDs prior to starting bDMARDs.

These administrative procedures and formalities for prescription of bDMARDs are perceived by patients to delay the treatment of RA patients residing in remote and rural areas of the country. Such administrative requirements will mean treating physicians and patients having to wait for longer time before starting treatment. Therefore the patient representatives feel the need to review the current reimbursement guidelines for prescription of bDMARDs in RA patients in Turkey. These reimbursement guidelines should be formulated to reduce the inconvenience to patients from remote and rural areas and make timely start of bDMARDs for better clinical and economic outcomes.

HTAs not only evaluate a health technology and its effectiveness but also consider organizational aspects surrounding its implementation, or sometimes removal, within a specific context or setting. This domain of an HTA examines how various types of resources (administrative, human, technological, etc.) need to be structured when implementing a technology. Any impacts that may result within the health care organization or the health system as a whole are considered.

In general, the organizational domain explored the following issues:

a. Health care delivery processes and how the use of DMARDs may affect current work flows
b. The structure of health care services and equitable access to DMARDs
c. Process related costs for purchasing, storing and distribution of DMARDs along with budget impacts
d. Management issues in dealing with the access and utilization of DMARDs in treatment of RA
e. Cultural issues including acceptance of the new technology by those within health care organizations and the patients

The above parameters were hard to find in published literature, as evidence on the organization and delivery of health services encompasses a wide range of disciplines and study types. The information required for this section of an HTA is often context (and often country) specific which can result in little to no published literature being available. Hence, we have tried to address this

through the discussions with the local Turkish experts in the Delphi exercise as well as the qualitative interviews with patients' representatives.

In general, we did not see organizational issues in Turkey for the procurement, storage and distribution of both csDMARDs and bDMARDs. Although the process for reimbursement of bDMARDs was perceived by some patient representatives to be complicated and leading to delays in start of bDMARDs, after the bDMARDs were started, there was a good acceptance of bDMARDs as a treatment in RA by both the treating physician and patients. Similarly, their usage by both physicians and patients was well accepted and in line with recommended guidelines.

Patients often perceive DMARDs as strong medications but also realize that these drugs will help alleviate their symptoms. While csDMARDs are easier to access and are also more affordable, bDMARDs are often expensive and reimbursed by the SGK (SSI) – the state funded health insurance only upon submission of a valid prescription from a rheumatologist from tertiary level health centers. The expenses incurred on treatment with DMARDs does not include other expenses such as hospital expenses, transportation expenses as many cities did not have the rheumatologists, which forced patients to travel from one city to another thereby leading to loss of daily wages and transportation expenses. It would be better if treatment was made available at most places in Turkey and closer to the patients.

The patients' representatives interviewed felt that there is lack of communication on part of the healthcare providers to explain the patients about the nature of their disease and involve them in all treatment decisions.

Many patients were not adherent to the DMARDs which led to increased disease activity and symptoms and poorer quality of life. There were both economic causes of non-adherence and disease/medication related causes of non-adherence.

International rheumatology guidelines emphasize shared decision making by involving the patients and their family members in the treatment of RA. Patients were happy that Turkey was "way-ahead" than rest of Europe in providing RA patients free access to latest medicines including bDMARDs.

However, more needs to be done to build the trust and confidence of patients in medical care, positive experiences with DMARDS (especially with the csDMARDs) among other patients, and

an expectation that medications will help maintain participation in life can motivate patients to adhere to DMARDs.

Due to the fact that DMARDs have been in usage for a considerable length of time, there are key legal issues behind the usage of DMARDs, including - Issues related to health care policy at the local, national or international level; Issues related directly to the in-country availability of DMARDs (both csDMARDs and bDMARDs) such as proper regulatory approvals, authorization, patent/license issues; Issues related to the process of local manufacture of bDMARDs in Turkey and finally; Issues directly related to the patient and his/her basic rights and freedoms (such as, autonomy, privacy and confidentiality) in use of DMARDs.

In examination of the above issues, there was no legal hurdles noted to the prescription and utilization of bDMARDs in Turkey. There are systems in place to critically review any new health technology prior to its availability in Turkey. With the recent availability of low cost biosimilars in the management of RA, the regulatory agencies in Turkey have defined clear rules for review, licensing, pricing and finally marketing of these medications in Turkey.

More details of the 9 core dimensions discussed in previous sections have been provided in the report within the relevant sections.

- **Use of csDMARDs has seen to be a clinically effective first-line treatment strategy, post diagnosis of RA.** Finding from this review show the superiority of biologics over csDMARDs. However, these findings should be interpreted considering the moderate to low quality of evidence and a lack of direct head to head comparison studies. In the absence of a higher quality evidence the clinical efficacy of csDMARDs can be considered like biologics for patients. Studies show that within the csDMARDs group methotrexate is a clinically efficacious option with a relatively smaller number of adverse events. In addition to the clinical indicators the ease of dose administration and low cost are added upsides
- **Combination of csDMARDs has demonstrated better improvement in clinical outcomes than monotherapy and should be considered before addition of bDMARDs.** Monothepary can be considered either with methotrexate or in case of resistance or failure, any switch made to other csDMARDs.

- **Head to head comparisons between the bDMARDs did not provide any conclusive findings.** Although attempts have been made to come to a statistical conclusion for this comparison, but the heterogeneity of the sample could not be ignored. Head to head studies with direct comparisons are warranted to arrive to a conclusive juncture in this regard
- **As studies have pointed out, after failure of csDMARDs combination, it may be more effective to start bDMARDs with a combination of methotrexate to achieve better clinical outcomes rather than starting bDMARDs as a monotherapy**. This was invariably the case with all the biologic subgroups. A similar finding was observed in terms of the tsDMARDs where combination with methotrexate had better outcomes. However, there are still some unrequited areas around the safety of these drugs
- **Use of tsDMARDs did provide clinical benefits for people who had shown an inadequate response to csDMARDs and biologics, including Anti-TNF.** However, these studies were underpowered in terms of their sample size and there is a requirement of studies that follow scientifically robust methodologies
- Based on the results of the search conducted on the local Turkish database, we did not find studies that met our inclusion criteria. Considering the dearth of the local evidence on, the **government must encourage robust scientific studies aiming to compare the clinical efficacy of the available treatment options for RA**
- Research initiatives should also be targeted at **understanding of the patient acceptability of the various health technologies**
- The findings from the cost-effectiveness analysis have presented the incremental cost required for adding the bDMARDs, early on for the treatment of RA. However, this decision requires a lot more clarity and direct evidence of clinical effectiveness, before implementation at a large scale
- The study also finds that bDMARDs have not been scientifically proven to clinically effective as a starting treatment in RA and as a monotherapy

This review provides an assessment of the management of current treatment of RA with the HTA method and reveals the current situation. However, there remain some information gaps that are

required to be answered with the appropriate understanding of the local context. These findings would be important to couple with appropriate understanding of below:

i. Inclusion of **effective treatment options of the health system into existing national guidelines in the light of international studies.** Considering that the there are frequent updates in the area of treatment of RA, we recommend a closer review of such changes in newer treatment options in the international treatment guidelines. They be can then included as necessary within the Turkish National treatment guidelines. It is necessary to conduct a systematic assessment of any newer treatment option within the local Turkish context before such treatments are formally recommended within the National guidelines

ii. Regular evaluation of issues related to the **availability of these treatment options and the mechanisms of implementation.** After review and inclusion of any newer treatment option within the Turkish National treatment guidelines, it is necessary for policy makers to determine how these newer treatment options will be acquired and made available to the general public. This could mean a thorough review of the supply-distribution and reimbursement mechanism of the health systems

iii. **Determining and implementing a strategy on the acceptability of these treatments by patient group.** In addition to ensuring sufficient availability of any newer treatment options, efforts will also have to be made to educate the patients on safety and efficacy of these treatments. It is noteworthy that no treatment option will succeed without proper adherence and compliance to treatment by the patients. We have found that patient education and support to the patients during therapy with DMARDs needs improvement in Turkey

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4. SUMMARY FOR PATIENT AND RELATIVES

Patients with RA can experience progressive joint damage, deformity, and disability, which can limit functioning and impair quality of life (1-4). DMARDs are recommended first-line treatment for RA with the aim of decreasing joint inflammation, achieving remission, and preventing permanent damage (5,6).

Based on 2015 American College of Rheumatology guidelines, in patients with mild disease, initial treatment with an non-steroidal anti-inflammatory drug (NSAID) for relief of symptoms and control of minor inflammation, while simultaneously starting a DMARD, preferably methotrexate (DMARDs typically take 4 to 6 weeks to achieve full effect), may result in control of disease activity. With moderate to severe disease activity, initial anti-inflammatory treatment with an NSAID or glucocorticoid as a "bridge" therapy while starting methotrexate may result in control of disease activity. If a patient is resistant to initial DMARD treatment with an agent such as methotrexate, combination DMARD treatment may be used, adding one or more conventional DMARDs (leflunomide, hydroxychloroquine, sulfasalazine) or a newer biologic treatment to methotrexate. Recent research suggests that combinations of conventional DMARDs may be effective as an early treatment approach to RA, as well as following inadequate response to methothrexate.

DMARD usage is associated with side effects and safety concerns. Physicians screen patients for specific physiologic parameters and diseases such as general laboratory tests, including complete blood count, serum creatinine, liver function tests, hepatitis test (for methotrexate, leflunomide, and newer biologic treatments), ophthalmic screening (for hydroxychloroquine), tuberculosis screening (for methotrexate and newer biologic treatments) carefully to minimize risk for side effects when selecting a DMARD. In addition, physicians may also need to screen the patients for immune responses to common childhood vaccinations and then suggest appropriate vaccines prior to starting the DMARDs.

After start of the DMARD therapy, regular follow-up visits are needed with the treating physician to monitor disease activity and check for any drug toxicities. These will need additional laboratory testing X-rays, ultrasonography, MRI scan and blood tests for C-reactive protein, ESR, anti-CCP antibodies.

Considering all these treatment requirements, non-adherence which derives from patients who do not remain adherent to the treatment, remains a major clinical challenge in RA.

- Patients with RA equate DMARDs with intensifying disease identity and distressing uncertainties and consequences
- Negotiating treatment expectations with a trustworthy, confident, and knowledgeable physician may improve medication adherence
- Patients wish to maintain control, are swayed by social influences, and appreciate privileged biologic agent access

Research estimates that only 66% of patients with RA are adherent to DMARDs (7). Nonadherence is associated with disease flares, increased disability, and increased health care costs in RA (8,9). The patient-physician relationship, patients' beliefs about medications, knowledge about their disease, and self-efficacy have been consistently identified as modifiable factors associated with adherence in RA (7,10–12).

International rheumatology guidelines emphasize shared decision making in RA (5,6,14). Shared decision making requires a comprehensive and detailed understanding of the patients' values, priorities, and preferences, yet there is sparse qualitative evidence for this approach in relation to DMARDs. In the literature review as well as the interviews with the representatives of patients, we noted that patients often believed DMARDs used in treatment of RA are associated with side effects. Patients were alarmed about potential side effects and were uncertain of treatment efficacy. Patients can find commencing DMARDs at the first consultation alarming, and fear changes and escalations of therapy. Some experiences and perceptions were unique to biologic DMARDs. Patients felt well supported by frequent clinic visits, nursing assistance provided, and counselling support during infusions. However, they also felt that if similar support is extended to patients receiving conventional synthetic DMARDs, it may improve their experience about sDMARD and may improve their adherence.

Patients receiving bDMARD may also experience rapid and dramatic treatment benefits and can feel privileged to receive restricted medications. However, regardless of the type of DMARD, arthritis, age, sex, and duration of disease, patients had similar concerns of DMARD toxicity, loss of efficacy, and desires to maintain control of their disease and social roles. Additionally, patients

taking either type of DMARD desired to have control of the decision to take their medications and reported experiences of mediocre benefits or recurrent failures.

However, studies have not consistently demonstrated that patient and treatment characteristics, including age, sex, disease duration, number of medications, and side effects, are all associated with adherence to treatment and treatment outcomes.

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5. SCOPE, METHODS & TARGET OF THE PROJECT

The aim of the project was to evaluate, assess and report on the subject of current use, description, technical features, safety and comparative clinical effectiveness of DMARDs and their evaluation in terms of costs and economic analysis, ethical analysis and review of organizational aspects, patient and social aspects, legal aspects.

The health technologies were assessed on the following nine dimensions.

Health Problem and Current Use of Technology; Description and Current Use of DMARDs; Safety; Clinical Effectiveness; Costs and Economics Evaluation; Ethical Perspectives; Organizational Aspects; Patient and Social Aspects; and Legal aspects

5.1. HTA Project PICO & Research Question

"The comparison of safety, disease activity (DAS-28), quality of life (HAQ-DI), work disability, cost-effectiveness and the results of RA / QALY in terms of economic analysis in patients over 16 years old diagnosed with RA".

Table 1. PICO Framework

Population	• All patients above age 16 diagnosed with RA
Intervention	Synthetic DMARDs (sDMARDs) classes • Methotrexate and any other sDMARDS used in combination with methotrexate • Tofacitinib (targeted synthetic DMARD) Biologic DMARDs (bDMARDs) classes • Interleukin-6 inhibitor (Tocilizumab) • B-cell kinase inhibitor (Rituximab) • T-cell-activation inhibitor (Abatacept)

	• JAK inhibitor (Tofacitinib) • 1 TNF inhibitor (Adalimumab)
Comparison	Intragroup comparisons were done between the biologic DMARDs against synthetic DMARDs
Outcome	• Safety • Disease activity (DAS-28) • Quality of life (HAQ-DI) • Work disability • Cost Effectiveness • Economic analysis of RA / QALY

5.2. Scope And Process of Systematic Review

5.2.1. Geographical Scope of The Systematic Review

United States (US) and five European Unions (United Kingdom (UK), Germany, Italy, Russia and France) and Turkey

5.2.2. Justification For Selection of Geographical Regions

Deficiency of literature in interventional research such as clinical trials and other epidemiological studies and health technology assessments in Turkey, the scope of the current review was extended to United States (US) and top five European Unions (namely United Kingdom (UK), Germany,

Italy, Russia and France). There were two main reasons for the choice of these countries for inclusion in the systematic review:

- Firstly, the demographic characteristics of the populations in the European countries was in resemblance to the Turkish population.
- Secondly, the bulk of the clinical trials, epidemiological assessments and the HTAs in RA has been conducted in these countries, leading to the coverage of a large volume of literature.

Completed systematic reviews and randomized control trials (RCTs) of csDMARDs, bDMARDs, and tsDMARDs for treatment of RA were considered for inclusion in this systematic review.

5.2.3. Inclusion Criteria

- Clinical randomized control trial (RCT) where the full paper was available,
- Patients in two arms must be receiving two of the following treatments (different): Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide, Tocilizumab, Rituximab, Abatacept and Adalimumab, Tofacitinib as monotherapy or in combination,
- Conference abstracts from the Rheumatology conferences,
- Systematic reviews with an objective of comparing the clinical efficacy or cost-effectiveness of one of the selected drugs.

5.2.4. Exclusion Criteria

- Non-randomized or uncontrolled studies or studies following different study design (such as observational, case studies, narrative reviews),
- Grey literatüre,
- Trials having only one of the selected DMARDs and being compared with only Placebo,
- Trials only comparing different doses of the same class of DMARD,
- Trials comparing a DMARD with a developed biosimilar drug,

was not included in the search.

All the key search terms were prepared and tabulated. MeSH equivalent each of the search terms too were prepared. Table-2, presents the summarized list of all the search terms used in the literature search.

Table 2. Summary of Key Search Terms Used in Literature Review

Name	Identifier	Search Terms
Age group	Population Group	ADOLESCENT: 13-18 YEARS; ADULT: 19+ YEARS
Rheumatoid Arthritis	Disease Group	"ARTHRITIS, RHEUMATOID"[MESH]) OR ARTHRITIS RHEUMATOID[TITLE]) OR ARTHRITIS, RHEUMATOID OR RHEUMATOID ARTHRITIS [TITLE/ABSTRACT]
Methotrexate	Intervention Groups	METHOTREXATE[TITLE/ABSTRACT]) OR METOART[TITLE/ABSTRACT]) OR METOJECT[TITLE/ABSTRACT]) OR EMTHEXATE S[TITLE/ABSTRACT]) OR METHOTREXAT EBEWE[TITLE/ABSTRACT]) OR METHOTREXATE KOCAK[TITLE/ABSTRACT]) OR TREXAN[TITLE/ABSTRACT]) OR METOART CON[TITLE/ABSTRACT]) OR MEXTU[TITLE/ABSTRACT]) OR ZEXATE[TITLE/ABSTRACT]
Sulfasalazine	Intervention Groups	SULPHASALAZINE[TITLE/ABSTRACT]
Hydroxychloroquine	Intervention Groups	HYDROXYCHLOROQUINE [TITLE/ABSTRACT]

Name	Identifier	Search Terms
Leflunomide	Intervention Groups	LEFLUNOMIDE[TITLE/ABSTRACT]
B-cell kinase Inhibitor	Intervention Groups	B-CELL KINASE INHIBITOR[TITLE/ABSTRACT]) OR RITUXIMAB[TITLE/ABSTRACT]) OR MABTHERA[TITLE/ABSTRACT]
JAK inhibitor	Intervention Groups	JAK INHIBITOR[TITLE/ABSTRACT]) OR TOFACITINIB[TITLE/ABSTRACT]) OR XELJANZ[TITLE/ABSTRACT]
Interleukin-6 inhibitor	Intervention Groups	INTERLEUKIN-6 INHIBITOR[TITLE/ABSTRACT]) OR TOCILIZUMAB[TITLE/ABSTRACT]) OR ACTEMRA[TITLE/ABSTRACT]
T-cell-activation inhibitor	Intervention Groups	T-CELL-ACTIVATION INHIBITOR[TITLE/ABSTRACT]) OR ABATACEPT[TITLE/ABSTRACT]) OR ORENCIA[TITLE/ABSTRACT]
TNF inhibitor	Intervention Groups	TNF INHIBITOR[TITLE/ABSTRACT] OR ADALIMUMAB[TITLE/ABSTRACT] OR HUMIRA[TITLE/ABSTRACT] OR ETANERCEPT[TITLE/ABSTRACT] OR ENBREL[TITLE/ABSTRACT] OR INFLIXIMAB[TITLE/ABSTRACT] OR REMICADE[TITLE/ABSTRACT] OR REMSIMA[TITLE/ABSTRACT] OR GOLIMUMAB[TITLE/ABSTRACT] OR

Name	Identifier	Search Terms
		SIMPONI[TITLE/ABSTRACT]) OR CERTOLIZUMAB PEGOL[TITLE/ABSTRACT] OR CIMZIA[TITLE/ABSTRACT]
Time Frame		PUBLICATION DATE FROM 1998/01/01 TO 2018/07/30
Setting	Filter for PubMed	TURKEY OR UNITED STATES OR UNITED KINGDOM OR GERMANY OR ITALY OR RUSSIA OR FRANCE

A detailed search strategy for all the databases is available as Appendix.

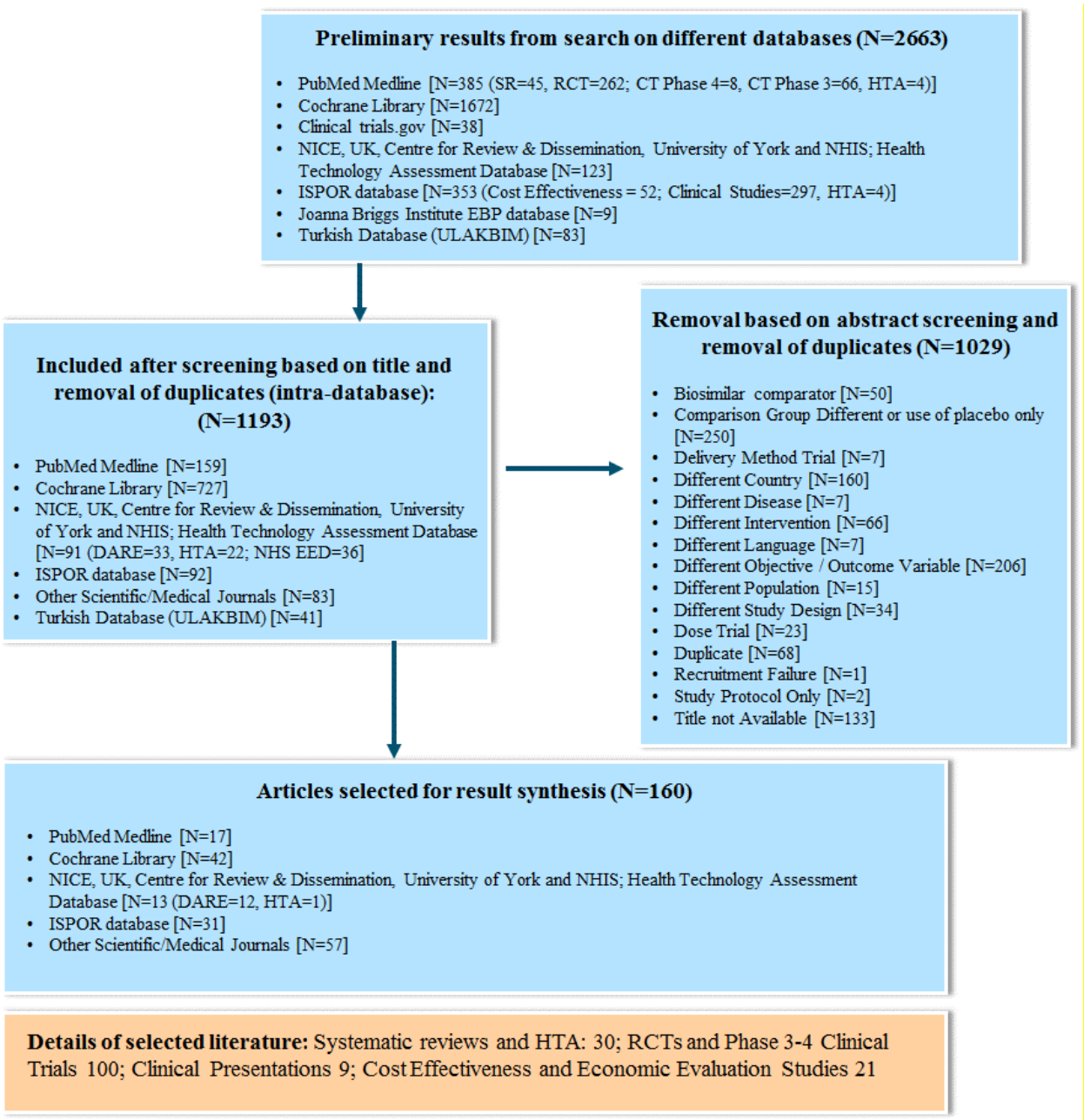
Table 3. Summary of The Scope of The Literature Review

The databases where the literature search has been performed	• ***MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations and MEDLINE*** • ***Ovid Journals with abstracts only*** • ***TOXLINE*** • ***Clinicaltrials.gov*** • ***International Clinical Trials Registry Platform (IRCTP) search portal*** • ***Health Technology Assessment Database*** • ***Cochrane Database of Systematic Reviews*** • ***Cochrane Central Register of Controlled Trials*** • ***NHS Economic Evaluation Database***

	• ***Conference Proceedings os EULAR & ACR 1998 to 2018*** • ***INAHTA Database*** • ***Joanna Briggs Institute EBP Database*** • ***ULAKBIM Turkish Medicine Database***
Time interval for literature review	***January 1998 - June 2018***
Start of literature search	***01 February 2018***
Conclusion of literature search	***31st July 2018***
Limitations in terms of language	***Only English and Turkish language articles were considered***

A total of 30 systematic reviews and HTAs, 100 RCTs and Phase 3-4 Clinical Trials; 9 Clinical Presentations and 21 Cost-effectiveness and economic evaluation studies were reviewed. However, none of the articles screened from the Turkish database met the inclusion criteria. The PRISMA flowchart in Table-4 illustrates the process and outcomes of the literature review.

Table 4. PRISMA Workflow



5.2.5. Data Abstraction Process

Abstraction of the data was carried out **by two independent researchers**, any discrepancy in the classification was resolved by discussion. Studies were screened to abstract data on – patient characteristics, safety, clinical efficacy and cost-effectiveness

5.2.6. Assessing Bias And Quality of Evidence In Systematic Review

We have used 2 tools to assess bias and evaluate the quality of evidence. **AMSTAR** is a popular instrument for critically appraising systematic reviews of randomized controlled clinical trials was used. (refer to appendix 3)

The methodological quality of the included reviews are assessed by two authors independently using the 'assessment of multiple systematic reviews' (AMSTAR) instrument. The AMSTAR instrument assesses the quality of systematic reviews using the following criteria:

1. Was an a priori design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies (study design, sampling, randomization, etc) provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

5.2.7. RCTs Risk of Bias Assessment

The Cochrane risk of bias assessment tool (refer to appendix 4) was further used to assess risk of selection bias, reporting bias, performance bias, detection bias and attrition bias in randomized trials.

- **Selection Bias**

Selection bias refers to systematic differences between baseline characteristics of the groups that are compared. The unique strength of randomization is that, if successfully accomplished, it

prevents selection bias in allocating interventions to participants. Its success in this respect depends on fulfilling several interrelated processes.

- **Performance Bias**

Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest. After enrolment into the study, blinding (or masking) of study participants and personnel may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes.

- **Detection Bias**

Detection bias refers to systematic differences between groups in how outcomes are determined. Blinding (or masking) of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes, such as degree of postoperative pain.

- **Attrition Bias**

Attrition bias refers to systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. Exclusions refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to the trialists. Attrition refers to situations in which outcome data are not available.

- **Reporting Bias**

Reporting bias refers to systematic differences between reported and unreported findings. Within a published report those analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences. This sort of "within-study publication bias" is usually known as outcome reporting bias or selective reporting bias and may be one of the most substantial biases affecting results from individual studies.

- **Other Biases**

In addition there are other sources of bias that are relevant only in certain circumstances. These relate mainly to trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get

'mixed', for example if participants pool their drugs); and there may be sources of bias that are only found in a clinical setting.

5.2.8. Interviews With Local Turkish Experts And Patient Representatives

A Delphi method of interviewing experts in Turkey was formulated along with in-depth interviews with representatives of patients' associations. A semi-quantitative questionnaire was drafted and finalized after expert inputs. 10 expert panelist attended Delphi exercise. 2 rounds of the Delphi exercise were conducted, and the resulting quantitative data averaged. The findings from in-depth qualitative interviews with patients' representatives was also included in consolidating the findings.

The following illustration is for the process of interviews in the Delphi exercise:

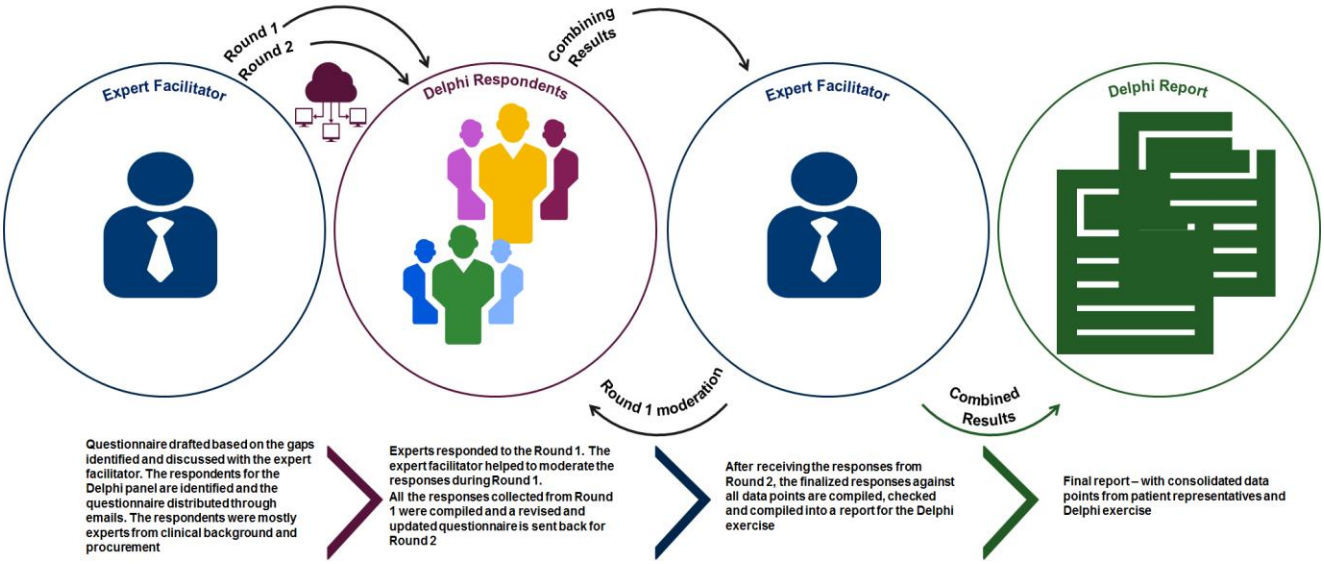


Figure 1. Process of Interviews in Delphi Exercise

During this DELPHI exercise, stakeholder comments were received that provided significant insight of the local context related to the treatment of RA in Turkey. A modified Delphi survey method was adopted, and a team of research experts guided the technical team in the formulation and validation of the survey tools at each round of the survey. The research experts did not take part in the survey in which recommendations were drawn.

The Delphi panel comprised of physicians with significant experience in RA (referred to as the expert panel) covering a wide range of disciplines involved in the management of RA. The research team contacted ten experts, and their consent for participation was sought. All the

contacted experts agreed to participate in the study. The first round of questionnaire consisted of 24 questions. This survey included open text options in which panel members could give comments to statements.

The survey included a set of questions around:

- Epidemiological burden of RA in turkey
- Drug prescription
- Clinical scenarios
- Cost of treatment
- Prescription and drug procurement system
- Overall Safety
- Patient acceptability of drugs
- Prescription of biosimilar drugs
- Research for evidence-based practice

All the members from the expert panel, responded to the survey. Comments from round 1 were then used to revise and refine the entire set of Delphi questionnaire. This process was carried out in conjunction with the consultant experts as well as the representatives. The questions/statements for which the consensus was reached in the first round did not feature in the next round. When there were low levels of disagreement, some questions were not edited and re-included in the next round. The new survey (round 2) was then sent out to the whole panel of experts. In round 2 all the panel members who took part in the first round responded. None of the experts used the option to decline to participate in Round 1 and Round 2.

5.3. Discussions With Patients' Representatives

It is always necessary to capture the end-beneficiary's perspective in therapeutic decision and choice of health technologies. Shared decision-making is in good conformance to the principle of informed consent, and it has an important bearing on the compliance and adherence to the treatment. This allows the patient to fully understand the benefit and safety of the treatment. In the RA care setting, the decision-making interactions usually occur between the health care provider, patient, and some nurse educators. The process may range from an autonomous decision-making pattern, where the patient may be fully responsible for the decision taken, to the paternalistic decision-making pattern, where the health care provider assumes full responsibility for the decision

taken. However, the ideal situation is one where a truly shared decision-making process happens, in which the doctor and patient/parents work together to choose an evidence-based option, in line with the patient's preferences and wishes.

The limited data available on shared decision making, the ethical and social issues at play during management of a chronic disease such as RA also needed to be explored to better understand the choice of health technologies. Understanding patients' perspectives also becomes necessary considering the variable efficacies and safety profile of medications in RA. Hence, in this project, we also decided to interview representatives of patients to capture some of the above determinants.

We prepared a discussion guide capturing the key information areas and questions to be posed to the patients' representatives. The discussion guide was reviewed by a technical advisor for this project and was refined to make it comprehensive.

A semi-structured qualitative interview was conducted with 3 representatives of patients' associations and the findings were captured in the form of interview transcript. The findings from the Delphi panel as well as the interviews with the patients were consolidated with the findings from the earlier systematic review of the literature. The results of both the modes of data collection are discussed in detail in the following sections.

5.4. Format of The Study Report

We have structured the study report in accordance to European Network for Health Technology Assessment (EUnetHTA's) recommended methodological framework – The HTA Core Model® 3.0 for production and sharing of HTA information. This framework 9 domains that have been detailed as relevant and, on the information, available from the systematic review and the interviews with the Turkish experts. These 9 domains are - description of the health problem and current use of technology; description and technical characteristics; safety; clinical effectiveness; costs and economic evaluation; ethical analysis; organizational aspects; patient and social aspects; and finally, legal aspects of the health technologies.

This report contains a comprehensive systematic review and assessment of key findings from experts in Turkey related to new or existing DMARD use in the treatment of RA. HTA experts will find easy to relate, which we hope will help further development of a HTA in Turkey.

Table 5. Study Schedule

Date	Progress
20 November	Contract Signing
1 December 2018	Project kick off meeting & research question with PICO framework
17 January 2018	Wide participation Opening Meeting
30 June 2018	Submission of the initial report
27 July 2018	I. Submission of the Progress Report
30 September	II. Submission of the Progress Report
29 October 2018	Submission of the Draft Health Technology Evaluation Report

The project plan and the more details are mentioned in the next section.

Table 6. Detailed Project Schedule

The project comprises of 4 phases, beginning with setting up the study, gathering evidence, synthesizing and analyzing the data and finally preparing the HTA report. Each phase has specific activities that are summarized below. Specific details of the activities and outcomes are described in detail in the main body of the report.

	Project Plan for HTA Study in RA	Dec 2017	Jan 2018	Feb 2018	March 2018	Apr 2018	May 2018	June 2018	July 2018	August 2018	Sept 2018	Oct 2018	Nov 2018	Dec 2018
1	Phase 1 : Set-up HTA Study													
1.1	Project Inception													
1.2	Research Question for Systematic Review of Literature													
	Develop a PICO framework to develop literature search strategies													
1.3	Define the scope of the systematic review of literature													
1.4	Finalise the scope and design of the systematic review with the SAGEM team													
2	Phase 2: Identify and collect relevant evidence for HTA													

2.1	Finalize search strategy and assemble review team														
	Prepare a the first project progress report for SAGEM														
2.2	Running the search for studies														
2.3	Validation of the results to minimize bias														
2.4	Data extraction, appraisal of the evidence and reporting the systematic review														
	Draft the technical report based on the findings of systematic review														
2.5	Additional data collection from Local Experts for missing Turkish context														
3	Phase 3: Synthesize data, analyse and prepare report														
3.1	Data synthesis and analysis														
3.2	Clinical and radiological end-points review														
3.3	Economic evaluation and review of end-points														

3.4	Review of other end-points													
3.4	Draft final report													
3.5	Consensus with Ministry of Health and other stakeholders													
4	Phase 4: Socialize and finalize the HTA report													

5.5. Project Team

Participants, stakeholders and responsibility

5.5.1. Participant Institutions

#	Name of Institution	Role in HTA Project
1	- SAGEM, SHGM	Project Owner and Coordinator, Editor, Coordinator, Author, Researchers
2	- SSI	Contributors
3	- TMMDA	Contributors
4	- Universities	Contributors
5	- Non Governmental Organizations	Contributors
6	- Patients/Patient Relatives	Contributors
7	- Companies	Contributors

5.5.2. Shareholders

#	Persons/Institutions	Role in HTA Project
1	- Institutions - Public - Private	Shareholder
2	- Non Governmental Organizations - Professional Organizations - Associations	Shareholder

	- Foundations	
3	- Companies - Pharmaceutical - Medical Device	Shareholder
4	- Patients - Patient Relatives	Shareholder

The project involved a wide set of participants. Before the start of the survey, convened a meeting with Turkish Medicines and Medical Devices Agency, SSI, the representatives of the pharmaceutical industry and patient association as well as the leading rheumatologists in Turkey to secure their views on the project and to further generate a consensus. It was agreed that the current study will review the findings of the global literature as well as the local literature when reporting for the outcomes of the health technology assessments undertaken for RA. It was also agreed that during the course of the study, while collecting information about the subject, the representatives of the patients' association and the key physicians in Turkey will be interviewed to seek their feedback on the currently available health technologies in RA in Turkey.

5.5.3. Responsibility

The HTA project on "Health Technology Assessment on Synthetic and Biologic DMARDs Used in the Treatment of Rheumatoid Arthritis" Report was created at the end of the process were published under the responsibility of the General Directorate of Health Services. All right of the HTA report belong to General Directorate of Health Services.

Project team and tasks of the HTA project are listed below.

a. Project Manager

The main responsibilities include designing the duties of all study group members who work in the Project in agreement with the Administration and ensure coordination among the study group members. She/he is accountable to the Administration fort he execution of the work.

b. Editors

The main responsibilities include editing the HTA report texts which are written in a period and in a way projected, planned and requested in the Terms of Reference and other relevant documents and for ensuring that these texts constitute a meaningful whole at the end of the study.

c. Writers

The main responsibilities include wiritng texts for the sections of HTA reports, which is delivered to the Administration at the end of the study, in a period and in a way projected, planned and requested in the Terms of Reference and other relevant documents. She/he is responsible for preparing draft and final HTA full report texts.

d. Researchers

The main responsibilities during the whole or time periods of the project include providing information in their areas of responsibility and expertise to the writer whenever they deem necessary about the subjects in the assessment element tables for medical and surgical interventions of HTA Core Model®

e. Contributors

The main responsibilities during the whole or time periods of the project include providing the required contributions in their areas of responsibility or expertise upon requests from the writers in regard to the subjects in the assessment element tables for medical and surgical interventions of HTA Core Model®

5.5.4. Project Manager, Editors, Authors, Researchers and Contributors

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- Project Contractor: Joint Venture of IMS Health Tıbbi İstatistik Ticaret ve Müşavirlik Ltd. Sti. and QuintilesIMS Information and Consulting Services India Pvt. Ltd.
- Project Manager:Dr. Sangameshwar Mahagaonkar (Project Executer and Technical Coordinator)
- Project Manager: Özgür Ertok (Project Executer and Local Coordinator)
- Project Editor: Dr.Umut Kalyoncu

- Project Editor: Dr. Nevsun İnanc
- Project Editor: Dr. Mark Lamotte
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- Project Author: Abhinav Bassi
- Project Author: Dr. Sachin Bhokare
- Project Author: Dr. Nilesh Maheshwari
- Project Researcher: Mehmed Celebi
- Project Researcher: Sumaiya Arfin

5.5.5. Researchers

#	**Name & Surname**	**Institution & Position**
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3	Elife DILMAC	SAGEM/SHGM
4	Gulcan TECIRLI	SAGEM/SHGM
5	Ilker SABUNCUOGLU	SAGEM/SHGM
6	Mustafa KILIC	SAGEM/SHGM
7	Olgun SENER	SAGEM/SHGM
8	Sevil AKDENIZ	SAGEM/SHGM

9	Sultan OGRAS	SHGM
10	Sangam MAHAGAONKAR	IQVIA
11	Ozgur ERTOK	IQVIA
12	Tripti BAJAJ	IQVIA
13	Abhinav BASSI	IQVIA
14	Mehmed CELEBI	IQVIA
15	Ritu BHARDWAJ	IQVIA
16	Sumit MITTAL	IQVIA
17	Sumaiya ARFIN	IQVIA
18	Sachin BHOKARE	IQVIA
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20	Umut KALYONCU	Danışman Hekim
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22	Cem BAYDAR	Danışman
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25	Sebnem ATAMAN	Danışman Hekim
26	Hatice BODUR	Danışman Hekim
27	Basak SONMEZ	Danışman- Romaturka Hasta Derneği
28	Gulin DINC	Danışman- Romaturka Hasta Derneği

5.6. No Conflict of Interest Declaration

Team members of the "Health Technology Assessment on Synthetic and Biologic DMARDs Used in the Treatment of Rheumatoid Arthritis" Project declare that they have committed to work without any material or moral influence that may negatively affect the scientific character of the work or without a relationship of interest and they have signed the declaration of conflict of interest (declaration of objectivity) in Appendix 2.

6. HEALTH PROBLEM AND CURRENT USAGE OF TECHNOLOGY

6.1. Introduction

This chapter provides information about rheumatoid arthritis (RA), including the current definitions, epidemiology, pathophysiology, and the diagnostic and treatment methods. Details of the treatment modalities and more specifically on the disease modifying anti-rheumatoid drugs (DMARDs) as the mainstay of modern day treatment of RA is discussed. The evaluations also provide answers to the questions in the first chapter titled as "the Healthcare Problems and The Current Use of Technology" in the assessment element tables (3.0) of the HTA Core Model® in Appendix.

Qualitative description of RA, including the underlying mechanism (pathophysiology), natural history (i.e. course of disease), available screening and diagnostic methods, prognosis, and epidemiology (incidence, prevalence), and the current available treatment are mentioned. In addition, regulatory information on the marketing authorisation, as well as on the reimbursement status for DMARDs is also included in this domain, as such information describes the formal position of the technology within health care system

6.2. Assessment

Table 7. Assessment Areas in Health Problem & Current Use of Technology

Topic	**Issue**	**Information and source**
Target condition	Epidemiology of RA	Review of literature – discussed later
Target population	Adults suffering from RA	Review of literature – discussed later
Current management of RA	What are the current DMARDs available for treatment of RA? How is RA currently diagnosed as per published guidelines and in practice?	Review of literature – discussed later

	How is RA currently managed as per published guidelines and in practice?	
Utilization	Which DMARDs are currently available? Which DMARDs are currently used in treatment of RA? Who decides which people are eligible for various DMARDs and what is the basis?	Review of literature and opinion of experts – discussed later
Regulatory status	What DMARDs are currently approved for RA? What indications other than RA is approved for the DMARD	Review of literature and opinion of experts – discussed later
Reimbursement status	Who pays for treatment with DMARDs and how is it reimbursed in case of out-of-pocket expenses by patients?	Review of literature and opinion of experts – discussed later

6.2.1. Epidemiology of RA

RA is a common autoimmune systemic inflammatory disease affecting approximately 1% of the worldwide population. While the specific causes for RA remain unknown, some factors can increase the risk of developing the disease. Researchers have studied a number of genetic and environmental factors to determine if they change person's risk of developing RA. The most common risks are advancing age (more than 60 years), elderly females, having HLA class II genotype, history of smoking, obesity, and women who have never borne children. The interaction of genetic and environmental factors results in a cascade of immune reactions, which ultimately lead to the development of synovitis, joint damage, and structural bone damage. These, in turn,

lead to pain, disability, and emotional, social, and economic challenges. A number of extraarticular manifestations and comorbidities are present in patients with RA, which result in increased mortality.

RA continues to cause modest global disability, with severe consequences in the individuals affected. The global prevalence of RA was 0.24% (95% CI 0.23% to 0.25%), with no discernible change from 1990 to 2010. DALYs increased from 3.3 million (M) (95% CI 2.6 M to 4.1 M) in 1990 to 4.8 M (95% CI 3.7 M to 6.1 M) in 2010. This increase was due to a growth in population and increase in aging. Globally, of the 291 conditions studied, RA was ranked as the 42nd highest contributor to global disability, just below malaria and just above iodine deficiency (measured in YLDs).

In a first nationwide epidemiological study (26) to estimate the prevalence of RA and SpA in Turkey, the investigators estimated the prevalence of RA to be 0.62% (95% CI; 0.38-0.86) in general population, 0.12% (95% CI; -0.05-0.29) for males and significantly higher prevalence of 0.98% (95% CI; 0.58-1.38) for females. The highest prevalence of RA was in the age group of 55-64 years (1.11%). The prevalence of RA was highest in the Northern region (2.00%) indicating a significant regional difference.

As per the ICD 10 classification, RA is categorized under Inflammatory polyarthropathies (M05-M14), of which M05 and M06 are of direct relevance here.

Table 8. : ICD 10 Classification of RA

Inflammatory Polyarthropathies (M05-M14)
M05 *Seropositive RA (excluding rheumatic fever (I00); juvenile RA (M08) and arthritis of spine (M45)*
M05.0 *Felty Syndrome*
M05.1 *Rheumatoid Lung Disease*
M05.2 *Rheumatoid Vasculitis*
M05.3 *RA with involvement of other organs and systems*
M05.8 *Other Seropositive RA*

M05.9 *Seropositive RA, Unspecified*
M05.0 *RA with involvement of other organs and systems*
M06 *Other RA*
M06.0 *Seronegative RA*
M06.1 *Adult Onset Still Disease*
M06.2 *Rheumatoid Bursitis*
M06.3 *Rheumatoid Nodule*
M06.4 *Inflammatory Polyarthropathy*
M06.8 *Other Specified RA*
M06.9 *RA Unspecified*

Natural history of RA has been modeled based on longitudinal population level studies, wherein there is a 'pre-clinical phase' of the disease development beginning with genetic risk (phase 1), followed by asymptomatic inflammation and autoimmunity (phase 2), before eventual progression to symptomatic inflammatory arthritis (IA) (phase 3) that may progress to classifiable RA (phase 4). If left untreated, RA can cause a number of short-term complications, particularly joint pain. And because RA affects the entire body, without treatment patients also experience general malaise, fever, and fatigue.

Untreated RA can also increase the risk for infections, the more severe the RA, the greater the risk for infection, according to the Arthritis Foundation. If left untreated, long term complications include deformities in joints with severely reduced mobility, vascular complications arising from inflammed blood vessels, progression of atherosclerosis, increased risk of cardiovascular complications such as ischaemic heart disease and stroke and an overall reduction of the life expectancy of the individual.

According to research findings presented at the American College of Rheumatology 's 2016 ACR/ARHP Annual Meeting, heart attack and stroke risk in RA patients is similar to that for people with longstanding type 2 diabetes mellitus.

According to another study published in Trends in Cardiovascular Medicine in February 2017, patients with RA have as much as twice the risk of heart disease as the general population.

6.2.2. Pathophysiology of RA

The pathogenesis of RA is not completely understood. An external trigger (eg, cigarette smoking, infection, or trauma) that sets off an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.

Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, whereas B cells produce autoantibodies (ie, rheumatoid factors). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with RA, including the following:

Pro-Inflmmatory Chemicals in RA

- Tumor necrosis factor alpha (TNF-α)
- Interleukin (IL)-1
- IL-6 & IL-8
- Transforming growth factor beta (TGF-ß)
- Fibroblast growth factor (FGF)
- Platelet-derived growth factor (PDGF)

Ultimately, inflammation and exuberant proliferation of the synovium (ie, pannus) leads to destruction of various tissues, including cartilage (see the image below), bone, tendons, ligaments, and blood vessels. Although the articular structures are the primary sites involved by RA, other tissues are also affected.

6.2.3. Social And Historical Descriptions of RA

The first description of RA acknowledged by modern medicine is found in the dissertation of Augustin Jacob Landré-Beauvais from the year 1800. Although Landré-Beauvais' dissertation is

considered to be the first accepted medical report of RA, some researchers have suggested that earlier descriptions are available in ancient texts. The Greek philosopher Hippocrates wrote:

> *In the arthritis which generally shows itself about the age of thirty-five there is frequently no great interval between the affection of the hands and feet; both these becoming similar in nature, slender, with little flesh…For the most part their arthritis passeth from the feet to the hands, next the elbows and knees, after these the hip joint. It is incredible how fast the mischief spreads.*

It seems very possible that Hippocrates was describing a patient with RA. Similar descriptions can be found in the writings of the Greek physician Arataeus, Caesar's physician Scribonius, the Byzantine physician Soranus, Emperor Constantine IX's adviser Michael Psellus, and various other ancient physicians.

Landré-Beauvais was only 28 years old and a resident physician at the Saltpêtrière asylum in France when he first noticed the symptoms and signs of what we now know to be RA. He examined and treated a handful of patients with severe joint pain that could not be explained by other known maladies at the time (such as "rheumatism" or osteoarthritis). Unlike gout, this condition mainly affected the poor, affected women more often than men, and had previously been ignored by other physicians who – concerned with earning acclaim and compensation for their work – usually chose to treat more affluent patients. He hypothesized that these patients were suffering from a previously uncharacterized condition, which he named Goutte Asthénique Primitive, or "Primary Asthenic Gout."1 Though Landré-Beauvais' classification of RA as a relative of gout was inaccurate, his dissertation encouraged other researchers in the field of bone and joint disorders to further study this disease.

The next important contributor to the study of RA was Alfred Garrod, an English physician during the mid to late 19th century. Alfred Garrod was the first to distinguish gout from other arthritic conditions. Archibald Garrod, the fourth son of Alfred Garrod, also conducted research on RA. In 1890 he authored the extensive Treatise on Rheumatism and RA. In this book he coined the term "Rheumatoid Arthritis" to refer to the disease first discovered by Landré-Beauvais and later referred to as "Rheumatic Gout" by his father. In the 120 years that had passed since its discovery, more than a dozen terms had been used to describe the same disease. Archibald Garrod chose "RA" because it more accurately described the disease's action on the human body.

In the 20th century, the American physician Charles Short challenged Archibald Garrod's paleopathological claims and sought to discredit the Ancient Origin hypothesis as presented by Archibald Garrod in his Treatise. Upon examination of the original paleontological reports cited by Archibald Garrod's Treatise, Short noticed that diagnoses of ankylosing spondylitis, osteoarthritis, and gout had been all confirmed in the skeletal samples. On the other hand he could not find a definitive diagnosis of RA, but rather only claims of RA which he deemed to be unconvincing. Claiming that Archibald Garrod's ideas were spurious, Short hypothesized that, due to the lack of evidence demonstrating otherwise, RA was actually a disease of modern origins.7 Though others had made similar conjectures in the past, it was Short's work that is most often credited as the basis of the Recent Origins view of RA.

In addition to analyses of historical medical writings and paintings, post-mortem investigations provide a venue for gathering scientific data about a disease's historical prevalence. The lack of widely accepted ancient medical texts regarding RA has forced researchers to turn to paleopathological studies. Due to the nature of buried skeletal remains, which generally lack soft tissues, bone and joint diseases (including RA) are typically easy to study on post-mortem specimens.

Two preliminary paleopathological studies independently carried out by Professor Flinders Petrie and Sir Armand Ruffer in the late 19th and early 20th centuries discuss human remains from Egypt that demonstrate skeletal damage similar to RA. Close inspection of Ruffer's work reveals many potential cases of ankylosing spondylitis (AS), but not one definitive case of RA. Ruffer and Petrie's works are generally not considered to be convincing evidence for RA in ancient times. However, their work demonstrated that evidence of rheumatic diseases could be identified in ancient human remains. Unfortunately these pioneering studies were done before the development of modern paleopathological methods. Furthermore, it was not until the 1970s that RA and (AS) were conclusively differentiated through genetic studies.

Recent research on the origins and etiology of RA highlights a molecular perspective for the disease causation rooted in genetic causes. There are some environmental causes such as smoking and certain infections that can contribute. It has further been suggested by researchers that the aforementioned causes (smoking, infectious triggers, etc.) are not actually causes, but rather risk factors. This would imply that RA could have been present in the populations of both the ancient

New and Old Worlds, albeit very rare in the Old World in the absence of important environmental triggers. After the opening of trade routes between the hemispheres, certain risk factors (especially tobacco) could have been introduced in parts of world where they did not exist and which contributed to the eventual appearance of RA as a more common disease in the Old World.

6.2.4. Clinical Diagnosis of RA (ACR and EULAR Criteria)

Historically, the diagnosis of RA was based on the 1987 American College of Rheumatology (ACR) criteria. These criteria were based on the persistence of arthritic symptoms over time; however, this classification system failed to identify patients with early inflammatory arthritis. With this focus, the ACR and the European League Against Rheumatism (EULAR) devised new classification criteria for early arthritis, which assess joint involvement, autoantibody status, acute-phase response, and symptom duration, as well as revised criteria for classifying RA in newly presenting patients, those with erosive disease typical of RA, and those with inactive disease with or without treatment. There is no gold standard test for RA and hence the diagnosis is based on multiple parameters.

The ACR/EULAR classification system is a score-based algorithm incorporating 4 parameters for diagnosis of RA, which has been detailed in the table-9 below. Each of the 4 parameter is scored by the treating physician on a maximum possible score of 10 points.

Diagnosis of RA is made if the overall score from the 4 parameters is 6/10 or higher. Patients with a score lower than 6/10 should be reassessed over time. If patients already have erosive changes characteristic of RA, they meet the definition of RA, and application of this diagnostic algorithm is unnecessary.

Joint involvement consists of swelling or tenderness upon examination. The presence of synovitis may be confirmed on imaging studies.

Table 9. Scoring System for RA

Scoring System for Involvement of Joints	
1 large joint (ie, shoulders, elbows, hips, knees, ankles)	0 point
2-10 large joints	1 point

1-3 small joints (with or without involvement of large joints), such as MCP, PIP, second to fifth MTP, thumb interphalangeal (IP), and wrist joints	2 points
4-10 small joints (with or without involvement of large joints)	3 points
More than 10 joints (at least 1 small joint, plus any combination of large and additional small joints or joints such as the temporomandibular, acromioclavicular, or sternoclavicular)	5 points
Scoring system for serology tests	
Negative rheumatoid factor (RF) and negative anti−citrullinated protein antibody (ACPA; in the ACR/EULAR criteria set, tested as anti−cyclic citrullinated peptide [anti-CCP])	0 points
Low-positive RF or low-positive ACPA	2 points
High-positive RF or high-positive ACPA	3 points
Scoring system for acute phase reactants	
Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0 points
Abnormal CRP or abnormal ESR	1 point
Scoring system for patients' self reporting of duration of symptoms / signs in joints involved	
Shorter than 6 weeks	0 points
6 weeks or longer	1 point

6.2.5. Validity of ACR / EULAR Diagnostic Criteria

A review by Radner et al concluded that the 2010 ACR/EULAR criteria have a pooled sensitivity for diagnosis of RA of 0.82 (95% confidence interval [CI], 0.79-0.84) and a specificity of 0.61 (95% CI, 0.59-0.64). These authors' review of research that directly compared the 2010 ACR/EULAR criteria with 1987 ACR criteria found that the ACR/EULAR criteria had higher

overall sensitivity (+0.11 compared with 1987 criteria) at the cost of lower overall specificity (-0.04). This indicates the shift to identifying patients earlier in the course of the illness rather than waiting for specific signs to develop and thereby losing precious time to initiate treatment.

6.2.6. Treatment Options for RA: Over The Years

Optimal care of patients with RA consists of an integrated approach that includes both pharmacologic and nonpharmacologic therapies. Many nonpharmacologic treatments are available for this disease, including exercise, diet, massage, counseling, stress reduction, physical therapy, and surgery. Active participation of the patient and family in the design and implementation of the therapeutic program helps boost morale and ensure compliance, as does explaining the rationale for the therapies used.

Medication-based therapies comprise several classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic DMARDs, immunosuppressants, and corticosteroids. Early therapy with DMARDs has become the standard of care, because it can both retard disease progression more efficiently than later treatment and, potentially, induce more remissions.

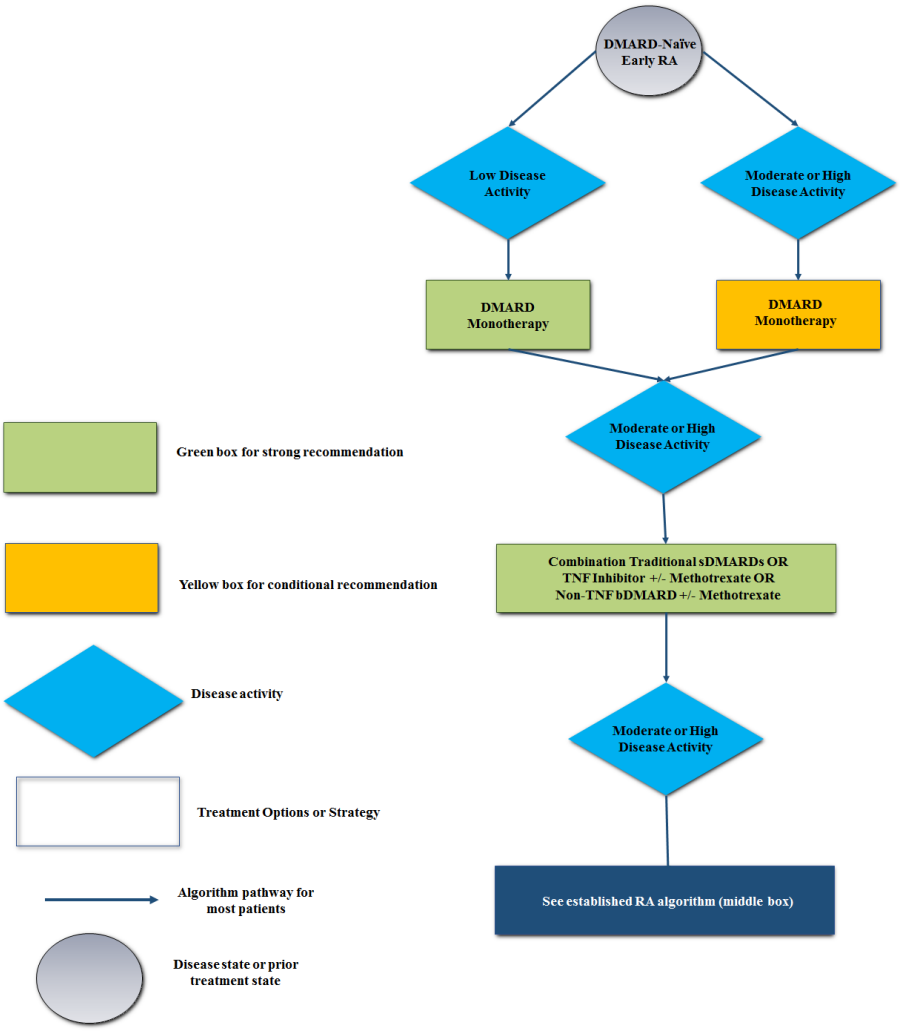

Figure 2. Treatment Algorithm for RA as Per ACR

In 2008, the American College of Rheumatology (ACR) developed recommendations and algorithms for the use of nonbiologic and biologic DMARDs for patients with RA with subsequent updates in 2012 and 2015.

Once a diagnosis is made, the main treatment goals are to control disease activity and slow the rate of joint damage, in addition to minimizing pain, stiffness, inflammation, and complications. Pharmacologic therapies that are used include nonbiologic and biologic DMARDs and adjunctive agents such as corticosteroids, NSAIDs, and analgesics.

The new 2015 RA pharmacologic treatment guidelines from ACR focus on 6 major topics:

1. Use of traditional /conventional synthetic sDMARD, biologic DMARDs (herein referred to as bDMARDs), and targeted synthetic tsDMARD tofacitinib, including tapering and discontinuing medications, and a treat-to-target approach;
2. Use of glucocorticoids
3. Caution of use of DMARDs in high-risk populations
4. Use of vaccines in patients prescribed DMARDs
5. Screening for tuberculosis for patients receiving bDMARDs & tsDMARDs
6. Laboratory monitoring for sDMARD

As can be seen, 5 of the 6 major topics concern DMARDs, which highlight the central role of these medications in the management of RA.

DMARDs represent the most important measure in the successful treatment of RA. These agents can retard or prevent disease progression and, thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications; however, until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling. Many studies have revealed that early treatment of RA (ie, within months of onset) with DMARDs not only can retard disease progression more efficiently than later treatment but also may induce more remissions. Thus, early DMARD therapy (< 6 months after the onset of symptoms) has become the standard of care.

Patients with early forms of arthritis should be evaluated by and, if necessary, referred to physicians who are experienced in the diagnosis and treatment of RA.

In the latest recommendations of ACR, before patients undergo pharmacologic treatment with either nonbiologic or biologic DMARDS, they should receive not only the pneumococcal, hepatitis, and influenza vaccinations but also vaccinations for human papillomavirus (HPV) and herpes zoster virus (HZV) (added in the 2015 updated ACR recommendations).

DMARDs can be classified into nonbiologic and biologic agents. The nonbiologic DMARDs include the following:

Methotrexate (MTX)	Sulphasalazine (SSZ)
Hydroxychloroquine (HCQ)	Cyclosporine
Azathioprine (AZA)	Leflunomide

The biologic DMARDs can be classified as TNF inhibitors (Anti-TNF or TNF biologics) and non-TNF inhibitors

TNF inhibitors (Anti-TNF or TNF biologics)	**Non- TNF inhibitors (Anti-TNF or TNF biologics)**
Etanercept	Rituximab
Infliximab	Anakinra
Adalimumab	Abatacept
Certolizumab	Tocilizumab
Golimumab	Tofacitinib

6.2.7. ACR Guidelines for Management of RA Using DMARDs

We have summarized the key recommendations of both ACR and EULAR with regard to use of DMARDs.

There is significant overlap between the 2 The recommendations have been graded as strong and conditional and are separate for early and established RA.

Table 10. ACR Guidelines for Management of RA Using DMARDs

Stakeholder	**Strong Recommendation**	**Conditional Recommendation**
Patients	Most people in your situation would want the recommended course of action and only a small portion would not	The majority people in your situation would want the recommended course of action but many would not

Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients to make a decision that is consistent with their own values
Policy Makers	The recommendation can be adapted as a policy in most situations	There is need for substantial debate and involvement of stakeholders

Table 11. ACR Recommendations for Patients With Early Stage RA

Recommendations for patients with early RA	**Level of evidence**
Regardless of disease activity level, use a treat-to-target strategy	Low (17)
If disease activity is low, in patients who have never taken a DMARD: Use DMARD monotherapy (methotrexate preferred) over double therapy Use DMARD monotherapy (methotrexate preferred) over triple therapy	 Low (18-21) Low (22-25)
If disease activity is moderate or high, in patients never taken a DMARD: Use DMARD monotherapy over double therapy Use DMARD monotherapy over triple therapy	 Moderate (18,20,21) High (22-25)
If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a Anti-TNF or a non-TNF biologic (all choices with or without methotrexate, in no particular order), rather than continuing DMARD monotherapy alone	Low (26-28)
If disease activity remains moderate or high despite DMARDs: Use a Anti-TNF monotherapy over tofacitinib monotherapy Use a Anti-TNF + methotrexate over tofacitinib + methotrexate	 Low (29) Low (30)

If disease activity remains moderate or high despite DMARDs or biologic therapies, add low-dose glucocorticoids	Moderate (31-37) Low (31-37)
If disease flares, add short-term glucocorticoids at lowest possible dose and for the shortest possible duration	Very low (38-43)

Table 12. ACR Recommendations for Patients With Established RA

Recommendations for patients with established RA	**Level of evidence**
Regardless of disease activity level, use a treat-to-target strategy	Moderate (44-46)
If disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (methotrexate preferred) over Anti-TNF	• Low (47,48)
If disease activity is moderate or high, in patients never taken a DMARD: • Use DMARD monotherapy (methotrexate preferred) over tofacitinib • Use DMARD monotherapy (methotrexate preferred) over combination therapy	• • High (49) Moderate (18,20-25)
If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a Anti-TNF or a non-TNF biologic or tofacitinib (all choices with or without methotrexate, in no particular order), rather than continuing DMARD monotherapy alone	Moderate to Very Low (23,26,29,30,47,48,50-59)
If disease activity remains moderate or high despite Anti-TNF therapy in patients who are currently not on DMARDs, add one or two DMARDs to Anti-TNF therapy rather than continuing Anti-TNF monotherapy	High (60-65)

If disease activity remains moderate or high despite use of a single Anti-TNF Use a non-TNF biologic, with or without methotrexate, over another Anti-TNF with or without methotrexate Use a non-TNF biologic, with or without methotrexate, over tofacitinib with or without methotrexate	Low to very low (66-72) Very Low*
If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without methotrexate, over tofacitinib with or without methotrexate	Very low*
If disease activity remains moderate or high despite use of multiple (more than 2) sequential Anti-TNF therapies, first use a non-TNF biologic, with or without methotrexate, over another Anti-TNF or tofacitinib with or without methotrexate	Very low*
If disease activity remains moderate or high despite use of multiple Anti-TNF therapies, use tofacitinib, with or without methotrexate, over another Anti-TNF, with or without methotrexate, if use of a non-TNF biologic is not an option	Low (29,30)
If disease activity remains moderate or high despite use of at least one Anti-TNF and at least one non-TNF biologic: First use another non-TNF biologic, with or without methotrexate over tofacitinib If disease activity remains moderate or high, use tofacitinib, with or without methotrexate over another Anti-TNF	 Very low (29,30) Very low (29)
If disease activity remains moderate or high despite use of DMARD, Anti-TNF or non-biologic therapy, add short-term, low dose glucocorticoid therapy	High to Moderate (33, 41, 76, 77)
If disease flares in patients on DMARD, Anti-TNF, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration	Very low (40-43)

If the patient is in remission: Taper DMARD therapy Taper Anti-TNF, non-TNF biologic, or tofacitinib	Low (78) Moderate to Very low (79,80)
If disease activity is low: Continue DMARD therapy Continue Anti-TNF, non-TNF biologic or tofacitinib rather than discontinuing respective medication	 Moderate (78) High to Very low (79,80)
If the patient's disease is in remission, do not discontinue all RA therapies	Very low*

** no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience*

6.2.8. The European League Against Rheumatism (EULAR) Guidelines for Management of RA

EULAR developed a first set of recommendations for the management of RA with DMARDs in 2010 and updated them in 2013. EULAR guidelines have been referred to by national rheumatology societies and regional leagues to inform the development of their own recommendations (such as Canadian, French, German, Mexican, Asia Pacific League of Associations for Rheumatology (APLAR), Pan American League of Associations for Rheumatology (PANLAR)), as well as by regulatory authorities.

RA is managed by rheumatologists and PTR specialists in Turkey. Rheumatologists and PTR specialists are represented by two associations in Turkey; Turkey Rheumatism Research and Control Association (TLAR), Turkish Society for Rheumatology (TSR) respectively.

The Turkish League Against Rheumatism (Turkiye Romatizma Arastirma ve Savas Dernegi (TRASD)) was established in 1947 and has been working for the cause of stimulating, promoting, and supporting scientific research in the field of rheumatic diseases in Turkey, also has largely adapted the recommendations of ACR and EULAR to develop local Turkish guidelines.

Turkish Society for Rheumatology (TSR) was established in 1993. The initial name of the association was Rheumatology Research and Education Association. In 2012, the association name was changed as Turkish Society for Rheumatology (TSR). The mission of TSR is to promote scientific research and physician training on RA and to increase the number and quality of

rheumatologists throughout the country. In addition, to encourage and support physician to research on rheumatology, to increase disease awareness and to inform patients about rheumatism diseases.

The latest guidelines from EULAR have 4 overarching principles and 12 recommendations. The recommendations address csDMARDs (methotrexate (MTX), leflunomide, sulfasalazine); glucocorticoids (GC); biological (b) DMARDs (tumour necrosis factor (TNF)-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, tocilizumab, clazakizumab, sarilumab and sirukumab and biosimilar (bs) DMARDs) and targeted synthetic (ts) DMARDs (Janus kinase (Jak) inhibitors tofacitinib, baricitinib).

Specific focus was on monotherapy, combination therapy, treatment strategies (treat-to-target) and the targets of sustained clinical remission (as defined by the American College of Rheumatology-(ACR)-EULAR Boolean or index criteria) or low disease activity.

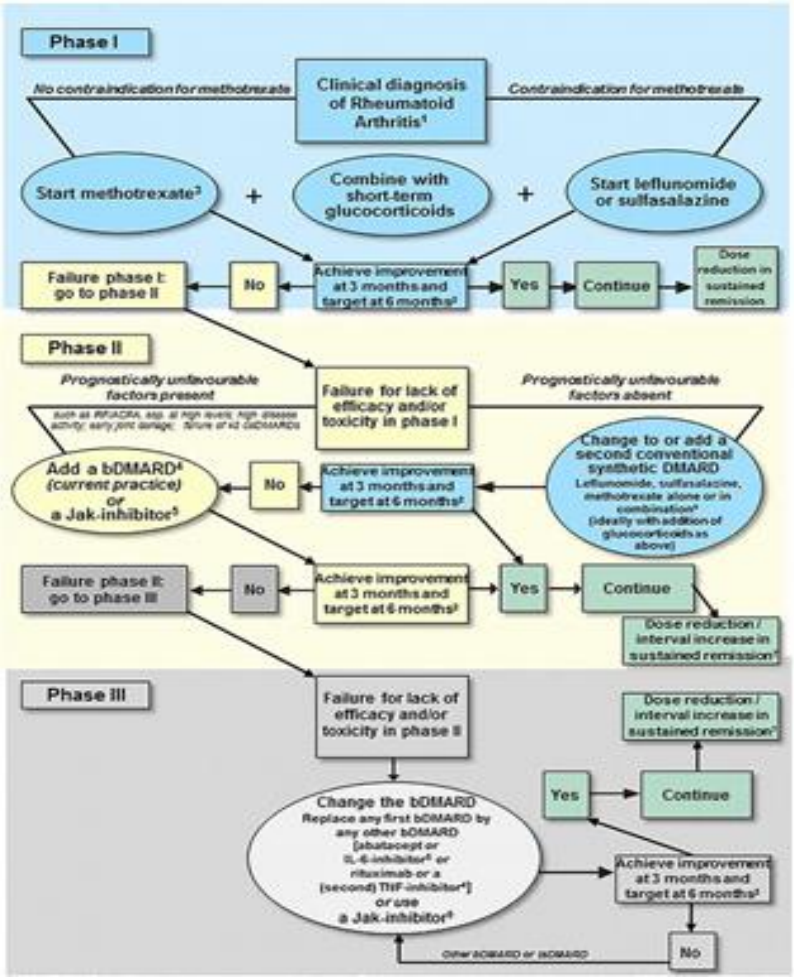

Figure 3. Algorithm Based on 2016 EULAR Recommendations on RA Management

Overarching Principles of EULAR Recommendations	
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
C	Rheumatologists are the specialists who should primarily care for patients with RA.
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

Shared decision-making between patient and rheumatologist involves all aspects of the disease: information on the disease and its risks, the modalities of disease assessment, decisions on the therapeutic target and the potential means to reach the target, the development of a management plan and discussions on the benefits and risks of individual therapies. However, over the last years, it was recognised that shared decision-making and considerations of patient factors should receive the most prominent recognition. There is compelling evidence that being cared for by a rheumatologist is advantageous for the patients in terms of early initiation of therapy, prevention of damage and reduction in surgical procedures. Moreover, rheumatologists have the most profound experience regarding the use of csDMARDs and bDMARDs. This includes the adverse event profiles of these drugs, as well as awareness of and experience with comorbidities in RA. Therefore, rheumatologists can provide the 'best care' in accordance with item A, in the sense of a holistic approach. The reasoning behind the term 'primarily' has been discussed amply in previous versions of the recommendations and relates to considerations of multidisciplinary care, including specialty nurses, and to the fact that in certain areas of the world rheumatology training is not sufficiently provided and other experts may have experience in the management of RA.

Moreover, some comorbidities, such as chronic hepatitis or interstitial lung disease, may require consultation of, and treatment by, other specialists.

Table 13. EULAR Recommendations For Management Of RA

Individual Recommendations	
1	Therapy with DMARDs should be started as soon as the diagnosis of RA is made. MTX preferred if no contraindication
2	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.
3	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.
4	Methotrexate should be part of the first treatment strategy
5	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6	Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
7	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.
8	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD* or a tsDMARD* should be considered; current practice would be to start a bDMARD§
9	bDMARDs* and tsDMARDs# should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.

10	If a bDMARD* or tsDMARD§ has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action
11	If a patient is in persistent remission after having tapered GC, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.
12	If a patient is in persistent remission, tapering the csDMARD could be considered.

The 12 individual recommendations form a logical sequence. They start with the need to initiate effective therapy immediately after diagnosis and the requirement to set a treatment target and to assess the disease on the way towards that target, employing a treat-to-target strategy. With these prerequisites in mind, different drugs or combinations of agents are recommended in the course of the therapeutic procedures, with suggested sequential increments, taking prognostic factors and all approved agents into account. They also mention some agents of potential future interest, even though not yet approved by international regulatory authorities. Thus, the recommendations also include a prospective view on drugs that have undergone phase III trials and were available for evidence assessment; obviously their actual prescription will depend on the regulatory approval status in individual countries. The set of recommendations concludes with suggestions towards reduction of therapy and even withdrawal of some drugs when the desired target has been attained and is sustained. Such recommendations will then need to be reviewed within the context of the available resources within a given health system.

We are presenting below the local Turkish revisions to the international guidelines.

6.2.9. Turkish League Against Rheumatism (TLAR) Recommendations Management of RA

The EULAR 2016 recommendations for the treatment of RA were voted by 27 specialists experienced in this field with regard to participation rate for each recommendation and significance of items. Afterwards, each recommendation was brought forward for discussion and any alteration gaining ≥70% approval was accepted. Also, Turkish version of each item was rearranged. Last version of the recommendations was then revoted to determine the level of agreement. Levels of agreement of the two voting rounds were compared with Wilcoxon signed-rank test. In case of

significant difference, the item with higher level of agreement was accepted. In case of no difference, the changed item was selected.

The Turkish clinical practice is mainly guided by the EULAR guidelines. The TLAR expert committee after reviewing all the four overarching principles and 12 recommendations from EULAR, advised changing 3 overarching principles and only one recommendation. The changed overarching principles emphasized the importance of physical medicine and rehabilitation specialists as well as rheumatologists for the care of RA patients in Turkey. An alteration was made in the eighth recommendation on treatment of active RA patients with unfavorable prognostic indicators after failure of three conventional disease modifying anti-rheumatic drugs. There were no other change made to the EULAR recommendations for management of RA in Turkey

Overarching Principles as Recommended by EULAR

A Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the **rheumatologist**.

B Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues

C **Rheumatologists** are the specialists who should primarily care for patients with RA.

D RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating **rheumatologist**.

Overarching Principles of EULAR as Revised by TLAR

A In the management of RA patients, providing the best care should be targeted and the treatment should rely on a co-decision between the **physician** and the patient.

B Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues

C	Rheumatologists **and physical medicine and rehabilitation specialists** are the primary experts to take care of RA patients
D	RA has high individual, medical, and societal costs. All these aspects should be considered by the **specialist** when treatment decisions are made.

Justifications for the changes to the overarching principles was because of the local Turkish context. The term "rheumatologists" in the original form was changed as "physicians." Due to insufficient number of rheumatologists in Turkey, physical medicine and rehabilitation specialists also take care of RA patients. In Turkey, rheumatology subspecialty within the physical medicine and rehabilitation clinics were founded in 1983 for the first time. The Ministry of Health and the Council of Higher Education approved rheumatology subspecialties of both internal medicine and physical medicine and rehabilitation departments since then. As the term "physiatrist" used in TLAR 2013 RA treatment recommendations is commonly misconceived as "physiotherapist", we preferred the term "physical medicine and rehabilitation specialist." However, a more comprehensive phrase; "physician" was chosen in the item since it comprises both these specialties.

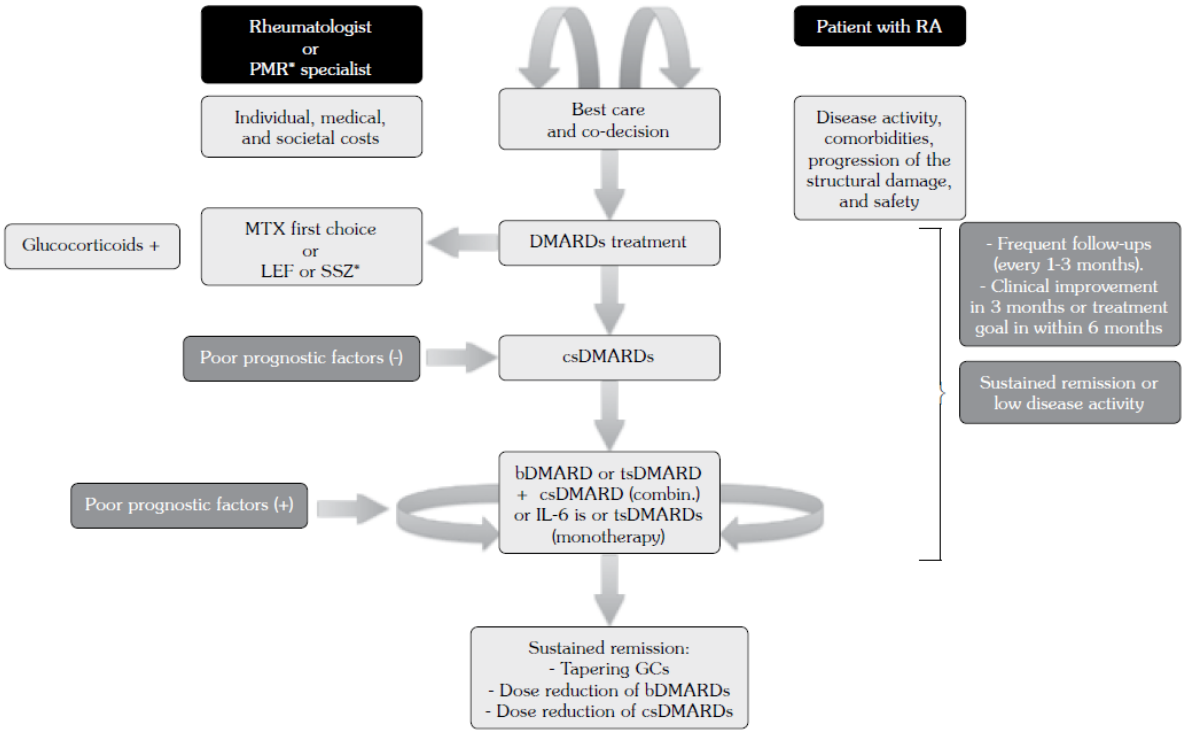

Figure 4. TLAR Algorithm of Managing RA

**PMR specialist – Physical medicine and rehabilitation specialist*

Despite not being underlined in the EULAR 2016 recommendations for the management of RA, patient education was also emphasized in the TLAR 2010 consensus recommendations for the management of RA as a separate item: "Patients with RA and their families should be informed and educated, and social support should be provided for the patients It has been demonstrated in numerous studies that educational-behavioral programs to protect joints have beneficial effects on pain, disease activity, functional and psychological status in RA. Along with making shared decisions regarding the treatment process with the patient, education programs would also contribute to patients' adherence to pharmacological therapy.

Table 14. TLAR Recommendations for Management Of RA

Individual Recommendations of TLAR 2018 Update
1 Treatment with DMARDs should be initiated soon after the RA diagnosis is made.
2 Treatment goal should be achieving sustained remission or low disease activity in all patients

3	In case of active disease, patients should have frequent follow-ups (every one-three months). The treatment should be re-adjusted if clinical improvement cannot be obtained in three months or the treatment goal cannot be reached within six months.
4	Methotrexate should constitute a part of the first treatment regimen
5	If MTX cannot be used because of contraindications or intolerance, LEF or SSZ should be started as a part of the first treatment regimen
6	In the periods of csDMARD initiation or change, GCs should be considered for short-term use with different dose and administration routes; however, it should be tapered rapidly when the clinical condition permits
7	If the treatment goal cannot be reached with the first treatment regimen, in the absence of poor prognostic factors, other csDMARDs should be initiated
8	If the treatment goal cannot be reached with the first treatment regimen, in the presence of poor prognostic factors, a bDMARD or tsDMARD addition should be considered. Generally, bDMARD is the first treatment choice
9	bDMARD and tsDMARDs should be used together with a csDMARD. For patients who cannot use csDMARDs along with these medications, IL-6 inhibitors or tsDMARDs may have beneficial effects over other bDMARDs.
10	In case of bDMARD or tsDMARD failure, treatment with another bDMARD or tsDMARD should be given. In case of one Anti-TNF failure, another Anti-TNF or medication with a different mechanism may be considered
11	In case of persistent remission after tapering GCs in a patient using csDMARDs as comedication, dose reduction of bDMARDs may be considered
12	In case of persistent remission after tapering bDMARDs, dose reduction of the csDMARD may be considered

6.2.10. Turkish Society for Rheumatology (TSR) Recommendations Management of RA

It was intended to develop a national guide for RA treatment by Turkish Society for Rheumatology. Ten experts met in April 2017. Recommendations were established and voted (0–10). There commendations were presented to members in March 2018.

RA treatment decision should be managed according to disease activity and other factors (whether or not structural damage exists or degree, comorbidities and safety).” is defined as overreaching principle.

Table 15. Turkish Society for Rheumatology (TRD) Recommendations Management of RA

Individual Recommendations of TRD 2018	
1	Treatment should be initiated soon after the RA diagnosis is made.
2	Treatment should be aimed to achieve sustainable / persistent remission or low disease activity.
3	In case of active disease, patients should have frequent follow-ups (every one-three months). The treatment should be re-adjusted if clinical improvement cannot be obtained in three months or the treatment goal cannot be reached within six months.
4	Methotrexate should be part of the first treatment strategy
5	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6	Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as soon as possible.
7	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.
8	If the treatment goal is not reached (Remission / Low Disease Activity) with csDMARD strategies (consecutive or combination) for at least six months, in the presence of poor prognostic factors, the addition of a bDMARD or a tsDMARD should be considered.

9	bDMARD and tsDMARDs should be used together with a csDMARD. For patients who cannot use csDMARDs along with these medications, IL-6 inhibitors or tsDMARDs may have beneficial effects over other bDMARDs.
10	If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action.
11	If a patient is in persistent remission after having tapered GC, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.
12	If a patient is in persistent remission, tapering and discontinuing the csDMARD may be considered.
13	In exacerbations, treatment can be managed by re-adjusting dose of GC and DMARDs without drastically changing treatment strategy

6.2.11. Process of Drug Regulatory And Registration Approvals in Turkey

The Turkish Medicines and Medical Devices Agency (TMMDA in English or Türkiye Ilaç ve Tibbi Cihaz Kurumu; TITCK in Turkish) is responsible for reviewing applications for new drugs and health technologies in Turkey. The TITCK performs a full review for all new active substance (NAS) applications. Submission of a Certificate of Pharmaceutical product (CPP) with an application is not required; however, evidence of approval in another country is required for final authorization by the TITCK. Pricing data are not required by the TITCK at the time of submission; however, pricing must be completed to enable products to be commercially available. Mean approval times at the TITCK exceeded the agency's overall target time suggesting room for improved performance, consistency, and process predictability. Measures of GRevP are in place, but the implementation by the TITCK is not currently formalized.

In 2012, TITCK has been transformed into institution from general directorate affiliated in the Ministry of Health, and it is the governmental regulatory authority responsible for regulation, evaluation, inspection, control and monitoring of human medicinal products, medical devices and cosmetics in Turkey. In Turkey, the registration review process of pharmaceutical products is conducted in accordance with the “Registration Regulation of Human Medicinal Products,” which

sets forth the principles, procedures, and policies regarding the registration of medicines (Ministry of Health, 2005). The main goals and focus areas of the Turkish health authority in the past decades have included alignment with international standards and the development of a robust high-quality regulatory health agency comparable to those of other mature developed health agencies, in order to ensure the timely access of patients to medicines.

According to McAuslane and colleagues, there are three basic types of scientific regulatory review of products.

The type 1 verification model is generally used to reduce duplication of review effort since it requires that the product be authorized by two or more recognized reference agencies. The regulatory agency is only responsible to verify and validate the application for local marketing to ensure that it conforms to that agreed in the reference authorization(s).

The type 2, the abridged assessment model conserves resources by not re-assessing scientific supporting data that has been reviewed and approved by at least one reference or competent regulatory agency and includes an abridged independent review of the product in terms of its use under local conditions.

The type 3 has 2 sub-types - 3A and 3B full assessment models the agency carries out a complete scientific review and evaluation of the supporting scientific data (quality, pre-clinical, and clinical) for a major application. While pre-registration by a reference agency is required for type 3A assessment, it is not required for type 3B.

The TITCK performs a full review for all new active substance applications and a marketing authorization application for a new active substance can be submitted in Turkey prior to any approval in the world. However, because evidence of approval in other countries like the EU or US must still be submitted prior to the final approval by the TITCK, the agency review type is considered to be type 3A.

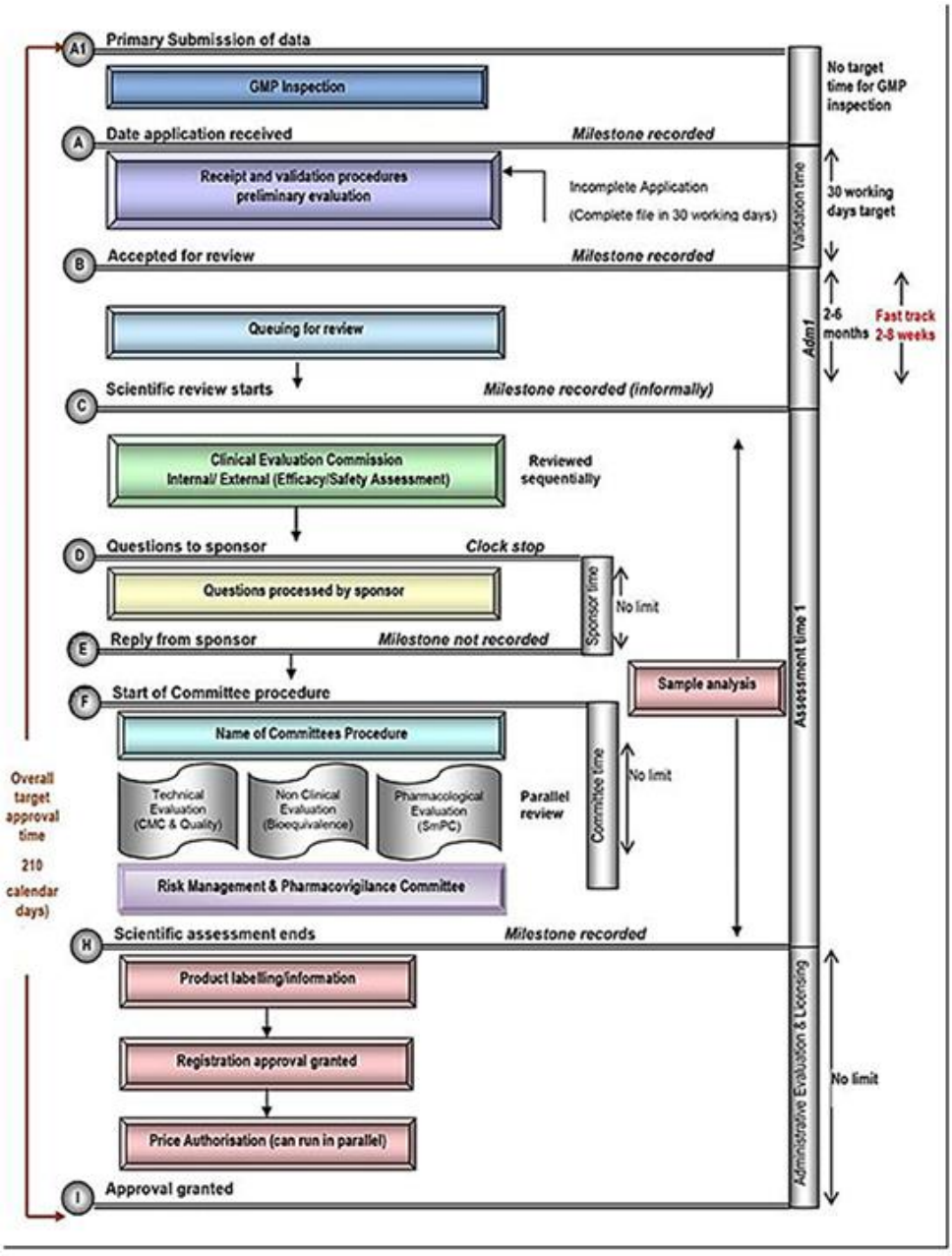

Figure 5. Product Registration and Approval Process Within TITCK

The process of approval illustrated above applies to the DMARDs (both synthetic and biologic) as well as all other medications used in the management of RA. This is explained below in greater detail with the pricing and reimbursement process.

6.2.12. Process of Pricing & Reimbursement of Drugs And Biosimilars in Turkey

a. Pricing And Reimbursement Process for Drugs

Manufacturers must have an approved price from the MoH before they can apply for reimbursement.

The usual timeline for pricing to be approved by the MoH is 9-12 months in Turkey. For the initial drug pricing to be approved by the MoH, application submissions can be made twice in a year. Pricing applications are processed within 90 days, although the MoH may take longer times to process if there is disagreement with the manufacturer's proposed price. Exceptionally, in larger public health interest, the TITCK can allow a priority assessment of the product pricing.

However, the priority of the application is assessed based on whether:

1. The product was locally produced in Turkey from an approved cell line
2. The product is providing a public cost advantage even if needs to be imported
3. The product will provide a viable alternative to the currently used first line biosimilar product

It is the SGK (Turkish National Social Security Institution – SGK (Sosyal Güvenlik Kurumu)) reimbursement price that is critical for drug companies, rather than the price set by the MoH. To gain access to the reimbursable list of drugs, a reimbursement price must be agreed with the SGK and compulsory discount rates are applied.

Manufacturers may voluntarily offer discounts on top of the mandatory discounts applied to the MSP retail price including VAT of the drug by the country's Social Security Institution – SGK (Sosyal Güvenlik Kurumu). The final decision is taken by the Drug Reimbursement Commission and it also determines reimbursement prices. The President of the SGK must approve of the reimbursement decision to be added to the positive list.

Alternative reimbursement models are largely used in relation to high-cost drugs and include further (and usually confidential) manufacturer discounts, applied on top of the mandatory discounts on the MSPs retail price including VAT of drugs reimbursed by the SGK, pay-for-performance schemes and waiving co-payments. Discounts are agreed with the manufacturers through negotiations involving the Alternative Reimbursement Commission, the SGK and manufacturers, with the drugs accessed through the hospital channel.

For pricing review, all importers and manufacturers must first, submit a pricing declaration application for biosimilars to obtain approval of Ex-manufacturer, Wholesaler and Pharmacy Retail Price (TL) by the Turkish MoH.

Alternative Reimbursement applications for a drug may be submitted to the Alternative Reimbursement commission by the SGK, institutions that are represented in the Commission's membership, or manufacturers.

For both the processes, based on the approval of the Head of SGK, the final decision is made and published.

The Drug and Alternative Reimbursement Commissions, operate parallelly and take the decisions for reimbursement. They have separate sets of regulations.

1. The Drug Reimbursement Commission (İlaç Geri Ödeme Komisyonu), part of SGK consist of 10 members which include representatives of the SGK, the Ministry of Health (MoH), the Ministry of Finance, the Ministry of Development and the Treasury.
2. The Alternative Reimbursement Commission (Alternatif Geri Ödeme Komisyonu), established in 2016, which is responsible for negotiating with manufacturers and devising "alternative reimbursement models" for services (including pharmaceuticals) reimbursed by the SGK

b. Pricing And Reimbursement Mechanisms for Biosimilars

Biosimilars are priced based on an external pricing system. The reference price in Turkey is determined by the lowest price of the same or similar products at manufacturer selling price (MSP) in these European countries (i.e. France, Greece, Italy, Portugal and Spain), import county and/or batch release county. If the product is not present in these 5 countries, then other European countries are considered.

- September 2017 drug pricing communiqué stipulates the following special pricing provisions that apply to biosimilar drugs:
    - The price of a biosimilar drug may be set at up to 100% of the international reference price unless the price is above originator's price in the country
    - Where an international reference product for the biosimilar drug is not available, it may receive a price of up to 100% of the reference product's (i.e. original product's) Turkish price
- Under previous regulations, biosimilars produced in Turkey could be priced based on the cost card, with prices of up to 115% of the reference price, although the Price Evaluation Commission was able to consider prices that were higher

- Prices of original biological drugs will not be changed upon the entry of a biosimilar product into the market

The government has given incentives in R&D and taxation etc to companies to manufacture biosimilars in Turkey.

6.2.13. Reimbursement Guidelines for RA Patients in Turkey

Currently, early treatment of RA with csDMARDs is fully reimbursed in Turkey with proper documentation of disease progression. Disease activity scores for 28 joints (DAS28) are the key indicator to assess the response to the treatment. Treatment usually proceeds with the addition of a 2nd csDMARD or combination with a short trial of corticosteroids before starting a TNF-inhibitor. Addition of a bDMARD also needs to be documented by the relevant specialist for the treatment to be fully reimbursed by general health insurance. These drugs are reimbursed by Social Security Institution based on HCP committee reports issued in secondary and tertiary health care institutions.

Reimbursement conditions are as follows

a. Reimbursement of cDMARDs

- Methotrexate can be given in outpatient and inpatient treatment, based on health report (specialist report / HCP committee report)
- Sulfasalazine and Hydroxychloroquine can be prescribed by all HCPs
- Leflunomide is prescribed by any one of internists, pediatricians or physiotherapy and rehabilitation specialists, based on a 1-year specialist report indicating this condition and issued by such specialists

b. Reimbursement of bDMARDs and tsDMARDs

In adult patients with RA; if at least three different disease-modifying anti-rheumatic drugs, one of which is methotrexate, have been used for at least three consecutive months each, but the disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1), the drug is initiated based on a 3-month HCP committee report. If the DAS 28 score has decreased by more than 0.6 points (1.2 for certolizumab) in the evaluation made 3 months after drug initiation , treatment is continued for 3 more months (6 months for certolizumab), provided that this is stated in the new 3-month (6 months for certolizumab) HCP committee report.

If the DAS 28 score decreases by more than 1.2 points at the end of this report's duration, patients' treatment can be continued, provided that this is stated in the new 6-month HCP committee report.

In the continuation of the treatment, DAS 28 criterion is examined every 6 months, and the initial and new DAS 28 scores are indicated in each HCP committee report. If, despite the treatment, there is no more than 1.2 point decrease in patient's DAS 28 score in comparison to the initial DAS 28 score, then the treatment is terminated.

In general, we have observed that the reimbursement guidelines followed by SSI were consistent with International and National Turkish treatment guidelines There were a few additions/Exceptions to the above reimbursement condition for bDMARDS and tsDMARD are:

- Anti-TNF drugs can be prescribed only based on an HCP committee report of maximum 6 months, issued by a committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists or by internists or pediatricians. Patients who have relapsed for a long period of time (longer than 3 months), are required again to meet initiation criteria. In cases where two different Anti-TNF and/or two different biological agents are used together for two different diagnoses, they are not reimbursed by the Institution
- **Tofacitinib** can be prescribed based on an HCP committee report of maximum 6 months, issued by a committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists or by internists
- For **Tocilizumab**, all prescribing conditions are the same as Anti-TNF drugs and Tofacitinib, except initial prescription condition: In adult patients with RA, who have used at least three different disease-modifying anti-rheumatic drugs, one of which is methotrexate, or an Anti-TNF treatment for at least three consecutive months, but the disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1), the drug is prescribed based on a 3-month health report issued by an HCP committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists

- For **Rituximab**, in combination with methotrexate, in adult patients with active RA whose disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1) despite one or more Anti-TNF treatment(s) or who are not eligible for TNF inhibitor use or who have intolerance for TNF inhibitors, it is prescribed by rheumatology or clinical immunology or physical medicine and rehabilitation specialists based on an HCP committee report which indicates this condition. For the HCP committee report; in healthcare institutions where a rheumatology specialist is present, the HCP committee must include at least one rheumatology specialist; in university hospitals and training and research hospitals, the HCP committee must include at least one rheumatology or clinical immunology or physical medicine and rehabilitation specialist
- For **Abatacept**, in adult patients with active RA, if at least three different disease-modifying anti-rheumatic drugs, one of which is methotrexate, have been used for at least three consecutive months each, but the disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1) despite at least one Anti-TNF treatment, it is prescribed with methotrexate based on a 3-month health report issued by an HCP committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists

6.2.14. Price Control Mechanisms & Drug Reimbursements in Turkey Relevant for DMARDs

a. International Reference Pricing & Local Pricing Controls

In Turkey, pharmaceutical product prices are determined based on an international reference price system. These are generally as follows:

- MoH determines five to ten "source countries" among EU members. Currently these countries are France, Spain, Italy, Portugal and Greece
- "Source price" for a pharmaceutical product is the lowest ex-factory (sale-to-warehouse) price (excluding discounts) in the (i) reference countries, (ii) the country where the product is released, or (iii) the country form which the product is imported. When converting this price in Turkish Liras ("TL"), if this price in Euros, it is multiplied by 60% of the previous calendar year's average EUR/TL Turkish Central Bank exchange rate. Consequently, for

2019, the source prices in EUROS are multiplied by 3,4037. If is in in another foreign currency, the Turkish Central Bank exchange rate for 13.02.2009 is taken into account.

- The maximum ex-factory prices for medicines placed in the Turkish market are as follows:
    - Original products without a generic: %100 of the source price.
    - Generics and originals with a generic on the market: %60 of the source price.
    - Products placed on the market before 01.08.1987: %80 of the source price.

The above rules apply only to medicines available in Turkey based on a marketing authorization offered by TITCK.

Prices of the medicines supplied from abroad without a Turkish marketing authorization, however, are not subject to the above rules and are determined by the Health Services Pricing Commission. Products placed on the market before 01.08.1987 and having an ex-factory price below TL 11,75 and all prescription products having an ex-factory price below TL 6,15, non-prescription products, blood products, medical nutritional products, radiopharmaceuticals, allergy products, orphan medicines, traditional herbal medicinal products, biosimilars, hospital products, serums, products which are not on the reimbursement list, vaccines, medicines having critical importance for public health are not subject to the above rules and their prices are determined by the Pricing Commission. Pricing Commission may also determine different prices for the products subject to alternative reimbursement schemes.

b. Drug Reimbursements And Public discounts

Social Security Institution ("SSI") reimburse the insured persons' payments for the pharmaceutical products.

For a product to be reimbursed, it must be in the SSI reimbursement list. Public discounts may be up to 41% depending on certain criteria set out by the SSI.

c. Pharmaceutical Warehouse (Wholesaler) And Pharmacy Profit Margins

Pricing Decision and Pricing Decree also sets out the profit margins for pharmaceutical warehouses and pharmacies. Accordingly; these profit margins are as follows, to be calculated over the ex-factory prices.

Table 16. Profit Margins for Pharmaceutical Warehouses And Pharmacies

Ex-Factory Price Category of Product	**Warehouse profit**	**Pharmacy profit**
Up to TL 10 (inclusive)	9%	25%
For the price portion between TL 10 (exclusive) - 50 (inclusive)	6%	25%
For the price portion between TL 50 (exclusive) - 100 (inclusive)	7%	25%
For the price portion between TL 100 (exclusive) - 200 (inclusive)	4%	16%
For the price portion above TL 200 (exclusive)	2%	12%

As per the information available through discussions with Turkish experts and patients' representatives, the treatment for RA including the costs of the laboratory tests used in treatment monitoring is fully reimbursed by the SGK. The reimbursement guidelines are as per the recognized International Treatment Guidelines. However, the reimbursement procedures follow a process, which were relatively easier for csDMARDs, but was perceived to be slower and more cumbersome for bDMARDs. This perception by some patient representatives was because bDMARDs can be prescribed only by a specialist rheumatologist or by a specialist physical medicine and rehabilitation physician who were available only in larger cities. This may limited delay the availability of bDMARDs to patients living in rural areas and smaller towns.

6.2.15. Access to DMARDs in Turkey

Currently all the DMARDs mentioned below are available in Turkey. The older generation DMARDs – gold salts and D-Penicillamine have been discontinued in Turkey and are no longer used by the physicians.

a. Nonbiologic DMARDs

Methotrexate (MTX)	Sulphasalazine (SSZ)
Hydroxychloroquine (HCQ)	Cyclosporine
Azathioprine (AZA)	Leflunomide

b. Biologic DMARDs

TNF inhibitors (Anti-TNF or TNF biologics)	**Non- TNF inhibitors (non-Anti-TNF or non-TNF biologics)**
Etanercept	Rituximab
Infliximab	Anakinra
Adalimumab	Abatacept
Certolizumab	Tocilizumab
Golimumab	Tofacitinib (JAK inhibitor) also called as targeted synthetic DMARD (tsDMARD)

The table-17 below includes the historical sales of the various approved DMARDs in Turkey between 2014 and 2018 (5 years). There has been an steady increase in the volume of the sales of the various DMARDs between 2014 and 2018 especially for all the bDMARDs and tofacitinib The sales of adalimumab almost doubled during this period. Only Leflunomide and hydroxycholorquine registered significant increase in sales.

Table 17. DMARD Sales (Unit)

DMARD sales	2014 (‘000 Units)	2015 (‘000 Units)	2016 (‘000 Units)	2017 (‘000 Units)	2018 (‘000 Units)

HYDROXYCHLOROQUINE	1,155	1,246	1,411	1,512	1,643
METHOTREXATE	1,459	1,471	1,463	1,540	1,638
SULFASALAZINE	1,374	1,375	1,459	1,358	1,369
LEFLUNOMIDE	293	328	363	429	461
ETANERCEPT	190	221	230	255	270
INFLIXIMAB	151	174	190	219	248
ADALIMUMAB	114	136	157	179	210
RITUXIMAB	77	84	86	92	119
GOLIMUMAB	34	46	54	62	69
CERTOLIZUMAB PEGOL	1	14	30	48	65
TOCILIZUMAB	8	20	28	38	51
TOFACITINIB	-	3	11	20	31
ABATACEPT	25	25	27	25	27
TOTAL	4,881	5,144	5,508	5,777	6,201

Please note that many of the DMARDs are indicated for conditions other than RA also. The sales figures presented here are represent 99% of the total DMARD sales for Turkey, which included public procurement figures.

The table-18 represents the sales of DMARDs in Turkish Liras for the period of 5 years.

While there has been a steady increase in the total sales value of the DMARDs as a result of the increase in the sales volume, the increase in the sales value will also need to factor the depreciation of the Turkish Lira in 2017 and 2018 and the resulting impact on the prices of the products.

To be noted again is that DMARDs are also indicated for conditions other than RA and hence these costs may not reflect exactly the costs of treatment for RA, which may be lesser.

Table 18. DMARD Sales (TL)

DMARD sales in Turkish Liras	2014 (Mio. TL)	2015 (Mio. TL)	2016 (Mio. TL)	2017 (Mio. TL)	2018 (Mio. TL)

ADALIMUMAB	109.9	134.8	162.7	184.9	235.3
RITUXIMAB	92.1	108.6	124.2	148.4	196.2
ETANERCEPT	91.3	111.8	116.0	126.0	147.0
INFLIXIMAB	76.6	84.9	96.2	120.5	145.8
GOLIMUMAB	37.3	49.3	61.3	75.6	87.1
CERTOLIZUMAB PEGOL	0.7	12.3	26.1	40.6	63.6
METHOTREXATE	24.2	24.0	25.8	30.2	35.8
TOFACITINIB	-	2.1	9.5	19.0	32.8
TOCILIZUMAB	4.0	7.8	11.9	19.8	29.2
ABATACEPT	9.3	13.5	16.6	17.3	20.5
HYDROXYCHLOROQUINE	6.6	7.3	9.4	11.2	14.1
SULFASALAZINE	8.7	8.7	11.4	11.5	13.5
LEFLUNOMIDE	9.5	8.3	9.7	9.5	11.2
TOTAL	470.1	573.6	680.9	814.5	1,032.2

6.2.16. Care of RA Patients And Access to DMARDs And Specialty Care in Turkey

RA patient care is managed by rheumatologists and physical medicine and rehabilitation specialists. Due to insufficient number of rheumatologists in Turkey, physical medicine and rehabilitation specialists also take care of RA patients. In Turkey, rheumatology subspecialty within the physical medicine and rehabilitation clinics were founded in 1983 for the first time. The Ministry of Health and the Council of Higher Education approved rheumatology subspecialties of both internal medicine and physical medicine and rehabilitation departments since then.

There are now increasing number of specialty rheumatologist clinics in bigger cities.

6.3. Discussion & Results

RAis a common autoimmune systemic inflammatory disease affecting approximately 1% of the worldwide population leading to pain, disability, and emotional, social, and economic challenges.

A number of extraarticular manifestations and comorbidities are present in patients with RA, which result in increased mortality. RA continues to cause modest global disability, with severe consequences in the individuals affected. The global prevalence of RA was 0.24%, with no discernible change from 1990 to 2010. DALYs increased from 3.3 million (M) in 1990 to 4.8 M in 2010. This increase was due to a growth in population and increase in aging. Globally, of the 291 conditions studied, RA was ranked as the 42nd highest contributor to global disability, just below malaria and just above iodine deficiency (measured in YLDs).

The prevalence of RA in Turkey reflects the global picture with significant regional variations. Investigators estimated the prevalence of RA to be 0.62% (95% CI; 0.38-0.86) in general population, 0.12% (95% CI; -0.05-0.29) for males and significantly higher prevalence of 0.98% (95% CI; 0.58-1.38) for females. The highest prevalence of RA was in the age group of 55-64 years (1.11%). The prevalence of RA was highest in the Northern region (2.00%) indicating a significant regional difference.

The Turkish League Against Rheumatism (Turkiye Romatizma Arastirma ve Savas Dernegi (TRASD)) established in 1947 and has been working for the cause of stimulating, promoting, and supporting scientific research in the field of rheumatic diseases in Turkey, also has largely adapted the recommendations of ACR and EULAR to develop local Turkish guidelines. TLAR has recently re-prepared RA, Axial Spondylarthritis, Psoriatic Arthritis and Knee Osteoarthritis Current Treatment Guidelines in 2018 and published these recommendations in international scientific refereed journals. RA-2011 and RA-2015 Treatment Guidelines of TLAR experts were last updated in 2018. The scientific activities of the Association include Archives of Rheumatology, Turkish Rheumatology Congress and TLAR School of Imaging, Young TLAR School, TLAR-Online web based education program, Rheumatology e-book study, TLAR-Network projects and BioSTar biological medication registry system.

Turkish Society for Rheumatology (TSR) was established in 1993. The initial name of the association was Rheumatology Research and Education Association. In 2012, the association name was changed as Turkish Society for Rheumatology (TSR). The mission of TSR is to promote scientific research and physician training on RA and to increase the number and quality of rheumatologists throughout the country. In addition, to encourage and support physician to

research on rheumatology, to increase disease awareness and to inform patients about rheumatism diseases.

Currently all the DMARDs (traditional synthetic and biologic) and pharmacological treatments recommended by the guidelines are available in Turkey. The older generation DMARDs – gold salts and D-Penicillamine have been discontinued in Turkey and are no longer used by the physicians.

The Turkish physicians manage RA based on the guidelines from the TLAR and, which in turn are adapted from international recommendations from the EULAR. Due to insufficient number of rheumatologists in Turkey, physical medicine and rehabilitation specialists have been leading the care of RA patients. In Turkey, rheumatology subspecialty within the physical medicine and rehabilitation clinics were founded in 1983 for the first time. The Ministry of Health and the Council of Higher Education approved rheumatology subspecialties of both internal medicine and physical medicine and rehabilitation departments since then. There are increasing number of subspecialty clinics in bigger cities to manage the RA patients. All the costs for the treatment for RA is fully reimbursed by the Turkish National Social Security Institution although the process is more detailed for reimbursement of the bDMARDs, which often pose inconvenience for patients residing in rural and remote areas of the country. Non-availability of specialist physicians in rural and remote areas of the country also increases the indirect costs for the patients such as days off work, travels, lodging, etc, even for out-patient consultations.

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7. DESCRIPTION & TECHNICAL CHARACTERISTICS

7.1. Introduction

The information given in this domain describes historical development of DMARDs tracing their origin from synthetic to the latest biologic and targeted synthetic DMARDs. Additionally the molecular mechanisms of action of the various DMARDs has also been described. The various assessment elements referred in this section are detailed below. Some assessment elements such as regulatory status of DMARDs have been already covered in the previous section.

7.2. Assessment

This domain contains 16 issues related to 4 main topics: (1) features of the technology, (2) training and information needed to use the technology; (3) investments and tools required to use the technology and (4) regulatory status.

Table 19. Assessment Areas in Description & Technical Characteristics of DMARDs

Topic	Issue	Information and source
Features of the technology	What are the DMARDs and their mechanisms of action? Which DMARDs are in development and which are under implementation? Who administers the DMARDs and at what level of care?	Review of literature and opinion of experts – discussed later
Training & information needed for using the technology	What are the skills and training needed for personnel / caregivers using DMARDs? What information & resources is currently available regarding DMARDs for patients and their care givers? Are there any gaps noted?	Review of literature and opinion of experts – discussed later

Investments & tools needed	What specialized infrastructure is needed for the use of DMARDs? Do use of DMARDs require special monitoring systems and registries?	Review of literature and opinion of experts – discussed later
Regulatory status	What DMARDs are currently approved for RA? What indications other than RA is approved for the DMARD	Review of literature and opinion of experts – discussed in earlier section as well briefly later

7.2.1. Pathophysiology of Rheumatoid Arthritis (RA)

RA is an inflammatory condition affecting synovial joints. Without treatment, the underlying inflammatory process leads to joint destruction, pain, deformity, disability and accelerated cardiovascular disease.

DMARDs will attenuate the inflammation. Their benefits are seen at all stages of the disease, however the best outcomes are achieved when they are used shortly after the onset. Patients with suspected RA who went to primary health care services should be referred promptly to secondary/tertiary care services.

DMARDs are often used in combination and can have serious adverse effects. Their safe use requires ongoing monitoring to identify potential adverse events.

Treatment with RA increases the risk of infection; and vaccination is best given before starting biologic DMARDs. Optimal management of RA requires an understanding of the therapeutic goals, the options available to attain them and the associated potential complications. DMARDs are only one part of the management of the patient. The illustration below shows how the inflammatory process affecting the tissues in the bony joints and progresses the disease state.

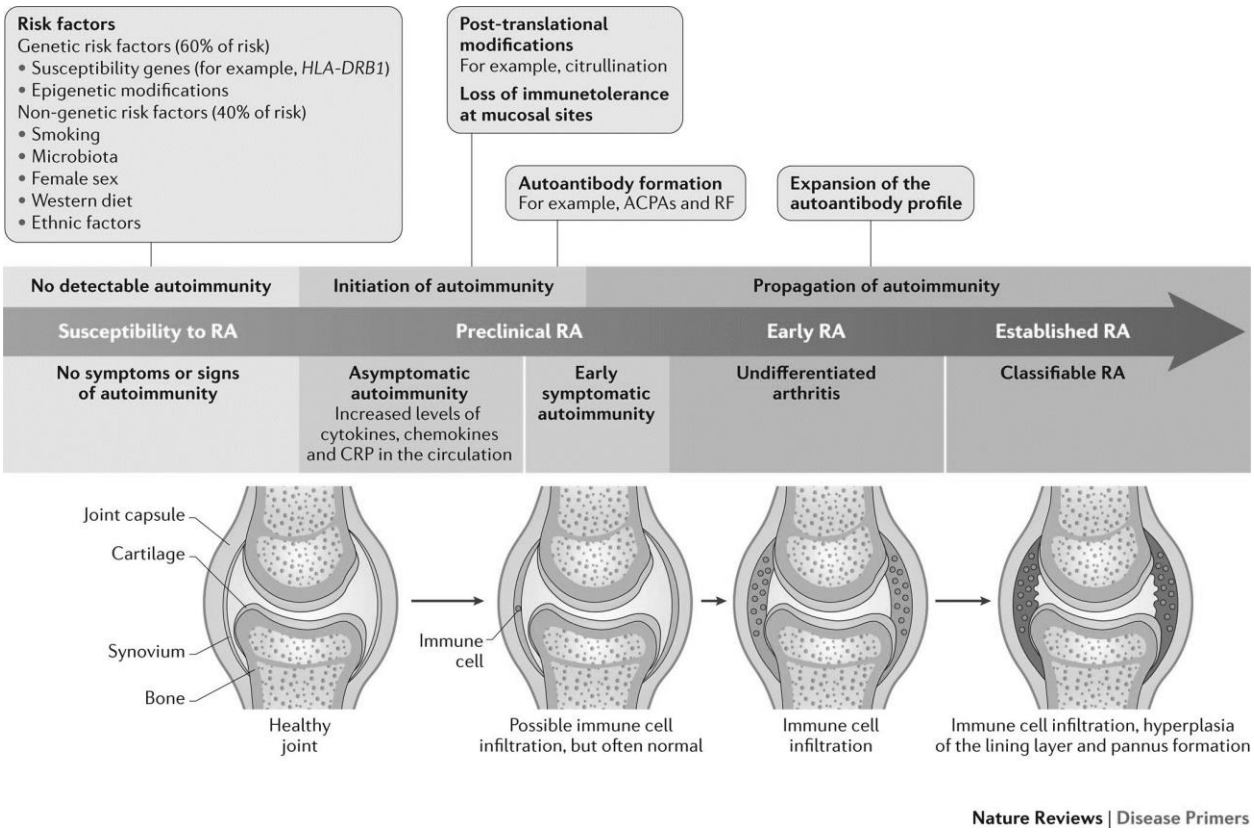

Figure 6. Role of Inflammation in the Progress of RA

Source: Smolen JS et al, Nature Reviews Disease Primers, 4, Article number: 18001 (2018))

Although RA is a systemic disease and a variety of immunological events occur outside the joint at mucosal surfaces and primary lymphoid tissues, the synovium is a central player. The synovium serves two main roles in homeostasis: producing lubricants that enable the cartilage surfaces to operate in a low-friction environment and providing nutrients to cartilage, which lacks its own blood supply. A healthy synovium is a fairly delicate structure with an intimal lining composed of macrophage-like synoviocytes (MLS) and fibroblast-like synoviocytes (FLS) and a sublining composed of fibroblasts, adipocytes, blood vessels and scattered immune cells. The intimal lining is not a barrier in the traditional sense because it lacks a basement membrane and tight junctions, it is leaky and allows relatively free trafficking of cells and proteins into the synovial fluid.

Two key pathogenetic changes in the synovium are evident in RA. First, the intimal lining greatly expands owing to an increase and activation of both MLS & FLS, which are a prominent source of cytokines and proteases. The MLS produce a variety of pro-inflammatory cytokines, including

IL-1, IL-6, tumour necrosis factor (TNF) and others. Although FLS express IL-6, their most prominent feature is the production of prodigious amounts of matrix metalloproteinase (MMPs) and small-molecule mediators such as prostaglandins and leukotrienes. FLS also express specific patterns of microRNAs that could contribute to their activated phenotype. In addition, FLS assume an invasive phenotype that is responsible for cartilage damage and can potentially migrate from joint to joint to propagate disease.

The second change associated with RA is infiltration of adaptive immune cells into the synovial sublining. About half of the sublining cells are CD4+ memory T cells that can either diffusely infiltrate the tissue or, in 15–20% of patients, form ectopic germinal centres in which mature B cells proliferate, differentiate and produce antibodies. B cells, plasmablasts and plasma cells are also present, many of which produce rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA).

Damage to cartilage and bone due to synovial invasion into adjacent articular structures is a cardinal sign of RA. Macrophages, neutrophils (particularly in the synovial fluid space) and mast cells contribute to joint damage via release of cytokines and MMPs. The role of cytokines in disease pathogenesis was prominently established for TNF by the advent of TNF-targeting agents on the basis of prior studies elucidating a pro-inflammatory role for TNF in leukocyte activation, MMP production, angiogenesis and promoting pain. Later studies targeting other cytokines, notably IL-6, demonstrated that the hierarchy of cytokines in patients with RA varies widely.

Synovial cells produce cytokines that act in a paracrine or autocrine fashion and can enhance and perpetuate inflammation in RA. For example, macrophages produce cytokines that activate adjacent FLS, T cells and dendritic cells. These cells in turn produce additional cytokines that can activate other cells in the joint environment.

7.2.2. Current DMARDs Approved for Use in Treatment of RA

a. Nonbiologic DMARDs

Methotrexate (MTX)	Sulphasalazine (SSZ)
Hydroxychloroquine (HCQ)	Cyclosporine
Azathioprine (AZA)	Leflunomide

b. Biologic DMARDs

TNF inhibitors (Anti-TNF or TNF biologics)	Non- TNF inhibitors (non-Anti-TNF or non-TNF biologics)
Etanercept	Sarilumab
Infliximab	Rituximab
Adalimumab	Anakinra
Certolizumab	Abatacept
Golimumab	Tocilizumab
	Tofacitinib & baricitinib (JAK inhibitor) also called as targeted synthetic DMARD (tsDMARD)

7.2.3. Pipeline of DMARDs for RA Under Investigation &/ Regulatory Review

Drug	Manufacturer	Status (as on 2018)	Target pathway
Sirukumab	GKS / Janssen	Not approved	IL-6
Clazakizumab	Vitaeris	Under Phase 2 trials	IL-6
Olokizumab	R-Pharm/UCB	Under Phase 3 trials	IL-6
ALX-0061	Ablynx	Under Phase 3 trials	IL-6R
MEDI5117	AstraZeneca/WuXI	Under Phase 1 trials	IL-6
Filgotinib	Gilead and Galapagos	Under Phase 3 trials	JAK inhibitor

7.2.4. Mechanism of Action of DMARDs

Traditional DMARDs act via various mechanisms. They interfere in combinations of critical pathways in the inflammatory cascade. Methotrexate, for example, stimulates adenosine release from fibroblasts, reduces neutrophil adhesion, inhibits leukotriene B4 synthesis by neutrophils, inhibits local IL-1 production, reduces levels of IL-6 and IL-8, suppresses cell-mediated immunity, and inhibits synovial collagenase gene expression. Other medications in this class serve to inhibit proliferation or cause dysfunction of lymphocytes.

Biologics or bDMARDs, on the other hand, are very selective in their mechanism of action. The overarching functional of biologics include (1) interfering with cytokine function or production, (2) inhibiting the “second signal” required for T-cell activation, and (3) depleting B-cells or

inhibiting factors that active B-cells (rituximab and belimumab). Tofacitinib is a small molecule inhibitor of JAK, a protein tyrosine kinase involved in mediating cytokine signaling.

7.2.5. Special Precautions While Administering DMARDs

a. Route of Administration

They can be administered orally or intravenously. Oral medications can be taken by the patients under supervision and independently while the intravenous medications will need help of nursing staff and supervision for any adverse effects.

b. Adverse Effects

Only the summary of the various adverse effects is described here but more details on the safety profile of the DMARDs will be discussed in the later sections.

DMARDs are very powerful drugs which modulate sequences in the immune system. Their adverse effects can range from mild (rash, nausea, vomiting, stomatitis) to severe, life-threatening infections; therefore, frequent monitoring is required. As a group, conventional DMARDs can cause gastrointestinal (GI) distress, bone marrow suppression, neutropenia, interstitial lung disease, and hepatotoxicity. Methotrexate has been known to cause neurotoxicity, pneumonitis and liver disease including cirrhosis. Of note, a recent study suggests methotrexate (in combination with bisphosphonates) is a risk-factor for bisphosphonate-induced osteonecrosis of the jaw. In another case, hydroxychloroquine (HCQ) can cause retinopathy (macular damage) and rash. Leflunomide can cause diarrhea, alopecia, and elevated liver transaminases.

Biologic agents also have increased the risk of fatal viral, bacterial, and/or fungal infections. Reactivation or primary viral infections of herpes zoster or hepatitis B/C or tuberculosis is also common. Specifically, the anti-CD20 (rituximab) and IL-1 receptor antibody can cause possible congestive heart failure and demyelinating central nervous system (CNS) disease. JAK inhibitors can cause elevated creatinine, LFTs, and hypertension. Cyclosporine can cause nephrotoxicity, hypertension, and gum hyperplasia on rare occasions.

Life-threatening adverse effects of these medications warrant immediate suspension of the drugs.

c. Contraindications

DMARDs are not to be taken by patients who have an active infection, those with preexisting bone marrow hypoplasia, leukopenia, chronic liver disease, or immunodeficiency syndromes. Methotrexate is contraindicated in pregnancy.

d. Need for Regular And Close Monitoring During Treatment

- All traditional synthetic DMARDs can cause myelosuppression and hepatotoxicity and hence should be monitored with a complete blood count (CBC) and liver function tests every 2-4 weeks in initiation and every 6-12 week in monitoring. Patients with impaired renal function should be monitored closely.
- Traditional DMARD that cause macular damage (hydroxychloroquine) should be monitored with funduscopic exams once yearly
- All biologics / bDMARDs can worsen any latent systemic infection such as latent tuberculosis or can make the patient vulnerable for new infections. Hence all patients receiving bDMARDs must be screened for TB, be given TB prophylaxis if needed and also given major vaccines. Also, hepatitis B and C screening should be performed before initiating synthetic and biological DMARDs and preventive treatment should be started if necessary.
- bDMARDs can cause injection site reactions where they are applied and cause allergic reactions that can cause anaphylaxis. Therefore, i.v. drugs (infliximab, rituximab, tocilizumab, abatacept) should be applied in hospitals with experienced specialists.

e. Skillsets for Treating Physicians

As per the recommendations of EULAR, TLAR and TSR, the care of patients with RA needs to be managed by specialist physicians, specifically, by rheumatology and PTR specialists.

Overarching Principles as Recommended by EULAR	
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the **rheumatologist**.
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
C	**Rheumatologists** are the specialists who should primarily care for patients with RA.
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating **rheumatologist**.

Overarching Principles of EULAR as Revised by TLAR	
A	In the management of RA patients, providing the best care should be targeted and the treatment should rely on a co-decision between the **physician** and the patient.
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
C	Rheumatologists and **physical medicine and rehabilitation specialists** are the primary experts to take care of RA patients
D	RA has high individual, medical, and societal costs. All these aspects should be considered by the **specialist** when treatment decisions are made.

RA is managed by PTR specialist and rheumatologists in Turkey. However, because the number of rheumatologists is around 300, PTR specialists participate more in patient management.

7.3. Discussion & Results

Because of special precautions to be exercised, healthcare workers who prescribe DMARDs must be well versed and familiar with all the medications, their indications and adverse effects. All patients prescribed DMARDs need to be closely followed to monitor their effectiveness and side effects. Sufficient information, is very important for increasing patient compliance with treatment and willingness to take preventive precautions.

DMARDs are drugs necessitating health literacy due to their nature. Some of the drugs may be administered weekly while the other may biweekly or even monthly. Taking these drugs more frequently or less frequently than recommended is inadvisable. Particularly in advanced age and illiterate persons, complying with dosing is a problem. Possible toxicities of DMARDs should be checked regularly with physical examinations and assays in certain intervals (1 week - 3 months). Healthcare workers should collect informed consent from patients for these drugs and provide them with an informative note. Again in the event of an adverse case, courts may open these forms to discussion (4).

Official standard consent form for biological DMARDs in Turkey mentions a predefined rate for the adverse event of the drugs; yet they don’t make it clear that these events are possible. This

uncertainty cause concerns in the minds of the patients at the beginning and even some of the patients discontinue the treatment for this reason. Tending to suppress the immune system more or less in general, infection risks of DMARDs cause consultations and examinations at the start and monitoring of the drug.

The reason is that Safety Monitoring Form required under the scope of the pharmacovigilance continues to be used for more than 15 years for certain drugs. Due to their nature, such practices are sufficient to be applied for a period of five years. Under the scope of the Safety Monitoring Form, it should be stated quarterly whether the patient has tumor or tuberculosis. Naturally, the physicians signing the document may go beyond the recommended guidelines of the Turkish Society for Rheumatology (TRD) and want to see lung x-rays, tumor markers and the results of other examinations frequently in order to be on the safe side. This issue results in burdening the system with additional costs and processes having patients undergo unnecessary examinations and worry in the meantime. The contribution of such applications to decreasing the responsibility of the administration or physician in the event of a possible adverse event..

As tsDMARDs (tofacitinib) are drugs taken by mouth, their use is relatively easy. However, the patients may not pay attention to the use of tsDMARDs as much as they pay to bDMARDs applied as injection even though these have the same adverse effects. Thus, as per informing on drugs, call centers supported by pharmaceutical industry and related patient associations take role beside the physicians and nurses. Today, information strategies are uniform for all groups of the population. Training of family members is very important particularly for the patients whose drug use is monitored through the family support.

At this point, patient associations play a great role. However, training activities under the present condition are insufficient. Like in some European countries, it can be seen as a good way for SSI to allocate resources and to do such studies to patient associations and to eliminate the educational burden of clinics.

Currently, RA patients are given information about DMARDs only when such drugs are considered necessary by the doctor. However, the doctors are unable to devote sufficient time for educating patients under the existing working conditions of hospitals. Therefore, such information should be given via patient hospital or patient meetings. Patient associations should be active in this area. As indicated above, training may be given outside the hospitals if SSI accepts patient

associations as its partner with respect to training of the patients and use its resources allocated to such training via patient associations. Brochures and websites can be used to explain DMARDs to the educated patients in an unbiased and simple basis. In this context, patients should be informed not only of DMARDs, but also the history of a molecule turning into a drug, analysis of proof and the concept of adverse effect.

Today, patient training events are insufficient in Turkey with respect to DMARDs as per the experts who were interviewed. For this purpose, Romaturka Patient Association is a member of the European Rheumatology Patient Organization (PARE), which is under the umbrella of EULAR. On 26 October 2018, in Ankara, "Arthritis Day Patient Meeting Organization", was organized for RA, spondylarthritis and osteoarthritis.

Biologics /bDMARDs drugs must be kept in cold chain makes power cuts an issue for patients. Untrained patients may cause the drug to lose its effect by heating their medication on the radiator prior to bDMARD applications. When biological DMARDs are administered via injection, patients are trained about the administration. This training is provided by the relevant bDMARD companies' support programs, nurses and related clinics.Drugs administered through injection or infusion impose burden on hospital nursing services. Rheumatology clinics are obliged to establish infusion departments for this reason. To assess tuberculosis risk before and during the biological treatment, PPD test applied in Tuberculosis Control Dispensary and Quantiferon TB test which is a laboratory test, Pulmonology Diseases and Clinical Microbiology and Infectious Diseases (in addition to vaccination protocols) results in additional cost to the system.

7.4. References

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5. Delphi panel and expert interviews, 2018.

8. SAFETY

8.1. Introduction

In this section, we mainly describe the safety parameters that are of importance to patients, or otherwise likely to be important in guiding the decisions of healthcare providers and policy makers. Detailed description has been provided for DMARDs highlighting the relative differences between the various DMARDs in the context of the published clinical effectiveness of the DMARDs. Safety for any health technology can be assessed in 4 contexts:

a. Direct harm to patients such as death, disability due to toxicity, immunogenicity, idiosyncrasy, hypersensitivity, invasiveness, etc.,

b. Indirect harm due to insufficient training or experience, lack of equipment maintenance, or inappropriate patient selection. This can be further classified into operator or setting dependent and patient dependent harms. The former can be modified by changing practices or improving user knowledge, skills and behaviour. The latter may indicate vulnerable patient groups that require special protection

c. Harms can be mild, moderate or severe, depending on the intensity or can be serious. The serious harms or adverse effects have significant medical consequences causing death, permanent disability or prolonged suffering. Even mild harms such as headache can be severe in intensity but may not be serious

d. Harms can affect patients, their caregivers, health care professionals providing the services, unborn foetus, other patients, and the environment. Harms can be both dose-related or time/exposure-related. Prolonging the exposure at same dose can also produce harm

All the safety parameters discussed in this section have been collected from clinical trials as well as real world data.

8.2. Assessment

Table 20. Assessment Areas in Safety of DMARDs

Topic	Issue	Information and source
Patient safety	How safe are the various DMARDs?	Review of literature and opinion of experts – discussed later

	Are the harms dose-related or time-related? Are the harms unique and different in specific settings and populations?	
Occupational safety for healthcare professionals	Are there any occupational harms to the health professionals prescribing and administering DMARDs?	Opinion of experts – DMARDs do not carry any special occupational risk for healthcare professionals but have similar risks as with any other medications given by oral and systemic routes
Environmental safety for general public	Are there any risks for general public and environment from DMARDs?	Opinion of experts – DMARDs do not carry any special environmental risk for general public and environment
Safety risk management	Based on the risks assessed, what are the effective mitigation strategies available to reduce the safety risks to patients, health professionals and others?	Review of literature and opinion of experts – discussed briefly later

A plethora of conventional synthetic DMARDs (csDMARDs; bDMARDs) and more recently also targeted synthetic DMARDs (tsDMARDs), which can be used in different sequences and/or combinations, is at the disposal of rheumatology and PTR specialists to offer to patients. This, naturally, also implies choices to be made when deciding on the best treatment for a particular patient. Regardless of the disease activity levels, using a "treat-to-target strategy" than a non-targetd approach is noted to achieve better clinical outcomes. The ideal target for treatment with DMARD was noted to be lowering disease activity or to achieve clinical remission

Treatment decisions, particularly in the case of patients with RA with insufficient response to a first csDMARD, are mainly made based on the expected efficacy of a drug while managing the

safety concerns. Due to various drug and non-drug related factors, first line csDMARDs may not offer the desirable reduction in disease activity. This necessitates addition of bDMARDs to achieve reduction and remission of disease activity.

Although the initiation of treatment could be with a csDMARD monotherapy, there are many studies that have shown to achieve better disease activity reduction with subsequent trials with combination of other csDMARDs before deciding to add bDMARDs. The decision to combine monotherapy with other csDMARDs should be on the basis of presence or absence of prognostically unfavourable factors (such as continued high disease activity, high serum marker levels, early join damage, etc).

Combination therapies have shown to improve response rates in some patients previously receiving monotherapy. If treatment target is not achieved with initial trial of csDMARD monotherapy or combination of csDMARDs, addition of a bDMARD should be considered after a thorough review of the safety parameters.

However, bDMARDs are not only more expensive treatment option but they have important safety concerns to be considered by the treating physician. Within bDMARDs, there are some newer variants that are more expensive than the older generation bDMARDs. Despite the apparent variance in the prices among different bDMARDs, available scientific evidence suggests no noticeable differences in efficacy across bDMARDs and tsDMARDs. Therefore, other aspects among which safety may have a more prominent place in decision-making. While short-term safety is addressed in clinical trials, it is long-term safety that we are primarily interested in when making our decisions.

The combination of biologics with methotrexate was observed to be as safe as the biologic monotherapies. tsDMARDs were found to be more safe than methotrexate. All bDMARDs (except rituximab) did have a common safety issue – that of triggering latent tuberculosis among patients with RA. In many countries around the world, infection with tuberculosis bacteria is very common but often such as infection remains latent without causing any obvious clinical symptoms. This is because of the person's strong immune system that often prevents the TB infection from becoming clinically manifest. However, bDMARDs by suppressing the body's cellular immunity can lead to reactivation of latent tuberculosis infection. Hence, any treatment initiation before bDMARDs requires a thorough evaluation for latent or past history of tuberculosis.

On further comparison between bDMARDs, there was not much difference in the safety profile The table-21 is a summary of the safety profile of bDMARDs as reported from randomized clinical trials.

Because of the large number of clinical trials, conference abstracts and systematic reviews referenced, the findings from the safety data for the DMARDs are being presented in the form of tables with mention of the favoured drug/combination.

8.2.1. Safety of DMARDs for Patients

Patients on bDMARDs compared with patients on conventional sDMARDs had a higher risk of serious infections (adjusted Hazard Ratio (aHR) 1.1 to 1.8)—without differences across bDMARDs—a higher risk of tuberculosis (aHR 2.7 to 12.5), but no increased risk of infection by herpes zoster. Patients on bDMARDs did not have an increased risk of malignancies in general, lymphoma or melanoma skin cancer, but the risk of no-melanomatic skin cancers may be slightly increased (aHR 1.5). The findings from the systematic review and the interviews with the local experts in Turkey confirm the known safety pattern of csDMARDs and bDMARDs, including both tumour necrosis factor-α inhibitor (Anti-TNF) and non-Anti-TNF, for the treatment of RA.

We reviewed a safety data from clinical trials as well as other epidemiological research for the various DMARDs. The study arms typically included either single intervention or combination therapies. The safety ranking and favoured drug/ combination of drugs was noted and summarized in the table-21,22 and 23 below. All the included studies and published trials have been mentioned in the refences at the end of the section.

We first reviewed all the randomized clinical trials data on the various DMARDs and have listed the number of studies that evaluated the various bDMARDs either in single or combination with csDMARDs. We then evaluated the number of trials that evaluated csDMARDs either in single or combination with bDMARDs before evaluating the trials on bDMARDs wherein there was a head-to-head comparison. Based on the overall scoring of the safety parameters, we identified number of trials that favoured a given bDMARD or csDMARD. However, safety concerns of minor nature should be always viewed against the comparative effectiveness of a DMARD and the overall risk-benefit options must be weighed before recommending a particular DMARD.

The findings from the various clinical trials and other observational studies are presented in tables 21 and 22 below. The study design, the safety end-points studied and the statistical analyses used

in the various studies included for comparison were different, To represent and score the comparative safety parameters of each DMARD, we have attempted to pool the results from all the studies that included both randomized and non-randomized clinical trials. The number of studies noted to be favouring a particular drug or drug combination was scored and an * symbol was used to further highlight this point.

To better understand and interpret the pooled results, we illustrate with an example in the Table-21 first bDMARD listed is– Adalimumab. We found a total of fifteen studies that had either Adalimumab (monotherapy) or Adalimumab and Methotrexate (combination) as one of the intervention arms. As can be seen in the table, only one study favoured Adalimumab (monotherapy), while an equal number of studies (seven) favoured Adalimumab and Methotrexate (combination) or Methotrexate (monotherapy) as the safest treatment options. Now, let us understand the significance of the * symbol used across these tables.

Key to the Asterisk Symbol *

1. No asterisk mark – Drug/combination favoured by the least number of studies on overall safety parameters
2. Single asterisk mark (*) – Choice of the most effective drug/combination is unclear as two different drugs/combination have been favoured by equal number of studies
3. Triple asterisk mark (***) - Drug/combination favoured by the most number of studies. There is a clear choice, based on the number of studies that the drug/combination was reported as safest

Table 21. Review of Data From Randomized Controlled Trials

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
bDMARDs (Anti-TNF)				
Adalimumab	15	ADA	16385520	1
		ADA + MTX	26138593 22739990 22562973 15146409 12528101 18821658 19369462	7*
		MTX	22915617 10364900 16926184 12115219 15001324 11096165 20187135	7*
Certolizumab	4	CTZ + MTX	26533965 22344576	2*
		MTX	19015207	2*

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
			19909548	
Etanercept	12	ETN	15001324 11096165 18794178	3
		ETN + MTX	24618266 20187135 15001324	3
		ETN + SSZ	18794178	1
		MTX	15001324 20187135 22915617 10364900	4***
		SSZ	18794178	1
Golimumab	15	GOL	20131276 20436075 20091667	3
		GOL + MTX	23861303 22661646 19066176	6*

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
			18383539 19644849 25005327	
		MTX	27803138 30808625 30971306 30091952 29667047 29618976	6*
Infliximab	10	IFX + MTX	16572442 15641102 15529377 11096166 10622295	5*
		MTX	30971306 30536757 30402698 30199187 30053896	5*
bDMARDs (B-cell kinase inhibitor)				

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
Rituximab	13	MTX	30615240 30574867 30536757 30199187 29884751 12357380	6***
		RTX + MTX	16947627 15201414 16649186 20488885 22012969	5
		RTX	17062648 16947627	2
bDMARDs (IL-6 inhibitor)				
Tocilizumab	13	MTX	30615240 30574867 30536757 30199187 29884751	5
		TCZ	16947782	2

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
			22972745	
		TCZ + MTX	18625622 22562983 21360490 19297346 18358926 16947782	6***
bDMARDs (T-Cell activation inhibitor)				
Abatacept	13	ABA	30979397	1
		ABA + MTX	22915624 19124524 16785473 16052582 25367713 18383390	6*
		MTX	30615240 30574867 30536757 30199187 29884751	6*

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
			12357380	
Targeted synthetic DMARD				
Tofacitinib	9	MTX	30615240 30574867 30199187 29884751	4***
		TOFA	24941177 27002108	2
		TOFA + MTX	23348607 22006202 25186034	3
Combination of Conventional Synthetic DMARDs + bDMARDs	6	ETN + MTX	22508468	1
		MTX + SSZ + HCQ	23755969	1
		MTX + SSZ + LEF	20102325	1
		Anti-TNF	27654603	1
		MTX+SSZ	22508468	1
		ETN + MTX	28388820	1
	3	MTX	16926184	1

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
		MTX + SSZ	10364900	1
		SSZ	30536757	1
Head to Head comparison of biologics	22	ABA + ETN	16935912	1
		ABA + MTX	18055472	1
		ADA + MTX	23148339	2*
		Alternate Anti-TNF	27654603	2*
		DMARDs	18821691	2*
		ETN + MTX	23148339	1
		ETN	11096165	1
		IFX + MTX	16572442	1
		MTX	10364900	1
		Non-Anti-TNF	27654603	1
		RTX	22012969	2*
		TCZ	22972745	1
		TCZ + DMARDs	18358926	2*
		TCZ + MTX	21360490	1
		Anti-TNF	20102325	1

DMARDs Studied & Mechanism of Action	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID / Trial Details	Number of studies favoured drug or combination on overall safety parameters
		Anti-TNF + MTX	20082236	1
		Anti-TNF + RTX + MTX	21360491	1

After review of the RCTs, we have evaluated the findings reported from other systematic reviews, most notably the systematic literature review that informed the 2016 update of the EULAR recommendations. This particular review was unique in including only observational studies, namely cohort studies/registries and study series with >30 cases.

This offered a view about the safety of the DMARDs as reported in the real world and outside of the clinical trial environment.

Table 22. Review of Data From Observational Studies (Comparison Between bDMARDs And csDMARDs)

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
Serious Infections					
Galloway 2011 Rheumatology	BSRBR	3 Anti-TNF	csDMARDs	1.2 (1.1 to 1.5)	Low
Greenberg 2010 ARD	CORRONA	3 Anti-TNF+MTX	MTX	1.1 (1.0 to 1.3)	Low
Grijalva 2011 JAMA	Claim database	3 Anti-TNF	csDMARDs	1.1 (0.9 to 1.2)	Moderate

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
Grijalva 2010 Rheumatology	Claim database	3 Anti-TNF	MTX	1.3 (0.8 to 2.2)	Moderate
Komano 2011 J Rheum	REAL	ETA/IFX	csDMARDs	RR 2.4 (1.1 to 5.1)	Moderate
Sakai 2012 AC & R	REAL	ETA/IFX	csDMARDs	RR 2.0 (1.3 to 3.2)	Moderate
Strangfeld 2011 ARD	RABBIT	3 Anti-TNF	csDMARDs	1.8 (1.2 to 2.7)	Low
Lane 2011 Medicine (Baltimore)	Claim database	3 Anti-TNF	csDMARDs	1.2 (1.0 to 1.5) vs HCQ, SSZ, gold	Moderate
Aaltonen 2015 J Rheum10	National Register for Biologic Treatment in Finland (ROB-FIN)	3 Anti-TNF	csDMARDs	0.9 (0.6 to 1.4)	Low
Aaltonen 2015 J Rheum10	National Register for Biologic Treatment in Finland (ROB-FIN)	RTX	No control	1.1 (0.6 to 1.9)	Low
Chiu 2014 Int J Rheum Dis	Taiwan's National Health Insurance Research Database	Anti-TNF (ETA/ADA)	csDMARDs	1.0 (0.9 to 1.2)*	High
Lampropoulos 2015 Clin Exp Rheumatol	Files Laiko University Hospital	bDMARDs (9-nubmer of intervention is not specificied)	csDMARDs	6.9 (3.1 to 15.4)	High

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
Miranda 2014 Rev Colom Rheumatol	Files Colombian Hospital	bDMARDs†	csDMARDs	2.7 (1.1 to 6.3)	High
Morgan 2014 Rheumatology	BSRBR	ETA	csDMARDs	1.0 (0.8 to 1.3)	Low
Cobo Ibanez 2014 Rheumatol Int	BIOBADASER	3 Anti-TNF	General population	♂ 16 (13–20); ‡♀21 (19–24)	Low
Cobo Ibanez 2014 Rheumatol Int	BIOBADASER	RTX	No control	♂ 32 (1–179); ‡♀186 (106–302)	Low
Herpes Zoster					
Galloway ARD 2013	BSRBR	3 Anti-TNF	csDMARDs	1.7 (1.1 to 2.7) adjusted for drop-outs 1.5 (1.0 to 2.4)	Low
McDonald 2009 Clin Inf Diseases	Claim Database	3 Anti-TNF	csDMARDs	1.4 (1.1 to 1.8)	Moderate
Strangfeld 2009 JAMA	RABBIT	3 Anti-TNF	csDMARDs	1.6 (1.0 to 2.7)	Low
Garcia-Doval 2010 ARD	BIOBADASER	Anti-TNF (3?)	General population	10 (3 to 26)	Low
Winthrop 2013 JAMA	Claim Dabatase	3 Anti-TNF	csDMARDs	1.0 (0.8 to 1.3)	Moderate
Pappas 2015 AC&R	CORRONA	csDMARDs	Anti-TNF	1.4 (0.8 to 2.3)	Low
Tuberculosis					

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
Dixon 2010 ARD(a)	BSRBR	3 Anti-TNF	csDMARDs	Not reported	Low
Tam 2010 Clin Exp Rheumatol	Hong Kong Cohort	3 Anti-TNF	General population	34.9 (8.9 to 137.2)	Moderate
Tam 2010 Clin Exp Rheumatol	Hong Kong Cohort	No intervention	csDMARDS	12.5 (3.5 to 44.7)	Moderate
Tubach 2009 A&R	RATIO	3 Anti-TNF	General population	12.4 (9.1 to 16.9)	Low
Winthrop ARD	Claim database	3 Anti-TNF	General population	NR	Moderate
Ke WM 2013 Tuberc Lung Diseases	Taiwan's National Health Insurance Research Database	Anti-TNF (ADA/ETA)	csDMARDs	4.9 (2.1 to 11.1)	Moderate
Baddley 2014 ARD	4 US insurance datasets—SABER study (claims dataset)	3 Anti-TNF	csDMARDs	4.2 (0.5 to 33.5)	Moderate
Chiu 2014 Int J Rheum Dis	Taiwan's National Health Insurance Research Database	Anti-TNF (ADA/ETA)	csDMARDs	2.7 (2.1 to 3.3)	High
Skin infections					
Wasson 2013 BMC Infect Dis	US Veterans (Claims database)	3 Anti-TNF	csDMARDs	1.1 (0.6 to 2.0)§	Moderate
Non-viral opportunistic infections					
Baddley 2014 ARD	4 US insurance datasets (SABER	3 Anti-TNF	csDMARDs	1.6 (0.9 to 3.1)	Moderate
		ADA		1.8 (0.6 to 5.3)	
		ETA		0.8 (0.4 to 1.8)	

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
	study (claims dataset)	IFX		2.6 (1.2 to 5.6)	

Table 23. Review of Data From Observational Studies

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
Serious Infections					
Aaltonen 2015 J Rheum10	National Register for Biologic Treatment in Finland (ROB-FIN)	RTX	Anti-TNF	1.4 (0.8 to 2.6)	Low
Chiang 2014 Comp methods16	Taiwan's National Health Insurance Research Database	ETA	ADA	2.0 (1.1 to 3.6)*	High
Chiu 2014 Int J Rheum Dis		ADA	ETA	1.8 (1.2 to 2.8)	High
Curtis 2014 AC&R17	US Veterans (claims dataset)	ABA	ETA	1.1 (0.6 to 2.1)	Moderate
		ADA		1.4 (0.9 to 2.2)	
		IFX		2.3 (1.3 to 4.0)	
		RTX		1.4 (0.8 to 2.6)	
Johnston 2013 Semin Arthr Rheum	MarketScan (claims dataset)	ABA	RTX	1.2 (0.8 to †)	Moderate
		ADA		1.1 (0.7 to 1.7)	
		ETA		1.3 (0.8 to 2.0)	
		IFX		1.6 (1.0 to 2.6)	
Lampropoulos 2015 Clin Exp Rheumatol	Files Laiko University Hospital	ADA	IFX	1.1 (p=0.819)	High

Study ID	Name of Registry	Intervention	Control	Adjusted Hazard Ratio (aHR)	Risk of bias
		ETA		0.7 (p=0.559)	
Sakai 2015 AR&T	REAL	TCZ	Anti-TNF	2.2 (0.9 to 5.4)	Moderate
Yun 2016 A&R	Medicare claims dataset	ADA	ABA	1.1 (0.9 to 1.3)	Moderate
		CZP		1.1 (0.9 to 1.3)	
		ETA		1.2 (1.1 to 1.5)	
		IFX		1.4 (1.2 to 1.6)	
		GOL		1.1 (0.9 to 1.4)	
		RTX		1.4 (1.2 to 1.5)	
		TCZ		1.1 (0.9 to 1.3)	
Herpes Zoster					
Pappas 2015 AC&R	CORRONA	Non-Anti-TNF	Anti-TNF	0.8(0.5 to 1.4)	Low
Tuberculosis					
Chiang 2014 Comp methods	Taiwan's National Health Insurance Research Database	ETA	ADA	2.4 (0.3 to 19.0)	High
Chiu 2014 Int J Rheum Dis		ADA	ETA	2.4 (1.3 to 4.2)	High
Non-viral opportunistic infections					
Baddley 2014 ARD	4 US insurance datasets—SABER study (claims dataset)	ADA	ETA	1.8 (0.8 to 4.0)	Moderate
		IFX		2.9 (1.5 to 5.4)	

8.3. Discussion & Results

Existing literature has further confirmed that patients on bDMARDs (both Anti-TNF and non-Anti-TNF) have an increased risk of serious infections compared with patients on csDMARDs and that in general there are no differences across bDMARDs. There is an increased risk for tuberculosis with Anti-TNF, whereas this has not been studied well for non-Anti-TNF. There does not seem to be an increased risk of herpes zoster with bDMARDs. In addition, bDMARDs are not

associated with an increased risk of malignancies, with the potential exception of melanoma, based on one study only.

Interestingly, more recent studies addressing serious infections, and especially those at low risk of bias, did not show an increased risk of infections anymore. This contrasts with earlier studies addressing the same outcome, in which a higher risk of infections had been reported consistently even in those at low risk of bias.

This effect may reflect a change in the attitude of physicians who now more carefully screen and monitor patients (including infection prophylaxis, when indicated) and treat infections in patients on bDMARDs appropriately.

The accumulating body of evidence related to bDMARDs is consistently showing us that patients with RA can be treated in a relatively safe way with these drugs. Although most of existing literature on safety of bDMARDs pertains to Anti-TNF, there is relative deficiency of studies on non-Anti-TNF bDMARDs and tsDMARDs in future.

It is also important to collect ongoing evidence of safety of DMARDs from observational studies in addressing safety aspects of treatment, particularly those studies that include a comparator and truly allow us to assign risks to patients on a particular intervention (eg, bDMARDs). Without a proper comparison, it is impossible to truly judge risks. In addition, such observational studies allow inclusion of all types of patients and follow them up for a long period of time, directly reflecting daily clinical practice, which increases their generalisability. This is what we need to get better insight into safety aspects of treatments as it complements the limited information derived from clinical trials. Admittedly, conducting this type of analysis in observational studies properly is challenging. Several confounders can influence the relationships of interest, and they need to be carefully considered. Even though this is done, even the 'best comparator' that we at the moment have to contrast safety of bDMARDs with, namely csDMARDs, also implies challenges and limitations, as we know that patients on csDMARDs have less severe disease, or sometimes historical data are used for comparison purposes, which also introduces some sources of bias. Increasingly complex analyses are being undertaken to circumvent the known challenges, for example, analysis adjusted for propensity score. Collaborations between registries are important in order to homogenise procedures, raise the overall quality and allow comparisons, and these should be encouraged. This will lead to better information for clinicians and better care to patients.

Over and above the current data from observational studies, other information previously obtained through randomised clinical trials (RCTs) or addressed in package inserts should be taken into account. The labels of each drug, including adverse events and lab monitoring, remain undisputed and it is good practice to follow them.

Among all the studies mentioned on bDMARDs, none of them included patients on biosimilars (yet). In addition, observational studies addressing tsDMARDs (Jak inhibitor(s)) have not yet been found as the experience with these newly approved drugs may not be sufficiently long to warrant a conclusion at a population level. However, RCT data point towards a higher risk of serious infections, infections caused by herpes zoster and tuberculosis among bDMARD users, risks that should not be ignored and that warrant further research. Finally, while glucocorticoids are gaining importance as bridging treatment for RA, no single study meeting the eligibility criteria could be found. These are all questions that should be addressed, likely in registries, and with the use of analytical techniques that have previously been used with success in safety studies with bDMARDs.

In Turkey, there are 3 different registration studies initiated by rheumatologists. The first is the TURK-BIO registration study, which was established in 2012 with the localization of the Danish registry study. This recording study contains 3737 bDMARD patient records. In 2017, TReasure registry study was created by 15 different rheumatology centers. There are 2556 patients registered in the TReasure registry. Furthermore, prospective patient registry has been ran since 2005 in the single-centered registry of Hacettepe University (HUR-BİO). This registry also records 1776 RA of bDMARD using patients.

The Turkish League Against Rheumatism (TLAR) studied data of 2359 patients from the TLAR-IP which was established in 2007 as web-based registry system to evaluate the clinical, laboratory and demographic characteristics of patients with RA and Ankylosing Spondylitis (AS). The data obtained from this study are referred to as TLAR-Monitoring Program patient record, and data analysis is published in many international journals. In 2018, TLAR set up the BioSTar system, a new web-based biological registry system.

These are good starting points for collection of safety and efficacy data from patients within Turkey and improve the quality of data. Data analysis of the registers of TRA and TLAR

associations showing the real life data will guide the planning of health policies as well as scientific studies in the future.

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9. CLINICAL EFFECTIVENESS

9.1. Introduction

This domain focuses on the assessment of the health benefits and the benefit-harm-balance from DMARDs. Once again as in the previous section, the evidence has been collected mainly from the randomized controlled trials (RCTs). There are also overlapping information between this and the previous sections.

Comparative clinical effectiveness research compares two or more alternative methods for preventing, diagnosing, treating and monitoring a clinical condition, or for improving the delivery of care. The two key elements of the research are that effective interventions should be directly compared and studied in patients who are typical in day-to-day health care settings.

The assessment of health benefits should primarily consider patient-relevant outcomes such as mortality, morbidity, and quality of life.

9.2. Assessment

Table 24. Assessment Areas in Clinical Effectiveness of DMARDs

Topic	**Issue**	**Information and source**
Effect on disease burden and morbidity	What are the expected benefits of DMARDs on RA patients? - How do DMARDs alter the course of RA progression? - How do DMARDs modify the magnitude and frequency of disease? - How does early initiation of DMARDs affect the effectiveness of later interventions?	Review of literature and opinion of experts – discussed later. The impact on disease progression and morbidity is discussed on the basis of internationally accepted markers such as American College of Rheumatology Score (ACR50), the Disease Activity Score from 28 joints (DAS28), Health Assessment Questionnaire (HAQ) and radiological assessment of disease progression.
Effect on human body?	What is the effect of DMARDs on patients' general body functions?	Review of literature and opinion of experts – discussed later

	What are the effects of DMARDs on patients' ability to work, their activities of daily living and generic health-related quality of life?	
Patient satisfaction	Are patients satisfied with DMARDs? With which DMARDs are patients more satisfied?	Opinion of experts and patients' representatives - discussed later

9.2.1. Effect of Disease Burden And Morbidity And Effect on Human Body

The clinical effectiveness of DMARDs were evaluated on the basis of response to the globally standardized tools of assessments including American College of Rheumatology percentage of improvement score (ACR50), the Disease Activity Score from 28 joints (DAS28), Health Assessment Questionnaire (HAQ) and radiological assessment of disease progression.

9.2.2. ACR 50

Outcome Variable - The ACR criteria is a dichotomous variable with a positive (responder) or negative (non-responder) outcome. The ACR Criteria measures improvement in tender or swollen joint counts in improvement in at least three of the following parameters: patient assessment, physician assessment, pain scale, disability/functional questionnaire, and acute phase reactant (ESR or CRP). ACR 50 has a positive outcome if 50% improvement in tender or swollen joint counts were achieved as well as a 50% improvement in at least three of the other five criteria.

Findings - The findings from the included randomized control trials provided a clear pattern where **Methotrexate in combination with the other csDMARDs showed better outcomes in terms of ACR50.** This pattern was also observed in the studies that aimed at comparing biologics monotherapy with biologic combination. A combination of a bDMARDs with methotrexate was

efficacious in terms of the improvements in ACR 50. Combination of tsDMARD with methotrexate yielded positive ACR scores in more number of studies as compared to tsDMARD alone. **The head to head comparisons between the bDMARDs provided an in conclusive evidence, and a trend favouring any biologic was not observed.**

We first reviewed all the randomized clinical trials data on the various DMARDs and have listed the number of studies that evaluated the various bDMARDs either in single or combination with csDMARDs. We then evaluated the number of trials that evaluated csDMARDs either in single or combination with bDMARDs before evaluating the trials on bDMARDs wherein there was a head-to-head comparison. Based on the overall scoring of the efficacy parameters in the form of adjusted Hazard's Ratio (aHR), we identified number of trials that favoured a given bDMARD or csDMARD. However, minor gains in efficacy of one DMARD over another should be always viewed against the overall safety and cost effectiveness of that particular DMARD over others.

Table 25. Review of Data From Randomized Controlled Trials

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
Conventional Synthetic				
Methotrexate +Sulfasalazine	3	MTX	16926184	1
		MTX + SSZ	10364900 12115219	2***
		SSZ	-	0
	2	MTX + HCQ	23755969	Not reported
		MTX + SSZ	12115219	1

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
Methotrexate + Sulfasalazine + Hydroxychloroquine			-	0
Leflunomide	2	LEF	-	0
		MTX+LEF	12416973	1
		MTX	-	Is this number of study or number of drug0
Biologic Anti-TNF				
Adalimumab	7	ADA	16385520	1
		ADA + MTX	26138593 22739990 22562973 15146409 12528101 18821658	6***
		MTX	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
Certolizumab	3	CTZ + MTX	26533965 22344576 19015207	3***
		MTX		
Etanercept	6	ETN	11096165	1
		ETN + MTX	24618266 20187135 15001324	3***
		ETN + SSZ	18794178	1
Golimumab	7	GOL	-	0
		GOL + MTX	23861303 22661646 19066176 18383539 20131276 19644849 25005327	7***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
Infliximab	5	MTX	-	0
		IFX + MTX	16572442 15641102 15529377 11096166 10622295	5***
Biologic B-Cell Kinase Inhibitors (non-Anti-TNF)				
Rituximab	7	MTX	-	0
		RTX	17062648	1
		RTX + MTX	16947627 15201414 16649186 20488885 22012969 16947627	6***
Biologic IL-6 Inhibitors (non-Anti-TNF)				
Tocilizumab	7	MTX	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
		TCZ	16947782	1
		TCZ + MTX	18625622 22562983 21360490 19297346 18358926 16947782	6***
Biologic T-Cell Activation Inhibitors (non-Anti-TNF)				
Abatacept	4	ABA	-	0
		ABA + MTX	22915624 19124524 16785473 16052582	4***
		MTX	-	0
Targeted synthetic DMARD (JAK Inhibitor)				
Tofacitinib	5	MTX	-	0
		TOFA	24941177	2

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
			27002108	
		TOFA + MTX	23348607 22006202 25186034	3***
Conventional synthetic + biologics				
		MTX + SSZ + HCQ	23755969	1
		MTX + SSZ + LEF	20102325	1
		Anti-TNF	27654603	1
		Anti-TNF + LEF	20082236	1
		Anti-TNF + MTX	20082236	1
Head-to-head trial of biologics				
		ABA + ETN	16935912	1
		ABA + MTX	18055472	1

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
		ADA + MTX	23148339	1
		Alternate Anti-TNF	27654603	1
		DMARDs	18821691	1
		ETN + MTX	23148339	1
		ETN	11096165	1
		IFX + MTX	16572442	1
		Non-Anti-TNF	27654603	1
		RTX	22012969	1
		TCZ	22972745	1
		TCZ + DMARDs	18358926	1
		TCZ + MTX	21360490	1
		Anti-TNF	20102325	1
		Anti-TNF + MTX	20082236	1

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on overall effectiveness
		Anti-TNF + RTX + MTX	21360491	1

9.2.3. DAS28 (Remission)

Outcome Variable - The DAS28 is a widely used combined index that uses either the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP), tender and swollen joint count of 28 joints (arms, hands and knees) and a patient reported global assessment on a visual analogue scale (VAS). The DAS28 can be used to assess whether an individual patient has a significant improvement of the disease activity, compared to baseline. A DAS28 value of 5.1 (high disease activity) 3.2 (low disease activity) or even 2.6 (remission) are often selected as threshold.

Findings - The rate of remission based on DAS 28 also followed the trend observed in terms of the ACR 50, methotrexate in combination with sulfasalazine was efficacious than respective monotherapies. The combination of biologics along with methotrexate were favourable for remission. No clear trend was observed in the head to head comparison of the biologics.

Table 26. Review of Data From DAS 28 (Remission)

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on DAS28
Conventional Synthetic				
Methotrexate +Sulfasalazine	2	MTX+SSZ	10364900 16926184	2*
		MTX	-	0
Biologic Anti-TNF				
Adalimumab	6	ADA	16385520	1
		ADA + MTX	26138593 22739990 22562973 18821658 19369462	5***
		MTX	-	0
Certolizumab	3	CTZ + MTX	26533965 22344576 19015207	3***
		MTX	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on DAS28
Etanercept	4	ETN	15001324	1
		ETN + MTX	24618266 20937671 20187135	3***
		MTX	-	0
Infliximab	3	IFX + MTX	16572442 15641102 15529377	3
		MTX	-	0
Biologic B-Cell Kinase Inhibitors (non-Anti-TNF)				
Rituximab	5	MTX	-	0
		RTX + MTX	22012969 20488885 16649186 15201414	4***
		RTX	16947627	1
Biologic IL-6 Inhibitors (non-Anti-TNF)				

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on DAS28
Tocilizumab	7	MTX	16947782	1
		TCZ	22972745	1
		TCZ + MTX	18625622 22562983 21360490 19297346 18358926	5***
Biologic T-Cell Activation Inhibitors (non-Anti-TNF)				
Abatacept	5	ABA	-	0
		ABA + MTX	22915624 19124524 16052582 25367713 18383390	5***
		MTX	-	0
Targeted synthetic DMARD (JAK Inhibitor)				
Tofacitinib	4	MTX	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on DAS28
		TOFA	24941177	1
		TOFA + MTX	23348607 22006202 25186034	3***
Conventional synthetic + biologics				
	4	ETN + MTX	22508468	1*
		MTX + SSZ + HCQ	23755969	1*
		MTX + SSZ + LEF	-	0
		Anti-TNF	27654603	1*
		Anti-TNF + LEF	-	0
		Anti-TNF + MTX	28388820	1*
Head-to-head trial of biologics				
	8	ABA + MTX	18055472	1
		ADA + MTX	23148339	1

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on DAS28
		Alternate Anti-TNF	-	0
		ETN + MTX	-	0
		IFX + MTX	18055472	1
		MTX	-	0
		Non-Anti-TNF	27654603	1
		RTX	24442884 28629665	2***
		TCZ	-	0
		TCZ + DMARDs	21949007	1
		TCZ + MTX	-	0
		Anti-TNF	-	0
		Anti-TNF + MTX	-	0
		Anti-TNF + RTX + MTX	21360491	1

9.2.4. Radiological Progression

Outcome Variable - The Sharp method for scoring radiographs of hands and feet in RA, is a reference method used in most of clinical trials and longitudinal observational studies. The method includes, in each hand, 16 areas for erosions and 15 areas for joint space narrowing, and, in each foot, 6 areas for erosions and 6 areas for joint space narrowing.

Findings - A trend of halting or slowing down of the radiographic progression of RA with the methotrexate as compared to leflunomide. The combination of bDMARDs along with the methotrexate was superior to bDMARDs monotherapies.

Table 27. Review of Data From Radiological Progression

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on radiological progression
Conventional Synthetic				
Leflunomide	1	LEF	10573044	2*
		MTX	-	0
Biologic Anti-TNF				
Adalimumab	6	ADA	19369462	1
		ADA + MTX	22739990 22562973 16385520 15146409	6***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on radiological progression
			22915617	
		MTX	-	
Certolizumab	2	CTZ + MTX	26533965 19015207	2***
Etanercept	7	ETN	18794178	1
		ETN + MTX	24618266 15001324 20187135	3***
		ETN + SSZ	18794178	1
		MTX	20187135	1
		RTX + MTX	20937671	1
Infliximab	2	IFX + MTX	15529377 11096166	2***
		MTX	-	0
Golimumab	5	GOL + MTX	23861303 22661646	4***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on radiological progression
			19066176 25005327	
		MTX	20187135	1
Biologic B-Cell Kinase Inhibitors (non-Anti-TNF)				
Rituximab	3	MTX	-	0
		RTX + MTX	22012969 16947627	2***
		RTX	17062648	1
Biologic IL-6 Inhibitors (non-Anti-TNF)				
Tocilizumab	2	MTX	-	0
		TCZ	-	0
		TCZ + MTX	16947782 22972745	2***
Biologic T-Cell Activation Inhibitors (non-Anti-TNF)				
Abatacept	5	ABA	-	0
		ABA + MTX	22915624	5***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on radiological progression
			19124524 16785473 16052582 25367713	
		MTX	-	0
Targeted synthetic DMARD (JAK Inhibitor)				
Tofacitinib	4	MTX	30615240	1
		TOFA	24941177	1
		TOFA + MTX	23348607 22006202	2***
Conventional synthetic + biologics				
	3	ETN + MTX	23755969	1*
		MTX + SSZ + HCQ	-	0
		MTX + SSZ	22508468	1*
		MTX	16926184	1*

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on radiological progression
		SSZ	-	0

9.2.5. HAQ – DI

Outcome Variables - The Health Assessment Questionnaire (HAQ) is a valuable, effective, and sensitive tool for measurement of functional status in RA. The disability assessMent component of the HAQ, the HAQ-DI, assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning which represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The HAQ-DI score range is between 0-3, the higher score reflects a worse status.

Findings - The combination of csDMARDs was equally effective as the methotrexate monotherapy for the improvement in HAQ-DI. However, the combination of bDMARDs and tsDMARDs with a background methotrexate showed improvements in the HAQ-DI score. Rituximab was the favoured choice from the head to head comparisons amongst the bDMARDs.

Table 28. Review of Data From HAQ-DI

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on HAQ-DI
Conventional Synthetic				
Methotrexate + sulfasalazine	2	MTX	10364900	1*
		MTX+SSZ	16926184	1*
		SSZ	-	0
Leflunomide	2	LEF	10888712	1*
		MTX	10573044	1
Biologic Anti-TNF				
Adalimumab	7	ADA	16385520	1
		ADA + MTX	26138593 22739990 22562973 15146409	4***
		MTX	26138593 16385520 22915617	3

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on HAQ-DI
Certolizumab	4	CTZ + MTX	26533965 22344576 19909548	3***
		MTX	19015207	1
Etanercept	3	ETN	24618266	1
		ETN + MTX	20937671	1*
		ETN + SSZ	18794178	1
		MTX	-	0
Infliximab	4	IFX + MTX	15641102 15529377 11096166	3***
		MTX	10622295	1
Biologic B-Cell Kinase Inhibitors (non-Anti-TNF)				
Rituximab	6	MTX	-	0
		RTX + MTX	22012969 20488885	5***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on HAQ-DI
			16649186 16947627 16947627	
		RTX	17062648	1
Biologic IL-6 Inhibitors (non-Anti-TNF)				
Tocilizumab	5	MTX	18625622	1
		TCZ	22562983	1
		TCZ + MTX	21360490 19297346 18358926	3***
Biologic T-Cell Activation Inhibitors (non-Anti-TNF)				
Abatacept	3	ABA	-	0
		ABA + MTX	19124524 16052582 25367713	3***
		MTX	-	0
Targeted synthetic DMARD (JAK Inhibitor)				

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on HAQ-DI
Tofacitinib	6	MTX	-	0
		TOFA	24941177	1
		TOFA + MTX	27002108 23348607 22006202 25186034 27734232	5***
Conventional synthetic + biologics				
	6	ABA + ETN	16935912	1
		ABA + MTX	18055472	1
		Alternate Anti-TNF	-	0
		ETN	-	0
		IFX + MTX	-	0
		MTX	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on HAQ-DI
		Non-Anti-TNF	27654603	1
		RTX	17062648 16947627	2***
		Anti-TNF	-	0
		Anti-TNF + MTX	-	0
		Anti-TNF + RTX + MTX	21360491	1

9.2.6. Health Related Quality of Life

Outcome Variable - The Short Form (36) Health Survey is a 36-item, patient-reported survey of patient health. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability.

Findings - A limited number of studies assessed the improvements in the quality of life. Only two studies compared the Quality of Life (QoL) outcomes amongst methotrexate and leflunomide with both these studies pointing in different directions. **The combination of bDMARDs with methotrexate was observed to be associated with a better improvement in the QoL scores.**

Table 29. Review of Data From Health Related Quality of Life

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
Conventional Synthetic				
Leflunomide	2	LEF	12416973	1*
		MTX	10888712	1*
Biologic Anti-TNF				
Adalimumab	7	ADA	-	0
		ADA + MTX	22739990 22562973 15146409 12528101	4***
		MTX	16385520 26138593 18821658	3
Certolizumab	4	CTZ + MTX	22344576 19015207	3***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
			19909548	
		MTX	26533965	1
Etanercept	3	ETN	18794178	1*
		ETN + MTX	24618266	1*
		ETN + SSZ	-	0
		MTX	-	0
		RTX + MTX	20937671	1*
		SSZ	-	0
Golimumab	6	GOL	-	0
		GOL + MTX	22661646 19066176 20131276 19644849	4***
		MTX	23861303 25005327	2
Infliximab	4	IFX + MTX	15529377	3***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
			11096166 10622295	
		MTX	15641102	1
Biologic B-Cell Kinase Inhibitors (non-Anti-TNF)				
Rituximab	6	MTX	-	0
		RTX + MTX	22012969 20488885 16649186 16947627 16947627	5***
		RTX	17062648	1
Biologic IL-6 Inhibitors (non-Anti-TNF)				
Tocilizumab	5	MTX	18625622	1
		TCZ	22562983	1
		TCZ + MTX	21360490 19297346 18358926	3***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
Biologic T-Cell Activation Inhibitors (non-Anti-TNF)				
Abatacept	3	ABA	-	0
		ABA + MTX	19124524 16052582 25367713	3***
		MTX	-	0
Targeted synthetic DMARD (JAK Inhibitor)				
Tofacitinib	6	MTX	-	0
		TOFA	24941177	1
		TOFA + MTX	27002108 23348607 22006202 25186034 27734232	5***
Conventional synthetic + biologics				
	3	ETN + MTX	23755969	2***

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
			22508468	
		MTX + SSZ + HCQ	-	0
		MTX + SSZ + LEF	28629665	1
		Anti-TNF	-	0
		MTX+SSZ	-	0
	2	MTX	10364900	1*
		MTX + SSZ	16926184	1*
		SSZ	-	0
Head-to-Head Biologics				
	6	ABA + ETN	16935912	1
		ABA + MTX	18055472	1
		Alternate Anti-TNF	-	0
		ETN	-	0

DMARDs Studied	Number of trials that included DMARD – single or combination	Intervention Arm	PUBMED ID	Number of studies favouring drug or combination on health related quality of life
		IFX + MTX	-	0
		MTX	-	0
		Non-Anti-TNF	27654603	1
		RTX	24442884 16947627	2***
		Anti-TNF	-	0
		Anti-TNF + MTX	-	0
		Anti-TNF + RTX + MTX	21360491	1

9.2.7. ACR 50: Systematic Reviews

The findings of the ACR 50 reported in the systematic reviews was considered as a proxy for the clinical efficacy. The findings from the systematic reviews were comparable with the findings of the RCTs. **Monotherapy with methotrexate was less clinically efficacious than the combinations of csDMARDs or biologics and methotrexate.** The comparison of B-cell kinase inhibitors with Anti-TNF showed no difference. Head to head comparisons between TNF inhibitors did not show any favourable intervention. **Early treatment with abatacept and methotrexate combination resulted in greater sustainable clinical, functional and radiographic benefits than methotrexate alone, with acceptable safety and tolerability.** The

methotrexate and bDMARDs combination showed better ACR outcomes as compared to bDMARDs monotherapy.

Table 30. Findings From Systematic Reviews (ACR 50)

DMARD Type	Study PubMed ID	Intervention	Comparison	Effect Size	Favored drug/combination
Conventional synthetic	19936725	MTX	TCZ + MTX	3.7 [2.4–5.9]	TCZ + MTX
	19917618	MTX	MTX + DMARDs	0.5 [0.3 - 0.8]	MTX + DMARDs
	20421343	MTX	MTX + DMARDs	1.7 [1.5 - 2.0]	MTX + DMARDs
	19054823	MTX	MTX + DMARDs	1.8 [0.6 - 4.8]	MTX + DMARDs
	27571502	MTX	MTX + ABA	1.8 [1.0 - 3.4]	MTX + ABA
	27571502	MTX	MTX + ADA	2.2 [0.8 - 6.1]	MTX + ADA
	27571502	MTX	MTX + CZP	1.5 [0.8 - 2.7]	MTX + CZP
	27571502	MTX	MTX + ETN	3.0 [2.02 - 4.6]	MTX + ETN
	27571502	MTX	MTX + GOL	1.3 [0.7 - 2.6]	MTX + GOL

DMARD Type	Study PubMed ID	Intervention	Comparison	Effect Size	Favored drug/combination
	27571502	MTX	MTX +IFX	2.0 [1.3 - 3.8]	MTX +IFX
	27571502	MTX	MTX + RTX	2.4 [1.3 - 4.4]	MTX + RTX
	27571502	MTX	MTX + TCZ	1.7 [0.9 - 2.9]	MTX + TCZ
	27571502	MTX	MTX + HCQ	0.8 [0.2 - 2.9]	MTX
	27571502	MTX	MTX + SSZ	1.1 [0.4 - 2.8]	MTX + SSZ
	28481462	MTX	MTX + Biologics	1.4 [1.3 - 1.5]	MTX + Biologics
	23141718	MTX	MTX + Biologics	2.1 [1.8 - 2.4]	MTX + Biologics
	20447954	MTX	csDMARDs	1.42 [0.65 - 2.18]	MTX
Biologic: TNF-α inhibitors	24316899	ADA + MTX	MTX + PBO	3.23 [2.35 - 4.44]	ADA + MTX
	23728649	ETN + MTX	MTX	2.0 [1.3 - 2.9]	ETN + MTX

DMARD Type	Study PubMed ID	Intervention	Comparison	Effect Size	Favored drug/combination
	19751268	ETN + MTX/ ETN	MTX	1.3 [1.2 - 1.5]	ETN
	20436075	GOL + MTX	MTX	2.6 [1.3 - 4.9]	GOL + MTX
	19771491	IFX	MTX	1.5 [1.2 - 2.1]	IFX
Biologic: B-cell kinase inhibitor	20473756	RTX	Biologics	3.6 [2.5– 5.4]	RTX
	20223500	RTX	Anti-TNF	1 [0.7 - 1.5]	No difference
	20223500	RTX	ABA	1 [0.7 - 1.5]	No difference
	25603545	RTX + MTX	MTX	3.3 [2.3 - 4.6]	RTX + MTX
Biologic: Interleukin-6 inhibitor	20223500	TCZ	Anti-TNF	1.3 [1.1 - 1.5]	TCZ
	20223500	TCZ	ABA	1.3 [1.0 - 1.6]	TCZ
	20223500	TCZ	RTX	1.3 [0.9 - 1.9]	No difference
	20223500	ABA	Anti-TNF	1 [0.8 - 1.2]	No difference

DMARD Type	Study PubMed ID	Intervention	Comparison	Effect Size	Favored drug/combination
Biologic: T-cell-activation inhibitor	22151924	ABA + MTX	ADA + MTX	0.4 [0.09 - 1.50]	ABA + MTX
	22151925	ABA + MTX	CZP + MTX	0.35 [0.08 - 1.33]	ABA + MTX
	22151926	ABA + MTX	ETN + MTX	1.05 [0.17 - 3.24]	ABA + MTX
	22151927	ABA + MTX	GOL + MTX	0.87 [0.16 - 5.15]	ABA + MTX
	22151928	ABA + MTX	IFX + MTX	1.31 [0.27 - 7.61]	ABA + MTX
	22151929	ABA + MTX	RTX + MTX	0.9 [0.2 - 3.5]	ABA + MTX
	22151930	ABA + MTX	TCZ + MTX	0.5 [0.1 - 2.9]	ABA + MTX
	20080922	ABA + MTX	DMARDs	2.2 [1.7 - 2.8]	ABA + MTX
Conventional synthetic + biologics	28282491	MTX + csDMARDs	Biologics + MTX	4.07 [2.76 - 5.99]	Biologics + MTX
	27855242	Biologic	MTX + csDMARDs	1.54 [1.14 - 2.08]	Biologic

9.2.8. Clinical Efficacy Findings From The Selected Conference Presentations And Abstracts

A table of baseline study, patient characteristics as well as the clinical outcomes from the selected conference abstracts is available in supplementary tables 9 and 10 in the Appendix. Combination therapy of csDMARDs and biologics appeared to be a favorable choice after inadequate response to methotrexate.

9.2.9. RCTs Bias Assessment

Many studies had not clearly explained the selection of the sample which led to questions on representativeness. Similarly, randomization and blinding processes followed were not clear in many studies. The blinding of the outcomes assessors was not reported in most of the trials. Such limitations in the study design impact the quality of the study outcomes too. We have noted many studies to have a selective reporting bias towards the interventions of interest. This too affected the overall scientific quality of the study as often the reporting was done at different time-points, thereby providing an advantage to the intervention of interest and raising questions about the sustainability of the achievements in clinical improvements in the long-run. Since a review is as good as the quality of the studies available in literature and those that are included for the review, therefore recommended that the findings of this review should be interpreted considering the methodological limitation in the included studies.

The table 31 below illustrates how the various types of risks mentioned before were assessed and colour coded.

Low risk of bias	Unclear risk of bias	High risk of bias

Table 31. Assessment of Various Risks of Bias in The Reported Studies

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Methotrexate +Sulfasalazine							
10364900							
16926184							
Methotrexate + Sulfasalazine + Hydroxychloroquine							
12115219							
Leflunomide							
12416973							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
10888712							
10573044							
Adalimumab							
26138593							
22739990							
22562973							
16385520							
15146409							
12528101							
18821658							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
19369462							
22915617							
Certolizumab							
26533965							
22344576							
19015207							
19909548							
Etanercept							
24618266							
15001324							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
11096165							
20937671							
20187135							
18794178							
Golimumab							
23861303							
22661646							
19066176							
18383539							
20131276							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
19644849							
25005327							
Infliximab							
16572442							
15641102							
15529377							
11096166							
10622295							
Rituximab							
22012969							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
20488885							
16649186							
15201414							
16947627							
17062648							
16947627							
Tocilizumab							
18625622							
22562983							
21360490							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
19297346							
18358926							
16947782							
22972745							
Abatacept							
22915624							
19124524							
16785473							
16052582							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
25367713							
18383390							
Tofacitinib							
27002108							
23348607							
22006202							
25186034							
27734232							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
DOI: 10.1056/NEJMoa1310476							
Conventional synthetic + biologics							
23755969							
22508468							
28388820							
20082236							
Head to head biologics							
18055472							

Study PubMed ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
21360491							
16935912							
18821691							
21949007							
27654603							
23148339							
26473625							
24442884							
28629665							

9.2.10. AMSTAR Rating for The Systematic Reviews

Apart from some minor exceptions the quality of the systematic reviews was good, nearly all the studies had done a comprehensive literature review which could be concluded from the available search strategies as well as the list of the included and excluded studies. All the systematic reviews had also conducted a thorough quality check of all the studies included wihhin the review.

Table 32. AMSTAR Rating For Systematic Reviews

Study PubMed ID	A priori design	Duplicate extraction	Literature search comprehensive	Status of publication used as criteria	Excluded/included list provided	Study characteristics provided	Quality assessed/presented
19054823	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19751268	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19771491	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19917618	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19936725	Yes	Yes	Yes	No	Yes	Yes	Yes
20080922	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20223500	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20421343	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study PubMed ID	A priori design	Duplicate extraction	Literature search comprehensive	Status of publication used as criteria	Excluded/included list provided	Study characteristics provided	Quality assessed/presented
20436075	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20447954	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20473756	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151924	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151925	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151926	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151927	Yes	Yes	Yes	No	Yes	Yes	Yes
22151928	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151929	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22151930	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23141718	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23728649	Yes	Yes	Yes	No	Yes	Yes	Yes

Study PubMed ID	A priori design	Duplicate extraction	Literature search comprehensive	Status of publication used as criteria	Excluded/included list provided	Study characteristics provided	Quality assessed/presented
23877486	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24139404	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24316899	Yes	Yes	Yes	Yes	Yes	Yes	Yes
25603545	Yes	Yes	Yes	Yes	Yes	Yes	Yes
27571502	Yes	Yes	Yes	Yes	Yes	Yes	Yes
27855242	Yes	Yes	Yes	No	Yes	Yes	Yes
28282491	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28481462	Yes	Yes	Yes	Yes	Yes	Yes	Yes

9.3. Discussion & Results

In this systematic review we attempted to compare DMARDs in adults with RA found few direct comparisons of different agents but no important differences among csDMARDs or anti-TNF drugs. Studies note that after initial trial and failure of methotrexate, other combinations of csDMARDs should be attempted and in general, the combination therapies of csDMARDs was found to have improved response rates and functional outcomes in patients failing monotherapy with any csDMARD including MTX.

Regardless of the disease activity levels, using a "treat-to-target strategy" than a non-targetd approach is noted to achieve better clinical outcomes. The ideal target for treatment with DMARD was noted to be lowering disease activity or to achieve clinical remission.

For newly diagnosed DMARD naïve patients with early, symptomatic RA, the treatment is guided by the disease activity. Literature recommends DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and conditionally recommend DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease with provision addition of short-term glucocorticoids. Based on its efficacy, safety (especially in the presence of folic acid), the possibility to individualise dose and method of administration as well as relatively low costs, MTX continues to be the anchor ('first') drug for patients with RA both as monotherapy as well as in combination with other drugs. Moreover, MTX appears to reduce comorbidities and mortality in RA.

However, for patients with contraindication to methotrexate, other csDMARDs such as leflunomide or sulfasalazine may be started, with a provision for addition of short-term glucocorticoids. Further change in the course of treatment with DMARDs should be based on reduction of disease symptoms at 3 months and achieving target at 6 months. Although the initiation of treatment could be with a csDMARD monotherapy, there are many studies that have shown to achieve better disease activity reduction with subsequent trials with combination of other csDMARDs. The decision to combine monotherapy with other csDMARDs should be on the basis of presence or absence of prognostically unfavourable factors (such as continued high disease activity, high serum marker levels, early join damage, etc). Despite the evidence of MTX being

efficacious and safe as initial treatment in RA, other csDMARDs given in MTX intolerant patients too have comparable efficacy and safety end-points. Combination therapies improve response rates in some patients previously receiving monotherapy. If treatment target is not achieved with initial trial of csDMARD monotherapy or combination of csDMARDs, addition of a bDMARD should be considered after a thorough review of the safety parameters. Among the bDMARDs, there is no difference in outcomes, irrespective of their target and the ultimate choice of bDMARDs to be used in combination with csDMARDs, will need to be on the basis of safety and cost considerations.

Therapies generally used in Turkey and globally were: csDMARDs, such as hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine; and biological DMARDs, such as TNF inhibitors (etanercept, adalimumab, infliximab) and non-TNF inhibitors (abatacept, anakinra, and rituximab) and the new generation targeted synthetic DMARD tofacitinib. As is noted, often, treatment if not started early and with a single DMARD, does not adequately control symptoms, leading clinicians to consider various combination strategies. There is no clear benefit on the comparative benefits of different combination therapies involving sDMARD and bDMARD. There are also serious concerns about the risks of these agents across a spectrum of adverse events from relatively minor side effects to severe and possibly life-threatening problems.

Scant head-to-head evidence showed no major or clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine) or among bDMARDs Anti-TNF (adalimumab, etanercept, and infliximab). When we compared combination therapies of Anti-TNF bDMARDs and methotrexate, we observed better radiographic outcomes but no important differences in clinical outcomes (such as ACR 20, 50, or 70 response rates). Various combinations of other bDMARDs plus methotrexate had better clinical response rates and functional outcomes than monotherapy with either methotrexate or one particular class of bDMARDs. In patients previously receiving monotherapy, combination therapy with sDMARDs improved response rates.

We feel that the evidence is insufficient to draw conclusions on whether one combination or treatment strategy outweighs another or is the best treatment regimen for early RA and whether subgroups experience different outcomes.

Several areas warrant further research on the comparative efficacy, effectiveness, quality of life, and harms of medications for RA.

Clinical decision making would benefit from examining the timing of initiation of therapies, applicability of combination strategies and bDMARDs therapy in community practice, and specific head-to-head comparisons focusing on different combination strategies and different bDMARDs.

Several therapies are available for persons with RA; no regimen is clearly better than another. Combination therapies improve response rates in patients previously receiving monotherapy, but available evidence does not allow firm conclusions about which combination strategy is best. Future studies, including those with good applicability to patients seen in community practices, will be useful; researchers should plan to perform subgroup analyses a priori in older patients and patients with comorbid conditions. Long-term adverse event studies, particularly with the newer agents, will help clinicians and patients better weigh the benefits of these drugs.

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10. COSTS AND ECONOMIC EVALUATION

10.1. Introduction

The aim of the Costs and Economic Evaluation domain is to inform value-for-money judgements about health technologies with information about costs, health-related outcomes and economic efficiency. In publicly funded healthcare systems, finite resources mean that not all technologies can be provided in every situation for all who may need or want them. The concept of opportunity cost is central to this area of health economics: choices have to be made between alternative, effective health technologies; a decision to fund one technology may mean that others cannot be funded, or that their use must be restricted. Economic evaluations of DMARDs focus mainly on the direct costs of acquiring the medications and the related costs of diagnostics tests and clinic costs. The economic cost of the RA is calculated using the direct disease costs which are the direct costs of prevention, diagnosis, treatment, and rehabilitations or the losses due to disability (morbidity-being ill) and premature mortality (mortality). These costs are the costs for which society is charged rather than sick people and their families.

Economic health assessments are carried out by a number of analysis methods;

Cost-Minimization Analysis – CMA/ Cost-Consequence Analysis – CCA/ Cost-Identification Analysis - CIA; It can be used to compare two health interventions or programs which are known or assumed to have the same results. The intervention / program with lower cost is more productive. There is no impact measurement. In CCA, cost and effectiveness are calculated separately, and the outcome is based on the relative importance given to these factors by the decision maker. The effect is measured on a clinical basis.

Cost Benefit Analysis-CBA; The results, such as the lifespan and the avoided complications, which are used in applications with different health outcomes, are often converted into a single monetary amount to create a common unit and their costs are compared. It is usually used to set priorities in health programs.

Cost Effectiveness Analysis – CEA; The costs are compared with the effectiveness of reaching a predetermined goal. Health outcomes such as life-years gained (LYG) are the same in all options which are compared. Achievement and costs may be different while reaching the result. In the comparison, unit costs per year gained are calculated.

Cost Utility Analysis – CUA; Utility is the value of an increase in the state of health or the level of health. It is measured by the preferences of the people or the community. Effects such as the number of healthy days, quality-adjusted life years (QALYs), number of days spent with disability (disability adjusted life years - DALYs) are measured.

CEA compares the effects of the practice on the cost and health to determine whether it is economically worthwhile to implement it. Cost-effectiveness ratios should be associated to the optimal amount of budget available to determine the most cost-effective strategies possible. All cost-effectiveness analyzes should be based on sensitivity analyzes which contains the findings. Cost-effectiveness is only a series of criteria which is used during decision making. Health problems, requirements and priorities must be considered in the decision-making and implementation process.

The choice of technique which will be used for the measurement depends on the nature of the specific pre-determined benefits. Benefits in cost-effectiveness analysis are expressed in non-monetary units. In the cost-utility analysis, a common unit is applied to all values on a specified scale, regarding the benefits for a variety of health conditions. The units for these benefits can be DALYs of the World Bank (WB) or the QALYs. On the other hand, the results of the cost-benefit analyses are expressed in monetary values. As in all economic analysis studies, the aim is to maximise the benefits and utilities on the healthcare system with the use of current possible resources while maintaining the financial sustainability.

A CEA includes comparison with an alternative treatment or treatments that require the consideration of the perspective, time frame, efficacy level, discount rate and assumptions in addition to cost. Various disease endpoints (such as risk markers, disease severity, and death) that are affected by treatment can be assessed with appropriate therapeutic output indicators (such as a reduction in milimeter mercury in the blood pressure, hospitalization to the prevention, and prolonged survival time).

10.2. Assessment

Original articles providing economic evaluation estimates including presentation of cost-utility analysis (CUA) data of the above-mentioned therapies work retrieved. Incremental Cost Effectiveness Ratio (ICER) was the most commonly used indicator for cost effectiveness and cost utility analysis. Other indicators included patient lifetime cost, mean cost-effective ness ratio and

annual cost per patient. The drug groups were compared either in monotherapy as combination therapies. The evidence of cost-effective ness of these treatments can be arranged in three broad categories, based on the patient characteristics (including pervious treatment history). These three categories are:

- bDMARDs given to methotrexate and other csDMARD naïve patients
- Patients with inadequate response to csDMARDs
- Patients with inadequate response to biologics (most commonly Anti-TNF)

Studies explored the cost-effectiveness of the addition of Anti-TNF for the treatment of methotrexate naïve patients. The incremental cost of adding Anti-TNF was shown to be more than the willingness to pay threshold set by some of the high-income countries (such as Japan, South Korea, Taiwan, UK, Australia and USA) which is in the range of US$ 50,000 to US$100,000/QALY gained. Studies also pointed out the cost of this addition could be more than US$ 100,000/QALY for any class of bMARDs, which would clearly exceed the current cost of csDMARDs.

The incremental cost of bDMARDs after the inadequate response to csDMARDs, was shown to be high in most of the studies. The drugs from Anti-TNF category were not considered to be cost-effective options, as compared to non-Anti-TNF. Based on the findings of the studies that we found the Anti-TNF group of drugs were seen to be cost-effective when used after all therapeutic options were exhausted including use of non-Anti-TNF bDMARDs. It would also be critical to account for the heterogeneity of the outcome variables. Most of these findings were from the analysis of randomized clinical trials that did not have cost-utility analysis as their primary outcome. However, these results should be interpreted considering the geographical variability and the socio-economic differences between these countries.

The willingness to pay for the incremental benefits does differ for different countries and is dependent of the available financial resources for the treatment of the health condition. It should therefore be considered to weigh these incremental benefits in the light of the available national resource for health and consider setting up a range of thresholds that provide the best possible treatment to the various groups of RA patients.

Clearly when compared on economic parameters alone, csDMARDs were most cost-effective than bDMARDs. However, as can be seen from the data illustrated in later sections, bDMARDs (mainly

adalimumab, etanercept, infliximab, and tocilizumab) combined with csDMARDs are showing better overall and long-term clinical outcomes than when treated with csDMARD monotherapies.

When assessing whether biologics are cost-effective or not, it should be known what the willingness to pay (WTP) for Turkey will be for an additional QALY gained. There is no widely accepted WTP threshold value for Turkey. Within bDMARDs, ADA and ETN monotherapies seem to have marginally higher ICERs, but when extrapolated to large populations, this incremental ICER was found to be insignificant in studies (15) . Similarly, Anti-TNF monotherapy too has not been found effective than its combination with MTX and therefore, bDMARDs as monotherapies are not currently recommended to treat RA. In the same studies it is noted that bDMARDs were found cost effective against csDMARDs only when the WTP threshold was higher (at more than €50,000–€100,000 /QALY). At lower WTP threshold (€35,000 or less /QALY), bDMARDs were not found to be cost effective.

Stronger evidence for cost-effectiveness is available for bDMARDs that have been around in the market for longer periods of time. bDMARDs such as ADA, ETN and IFX have been more thoroughly evaluated on economic parameters than some of the more recently launched bDMARDs. Because economic assessments vary in their design, measurement, comparators and population, older bDMARDs such as ADA, ETN and IFX that have been more thoroughly evaluated on different economic assessments have different cost-effectiveness analysis end-points.

The same level of evidence is however not available for newer bDMARDs such as ABT and TOC which is probably reflect because of the lower number of cost-effectiveness studies conducted using these medications than lower cost-effectiveness of these agents. Health technology assessment reports provided by independent organizations such as NICE have more stringent design, measurement, comparator, population and analytical considerations in their economic evaluations. They also leverage economic evaluations and scientific evidence conducted by other public entities. Such publicly funded projects and independent reports are not yet available for the newer agents such as ABT and TOC, which also may at least in part explain inconsistent ICERs. Among the patients with an inadequate response to one Anti-TNF, RTX appears cost-effective with the threshold of €35,000 /QALY. With the higher thresholds of ICER, other Anti-TNFs and ABT might appear to be cost effective.

Analyses counting only direct costs give an incomplete view of the pros and cons of different treatments, while various methods used to estimate indirect costs remain controversial.

In the table-33,34 and 35 below, we have listed the key findings of the cost effectiveness of bDMARDs among patients who are naïve to csDMARDs and among patients with an insufficient response to csDMARDs.

10.2.1. Cost-Effectiveness of Biologics in Patients With Early RA And Naïve to csDMARDs

The ICERs of Anti-TNF in comparison to csDMARDs during early RA and in patients naïve to csDMARDs ranged from €39,000 to €1,273,000 /QALY when only direct costs were considered. IFX was associated with the highest ICERs ranging from €422,000 to €1,273,000 /QALY while ICERs for ETN and ADA as a monotherapy were below €100,000 /QALY. As a combination therapy with MTX, ICERs for ETN and ADA were substantially higher. When both direct and indirect costs were considered, ICERs for csDMARDS were more favourable than biologics.

10.2.2. Cost-Effectiveness of Biologics Among Patients With an Inadequate Response to csDMARDs

When only direct costs were considered ICERs for IFX, ADA and ETN were EUR 12,000–EUR 282,000; EUR 44,000–EUR 274,000 and EUR 40,000–EUR 708,000, respectively. ABT and TOC were associated with narrower ranges of ICERs (EUR 42,000 to EUR 47,000 and EUR 19,000 to EUR 21,000, respectively). ICERs below EUR 35,000 /QALY were found in three studies and below EUR 50,000 /QALY in ten studies.

Two studies found ETN to be dominant over IFX and ADA, while three of the other studies reported ICERs ranging from EUR 23,000 to EUR 109,000 /QALY for ETN when only direct costs were included.

10.2.3. Cost-Effectiveness of Biologics Among Patients With an Inadequate Response to at Least One TNF Inhibitor

RTX was associated with the lowest ICERs ranging from 26,000 to 48,000 EUR/QALY. Three of four studies evaluating RTX provided ICERs below EUR 35,000 /QALY and none of the studies reported ICERs more than EUR 50,000 /QALY. ANA was associated with the highest ICERs with

a range of EUR 234,000–EUR 1,347,000 /QALY. ICERs for the other agents ranged from EUR 41,000 to 143,000 /QALY.

Table 33. Cost-Effectiveness of Biologics in csDMARD Naïve Patients

Treatments	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic (sensitivity analysis EUR/QALY)
Anti-TNF vs. csDMARDs				
IFX	Chen et al. 2006	1 273,007	-	40,876—dominated
	Davies et al. 2009	Extended dominance by ADA	Extended dominance by ADA	-
	Spalding & Hay 2006	422,215	-	422,114–573,650
ADA	Chen et al. 2006	152,021 (ADA+MTX)	-	40,876—dominated (ADA+MTX)
	Chen et al. 2006	58,672 (ADA)	-	36,983—dominated (ADA)
	Davies et al. 2009	41,178 (ADA+MTX)	20,413	31,435–61,124
	Davies et al. 2009	37,309 (ADA+MTX➔ ETN)	-	-
	Spalding & Hay 2006	200,620 (ADA+MTX)	-	200,570 (ADA+MTX)

Treatments	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic (sensitivity analysis EUR/QALY)
	Spalding & Hay 2006	65,745 (ADA)	-	67,962 (ADA)
ETN	Spalding & Hay 2006	92,503	81,408	80,027–108,051
	Davies et al. 2009	Extended dominance by ADA	Extended dominance by ADA	-
	Kobelt et al. 2011	38,639	15,315	2,473–38,639
	Chen et al. 2006	332,850 (ETN+MTX)	-	35,037—dominated (ETN+MTX)
	Chen et al. 2006	96,157 (ETN)	-	35,037–231,633 (ETN)
Comparison of treatment strategies containing Anti-TNF				
1) MTX➔MTX+SSZ➔ MTX+SSZ+HCQ➔ MTX+SSZ+HCQ+CS➔ IFX(MTX+CSA+CS➔ LEF➔ AZA+CS	Van den Hout et al. 2009	2 vs.1: 215,256	2 vs.1: 147,280	24,924–362,537

Treatments	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic (sensitivity analysis EUR/QALY)
2) IFX(SSZ➔LEF➔ MTX+CSA+CS➔GST+CS➔AZA+CS				
1)1.Anti-TNF➔2.Anti-TNF➔RTX 2) MTX+LEF➔1.Anti-TNF➔ 2.Anti-TNF➔RTX 3) MTX➔MTX+LEF ➔1.Anti-TNF ➔2.Anti-TNF➔RTX	Schipper et al. 2011	2 vs.3: 462,576	2 vs.3: 461,476	2 vs.1: 456,946–791,788
	Schipper et al. 2011	1 vs.3: 145,784	1 vs.3: 143,831	1 vs.3: 120,136–545,603
	Schipper et al. 2011	2 vs.1: 1 dominates	2 vs.1: 1 dominates	-
1)sDMARDs ➔ 1.Anti-TNF ➔ 2.Anti-TNF ➔ 3.Anti-TNF 2.➔1.Anti-TNF➔2.Anti-TNF➔3.Anti-TNF➔cDMARDs 3)NSAID➔cDMARDs➔1Anti-TNF➔2.Anti-TNF➔3.Anti-TNF	Finckh et al. 2009	1 vs.3: 4,234	1 vs.3: 1 is cost-saving	1 vs.3: 1 is cost saving 14,378
	Finckh et al. 2009	2 vs.3: 635,597	2 vs.3: 471,575	2 vs.3: 30,624–3 dominates
	Finckh et al. 2009	2 vs.1: 1 dominates	2 vs.1: 1 dominates	2 vs.1: 40,956–1

➔ = switch to next treatment in case of an inadequate response, ADA = adalimumab, AZA = azathioprine, csDMARD = conventional disease-modifying antirheumatic drugs, CS = corticosteroids, CSA = cyclosporin A, ETN = etanercept, GST = Gold, HCQ = hydroxychloroquine, ICER = Incremental cost-effectiveness ratio, IFX = infliximab, LEF = leflunomide, MTX = methotrexate, NICE = National Institute for Health and Care Excellence, NSAID = non-steroidal anti-inflammatory drug, QALY = quality-adjusted life year, SSZ = sulfasalazine, Anti-TNF = TNF inhibitor

Table 34. Cost-Effectiveness of Biologics in Comparison With csDMARDs Among Patients With an Insufficient Response to csDMARDs

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
IFX	Bansback et al. 2005	69,717–93,665	-	-
	Barbieri et al. 2005	12,438–89,108	-	9,325–103,753
	Barton et al. 2004	166,921	-	96,287–213,008
	CADTH 2010	Extended dominance by ADA	-	-
	Chen et al. 2006	59,173–270,563 (IFX➔csDMARDs)	-	37,957—dominated (IFX➔csDMARDs)
	Chen et al. 2006	73,772 (csDMARDs➔IFX)	-	50,027–117,763 (csDMARDs➔IFX)
	Coyle et al. 2006	98,132 (IFX➔GST)	-	85,279–138,948 (IFX➔GST)
	Coyle et al. 2006	84,931 (GST➔IFX)	-	71,298–101,084 (GST➔IFX)
	Jobanputra et al. 2002	282,151 (IFX➔csDMARDs)	-	128,590–641,955 (IFX➔csDMARDs)

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Jobanputra et al. 2002	230,698 (csDMARDs➔IFX)	-	68,157–413,593 (csDMARDs➔IFX)
	Kobelt et al. 2003	38,945–76,392	4,684–65,635	IFX is cost saving—60,597
	Lekander et al. 2010	-	27,321	10,005–56,246
	Marra et al. 2007	-	30,267–66,008	IFX dominates—139,343
	Wu et al. 2012	20,254 (IFX)	20,150 (IFX)	-
	Wu et al. 2012	21,946 (IFX➔RTX)	21,833 (IFX➔RTX)	-
	Wong et al. 2002	44,737	13,348	IFX is cost saving—137,292
ADA	Bansback et al. 2005	49,284–63,493 (ADA+MTX)	-	-
	Bansback et al. 2005	59,949–94,478 (ADA)	-	-
	CADTH 2010	92,326	-	-
	Chen et al. 2006	58,784–125,354 (ADA+MTX➔csDMARDs)	-	37,178–291,974 (ADA+MTX➔ csDMARDs)

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Chen et al. 2006	67,349–274,456 (ADA➔ csDMARDs)	-	41,266- dominated (ADA➔ csDMARDs)
	Chen et al. 2006	57,811 (csDMARDs➔ ADA+MTX)	-	43,018–83,699 (csDMARDs➔ ADA+MTX
	Chen et al. 2006	78,054 (csDMARDs➔ADA)	-	52,750–124,770 (csDMARDs➔ADA)
	Wu et al. 2012	43,943 (ADA)	43,876 (ADA)	-
	Wu et al. 2012	38,689 (ADA➔ RTX)	38,641 (ADA➔ RTX)	-
ABT	CADTH 2010	Extended dominance by ADA	-	-
	Vera-Llonch et al.2008	42,382–47,177		36,976–69,134
GOL	CADTH 2010	Extended dominance by ADA	-	-
TOC	Soini et al. 2012	18,693–20,776	18,731–20,813	7,629–53,17
Anti-TNF	Brennan et al. 2007	46,486 (Anti-TNF as a group)	-	24,378–93,833
	Kobelt et al. 2004	62,419	61,016	51,759–180,244

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Lekander et al. 2013	75,799 (Anti-TNF+csDMARD)	57,092 (Anti-TNF+csDMARD)	34,472–88,294 (Anti-TNF+csDMARD)
	Lekander et al. 2013	106,062 (Anti-TNF)	88,146 (Anti-TNF)	50 315–169 383 (Anti-TNF)
ETN	Bansback et al. 2005	51,581–74,972 (ETN+MTX)	-	-
	Bansback et al. 2005	53,265–61,274 (ETN)	-	-
	Barton et al. 2004	122,754	-	73,350–157,370
	Brennan et al 2004	39,740	18,950	18 950–103 145
	CADTH 2010	Dominated by ADA	-	
	Chen et al 2006	55,475–96,935 (ETN+MTX➔csDMARDs)	-	34,648–187,058 (ETN+MTX➔csDMARDs)
	Chen et al 2006	59,173–92,264 (ETN➔csDMARDs)	-	36,399–185,695 (ETN➔csDMARDs)

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Chen et al 2006	46,327 (csDMARDs➔ ETN+MTX)	-	35,037–66,181 (cDMARDs➔ ETN+MTX)
	Chen et al 2006	46,132 (csDMARDs➔ ETN)	-	35,232–65,013 (csDMARDs➔ ETN)
	Coyle et al 2006	125,661 (ETN➔ GST)	-	109,335–173,251 (ETN➔ GST)
	Coyle et al 2006	109,161 (GST➔ETN)	-	94 919–129,916 (GST(ETN)
	Jobanputra et al 2002	202,218 (ETN➔ csDMARDs)	-	93,643–448,885 (ETN➔csDMARDs)
	Jobanputra et al 2002	174,388 (csDMARDs➔ ETN)	-	51,662–312,186 (csDMARDs➔ETN)
	Kobelt et al 2005	69,550 (ETN+MTX)	49,314–72,058 (ETN+MTX)	-
	Kobelt et al 2005	-	Dominated by ETN+MTX (ETN)	33,704–69,550
	Lekander et al 2013	-	52,671 (ETN+csDMARD)	33,922–78,770 (ETN+csDMARD)
	Lekander et al 2013	-	68,535 (ETN)	40,818–127,988 (ETN)

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Soini et al 2012	22,745		9,437–57,025
	Tanno et al 2006	-	25,993	19,547–32,439
	Welsing et al 2004	233,867 (LEF➔ ETN➔ Usual care Vs usual care)	216,059 (LEF➔ ETN➔ Usual care vs. Usual care)	
	Welsing et al 2004	413,169 (ETN➔ LEF➔ Usual care	392,539 (ETN➔ LEF➔ Usual care Vs. Usual care)	
	Welsing et al 2004	440,322 (LEF➔ ETN (Usual care Vs. LEF➔ Usual care)	419,588 (LEF➔ ETN➔ Usual care vs. LEF➔ Usual care)	
	Welsing et al 2004	708,060 (ETN➔ LEF➔ Usual care Vs. LEF➔ Usual care)	683,041 (ETN➔ LEF➔ Usual care vs LEF➔ Usual care)	
	Wu et al 2012	58,711 (ETN)	58,684 (ETN)	
	Wu et al 2012	50,409 (ETN➔ RTX)	50,389 (ETN➔ RTX)	

➔ = switch to next treatment in case of an inadequate response, ABT = abatacept, ADA = adalimumab, CADTH = Canadian Agency for Drugs and Technologies in Health, cDMARD = conventional disease-modifying antirheumatic drugs, CER =

certolizumab pegol, ETN = etanercept, GOL = golimumab, GST = Gold, ICER = Incremental cost-effectiveness ratio, IFX = infliximab, LEF = leflunomide, MTX = methotrexate, NICE = National Institute for Health and Care Excellence, QALY = quality-adjusted life year, SSZ = sulfasalazine, Anti-TNF = TNF inhibitor, TOC = tocilizumab

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There is no doubt that bDMARDs help in attaining clinical remission in patients with RA faster than csDMARDs alone. However, in patients who receive bDMARDs, a key clinical decision needs to be made on continuing the bDMARDs after achieving clinical remission. This decision will help determine the true economic impact of bDMARDs in management of RA over the life-time of a person. More often than not, many patients continue to receive bDMARDs even after clinical remission and significant reduction in disease activity scores, which may not be needed. More clinical evidence is needed to support this practice.

Table 35. Cost-Effectiveness of Biologics in Comparison With csDMARDs Among Patients With an Insufficient Response To At Least One Anti-TNF

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
IFX	Yuan et al. 2010	47,931	-	57,370–96,012
	Kielhorn et al. 2008	28,594	-	9,758–67,321
	Brodszky et al. 2004	26,304–46,389	31,382–37,266	96,287–213,008
	Hallinen et al 2010	34,269	-	24,929–52,929
	Malottki et al. 2011	30,021	-	16,220–65,448
IFX	Hallinen et al 2010	40,923	-	36,174–48,483

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Malottki et al 2011	51,362	-	40,976–98,029
ADA	Hallinen et al 2010	57,713	-	48,963–68,930
	Malottki et al. 2011	48,801	-	39,980–87,216
ETN	Hallinen et al. 2010	57,068	-	48,294–68,285
	Malottki et al. 2011	55,346	-	44,248–108,558
	Lekander et al. 2013	-	74,743 (ETN+csDMARD)	47,164–113,453 (ETN+csDMARD)
	Lekander et al. 2013	-	88,861 (ETN)	53,769–175,126 (ETN)
ABA	Hallinen et al 2010	75,910	-	65,232–90,234
	Malottki et al 2011	54,635	-	45,671–90,062
	Vera-Llonch et al. 2008	45,275–49,802	-	40,211–79,438
	Yuan et al. 2010	41,207	-	49,912–81,509
ANA	Clark et al. 2004	620,109–1,347,287 (ANA➔csDMARDs)	-	100,378–671,413

Biologic	Study	ICER EUR/QALY (only direct costs)	ICER EUR/QALY (direct and indirect costs)	Results of deterministic sensitivity analysis EUR/QALY
	Clark et al. 2004	234,214–292,210 (csDMARDs➔ANA)	-	82,533–216,370
Anti-TNF	Lekander et al. 2013	101,618 (Anti-TNF+csDMARD)	84,363 (Anti-TNF+csDMARD)	50,316–134,016 (Anti-TNF+csDMARDs)
	Lekander et al. 2013	143,745 (Anti-TNF)	126,813 (Anti-TNF)	71,022–328,903 (Anti-TNF)

➔ = switch to next treatment in case of an inadequate response, ABT = abatacept, ADA = adalimumab, ANA = Anakinra, BMS = Bristol-Myers Squibb, csDMARD = conventional disease-modifying antirheumatic drugs, ETN = etanercept, ICER = Incremental cost-effectiveness ratio, IFX = infliximab, NICE = National Institute for Health and Care Excellence, QALY = quality-adjusted life year, RTX = rituximab, Anti-TNF = TNF inhibitor

We have collected cost effectiveness results from the various studies using the incremental cost-effectiveness ratio (ICER) as the most frequently reported outcome in cost-effectiveness analyses (CEAs). ICER reflects the additional cost per QALY gained by a particular treatment.

Benucci and co-workers in their review noted that DMARDs with ICERs below USD 50.000–100.000 or EUR 30.000 or EUR 50.000 per QALY, as being cost effective.

In the same review the authors compared the ICERs of the various sDMARDS across the studies and countries. This review specifically excluded bDMARDs. Recent therapeutic strategies in RA aim to slow down disease progression and reduce functional impairment. Anti-TNF bDMARDs are the forerunners in achieving such a therapeutic goal as they have been proven to suppress disease activity. Procurement of Anti-TNF bDMARDs is associated with incredibly high costs when compared with traditional sDMARD therapy. In this assessment, Benucci & co-workers chose health assessment questionnaire to assess the improvement achieved through biological intervention, since a close correlation was reported between HAQ and health care costs. A unit of improvement in the HAQ (any 1 unit difference between 0 and 3) was chosen as a health outcome benefit in order to assess the ICER. The resulting ICERs per unit of HAQ varied between EUR 1,201 and EUR 26,030 with a mean of EUR 6,588 per unit of HAQ.

Table 36. Cost Effectiveness of csDMARDs

Authors and years of publication	DMARDs and comparisons	Countries	Overall time	Evaluation's model	Outcomes	Cost-effectiveness ratio
Anis et al. 1996 (32)	CyA versus AZA versus D-Pen	Canada	12 months	ITT	ICER	USD 20,698
Verhoeven et al. 1998 (33)	SSZ versus COMBO	Netherland	56 weeks		QALY	USD 6,511

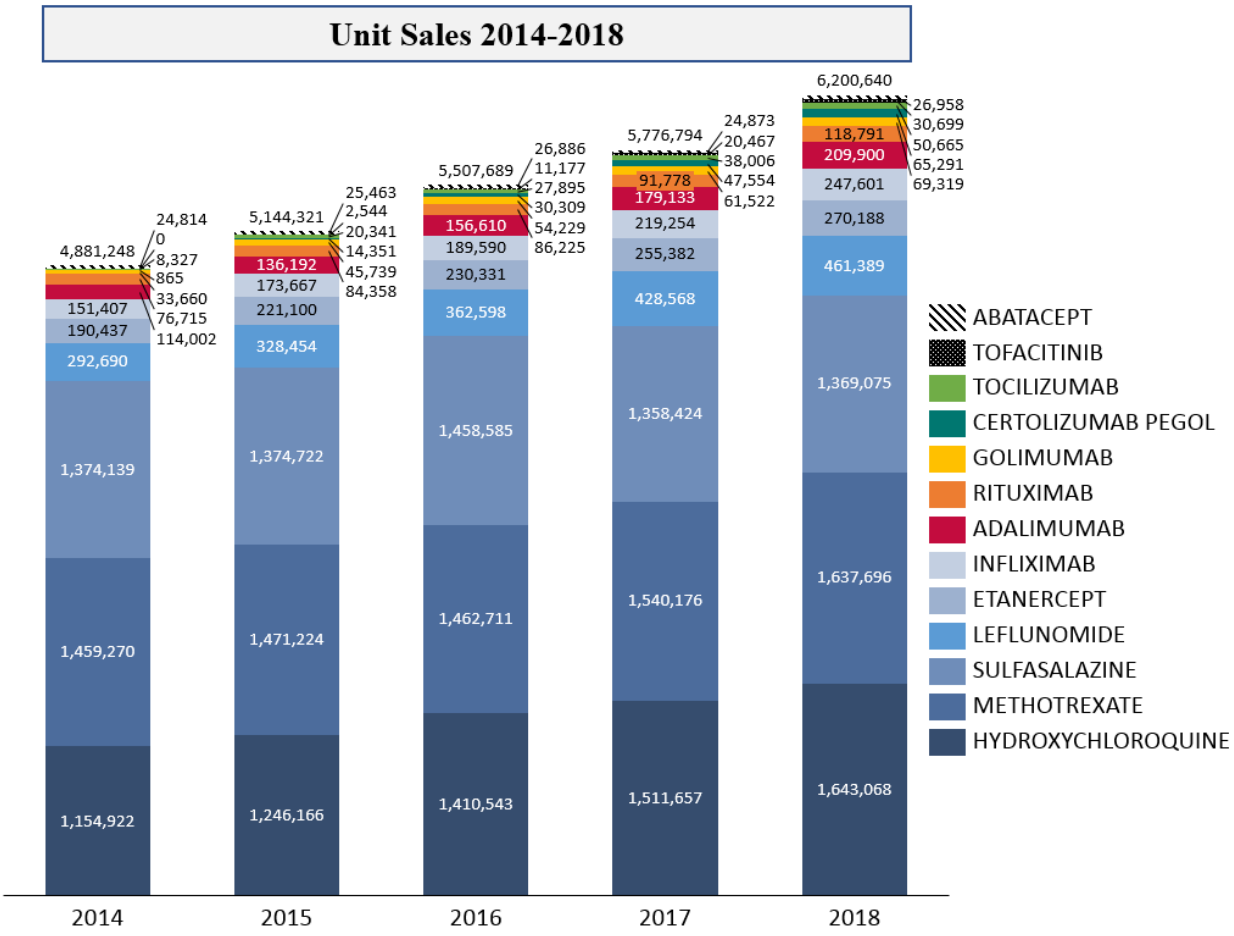
Maetzel et al. 2002 (34)	LFN	Canada	12 months	ACR 20	QALY	USD 54,229
Maetzel et al. 2002 (35)	LFN vs MTX	Canada	12 months	ACR 20	QALY	USD 3,853
Kobelt et al. 2002 (36)	LFN versus	UK	15 years	Markov	QALY	£ 35,855
	MTX versus					£ 44,988
	SSZ					£ 37,731
Bruns et al. 2000 (37)	MTX versus ETN versus MTX + ETN versus MTX + CyA versus HCQ + MTX + SSZ	USA	6 months	ACR 20	Tree Model	USD 1,100
				ACR 70WN		USD 1,500
Choi et al. 2002 (38)	MTX versus ETN versus LFN versus SSZ	USA	6 months	ACR 20	Tree Model	USD 900
				ACR 70WN		USD 1,500
Osiri et al. 2007 (39)	MTX versus DMARDs	Thailand	1 year	HAQ	ICER	USD 834
						USD 2,061

Schädlich et al. 2005 (40)	MTX versus LFN	Germany	1 year	HFAQ	Tree	USD 708
						USD 2,010
Korthals-De Bos et al. 2004 (41)	COBRA versus SSZ	Netherland	28 weeks	HAQ	QALY	USD 2,578
						USD 3,638
Hartman et al. 2004 (42)	MTX versus MTX + folic acid	Netherland	48 weeks	EuroQol	QALY	USD 1,398
Schipper et al. 2011 (43)	MTX versus MTX + LFN versus MTX + TNF	Netherland	5 years	Markov	QALY	USD 16,620
						USD 17,574

CyA: cyclosporine A; HCQ: hydroxychloroquine; TNF: tumour necrosis factor; LNF: leflunomide; MTX: methotrexate; ETN: etanercept; SSZ: sulphasalazine; DMARDs: disease modifying antirheumatic drugs; ACR: American College of Rheumatology; HAQ: health assessment questionnaire; ITT: intention to treat; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio HFAQ: Hannover Functional Ability Questionnaire; UK: United Kingdom; USA: United States of America.

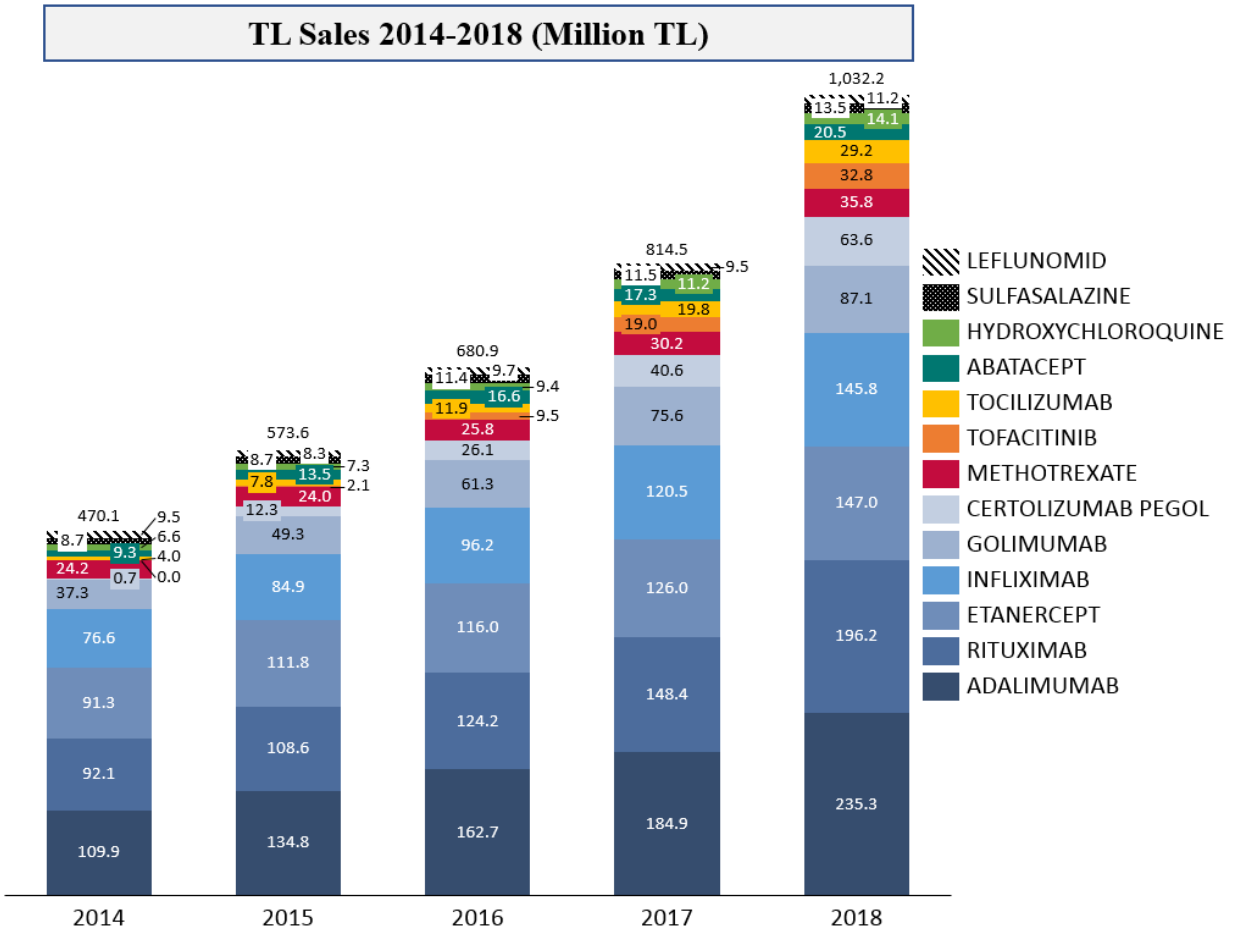
10.2.4. Cost of Treatment of RA in Turkey

The graphs below illustrate the trend of historical sales of DMARDs in Turkey. [29]



This shows that sales of the traditional synthethic DMARDs is far higher than bDMARDs. Within the bDMARDs the sales of TNF inhibitors etanercept and infliximab lead followed by the sales of the other TNF inhibitor adalimumab. However, these sales figures represent the overall sales across all rheumatological indications and not limited to the RA. Therefore, the actual sales of the DMARDs for RA in Turkey will be lower. The sales figures for Tofacitinib was zero for 2014 as the product was not approved for prescription in Turkey at that time.

We will now look at the sales figures in Turkish Liras for the same period for the various DMARDs.



Between 2015 and 2016, average prices of the DMARDs abruptly spiking, which may be the result of the devaluation of the Turkish Lira resulting in an apparent increase. Once again, the sales figures above are for the overall sales of the DMARDs, which also included all rheumatological indications. The relative share of RA in these sales will be however smaller.

The expert panel has provided an indicative cost for medications used in the management of RA in Turkey from the estimated public price in Turkish Liras per unit of the drug and subsequently the annual costs of treatment using each of the drugs. It is to be clarified that not all medications/drugs mentioned in the table-37 may be used in the management of RA. The average estimated unit costs per year for drugs only (direct costs) for treating RA patients in Turkey obtained from the panel of experts. This figure reflects the costs incurred by the health facilities and insurance and not necessarily the expense incurred out-of-pocket by patients. The costs as clarified are direct costs of treatment and do not reflect other costs such as laboratory evaluations,

hospitalizations, loss of productivity, etc that may be needed to compute the overall economic impact of treatment of RA in Turkey.

Table 37. Estimated Unit Costs of DMARDs for RA in Turkey as in November 2018

Drug Type	Estimated Public Price in TL	Average unit costs per year in TL
csDMARD		
Methotrexate (Oral) 15 mg pack	**39.11**	**156**
Hydroxychloroquine 200 mg pack	**13.02**	**312**
Sulfasalazine 500 mg pack	**15.28**	**458**
Leflunomide 20 mg pack	**35.06**	**421**
bDMARD		
Adalimumab 40 mg pack	**1454.36**	**18,907**
Certolizumab 200 mg pack	**1287.74**	**16,741**
Etanercept 50 mg pack	**715.13**	**18,593**
Infliximab 100 mg pack	**787.65**	**16,541**
Golimumab 50 mg pack	**1576.93**	**18,923**
Abatacept 250 mg pack	**606.21**	**15,761**
Rituximab 500 mg pack	**2232.54**	**8,930**
Tocilizumab 400 mg pack	**1291.67**	**16,792**
tsDMARD		
Tofacitinib 5 mg pack	**1397.92**	**17,939**

10.2.5. Costs of Drug Treatment in Turkey

Research shows that the mean annual direct cost was of treatment per patient was EUR 4,954 (median, EUR 1,805), whereas the mean annual indirect cost was EUR 2,802 per patient (median, EUR 608). When these direct and indirect costs are extrapolated to the total number of patients with RA (0.5% of adult population) in Turkey and in Turkish liras, it is estimated that an annual

amount of approx..19.5 billion Turkish Liras was spent on management of RA in Turkey in 2016 (1).

In our study, we have attempted to estimate the direct costs of medications for RA patients after adjusting the treatment compliance and the approaximate number of patients actually receiving treatment for RA. Accoridngly, we find that the total annual direct costs for medications for all RA patients was approximately TL 458 million (approximately EUR 70 million in currency conversion rates in April 2019) and the average annual direct costs for medications for per RA patient was approximately TL 2480 (approximately EUR 390 in currency conversion rates in April 2019). Details of these calculations are available in the subsequent sections.

It is therefore of vital economic importance to determine the most effective treatment option(s) and to contribute to the sustainability of resources allocated to healthcare services by reducing the financial loss to the minimum level possible

Assuming that the unit costs of laboratory investigations, physician and clinic costs are all constant, we can see that csDMARDs are far more cost effective. Within the bDMARDs, rituximab based on the price point alone, is clearly the most cost-effective bDMARD. From the earlier tables 21 and 22 on the comparison of safety parameters, we can also see that RTX has a more favourable safety profile than other bDMARDs. Comparison of bDMARDs on overall clinical effectiveness and disease specific outcomes such as DAS28, ACR50, HRQoL, RTX had comparatively higher scores along with anti-TNF bDMARDs. Therefore, given the price considerations and the comparatively higher scores in safety and clinical effectiveness, RTX appears to be the most cost-effective biologic to be used.

We have attempted to construct the annual costs and the total costs of treatment of RA with certain assumptions.

We have attempted to construct the annual costs and the total costs of treatment of RA with certain assumptions.

From the published literature on the prevalence of RA among general population in Turkey.

- Of the prevalent pool of patients in Turkey (0.56% of adult population in Turkey),
- 70% of this population to be diagnosed with RA and of those diagnosed,

- 75% of the diagnosed patients receiving DMARDs.

Again on the patients who were initiated on DMARDs, we have assumed patients to be categorized in 3 distinct categories;

A. Newly diagnosed or still on treatment evaluation with Methotrexate or conventional DMARDs

B. Patients with confirmed diagnosis with MTX & other bDMARD / tDMARD

C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment but may be on regular lab tests

Each of these 3 categories of patients were assumed to be on monotherapy or combination therapy. We have included only the costs of medications while computing.

Based on the unit prices of individual DMARDs available from Turkey, we have finally calculated the annual costs of DMARDs in Turkey.

All the cost model and assumptions are shown below in details;

Table 38. Model and Assumptions For Estimating Cost of Treatment For RA in Turkey

1. Population of Turkey in 2018 (1)		82,003,882
2. Adult Population (Above 14)(1)		62,819,553
3. Prevalence of RA in adult population in Turkey (2)		0.56%
4. Total number of RA patients in Turkey (2*3)		351,789
5. RA Diagnosis Rate in Turkey (%) (3)		70%
6. . # of RA Diagnosed Patient (4*5)		246,253
7. RA Treatment Rate in Turkey * (3)		75%
8. # of RA Treated Patient (6*7)		184,689
9. Patient Breakdown (%) (4)	A. Newly diagnosed or still on treatment evaluation with csDMARDs	60%
	B. Patients with confirmed diagnosis with MTX & other bDMARD / tsDMARD	12%

	C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment	28%

**Adherence rate included.*

10.1. csDMARD Treatment Regime for Category A Patients (5)					
Patient Categories	MTX	LEF	HCQ	SSZ	Total*
A. Newly diagnosed or still on treatment evaluation with csDMARDs	65%	25%	55%	25%	170%

**Total is greater than 100% due to combination usages.*

10.2. Treatment Regime for Category B and C Patients (5)						
Patient Categories	No csDMARD	MTX	MTX+ HCQ	MTX+ HCQ+SSZ	MTX+HCQ+ SSZ+LEF	Total
B. Patients with confirmed diagnosis with MTX & other bDMARD / tsDMARD*	11%	24%	38%	21%	6%	100%
C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment**	100%	0%	0%	0%	0%	100%

** Additional csDMARD treatment regimes are shown in addition to bDMARD/tsDMARD*

*** These 28% of patients who may be in remission at any point in time, are not on any DMARDs*

After extrapolating the above frequencies to absolute numbers from the prevalent, diagnosed and treated pool of patients in Turkey, we get some indicative number of patients in each category. This has been illustrated in the table below. It needs to be highlighted here that these numbers are only indicative and may not be an accurate reflection of the patients in the community.

11.1. Patient numbers for Category A patients (8*9*10)					
Patient Categories	MTX	LEF	HCQ	SSZ	Total*
A. Newly diagnosed or still on treatment evaluation with csDMARDs	72,029	27,703	60,948	27,703	110.814

**Unique patient numbers are shown (due to combination treatment total of cell is higher)*

11.2. Patient numbers for Category B and C patients (8*9*10)						
Patient Categories	No csDMARD	MTX	MTX + HCQ	MTX+ HCQ+SSZ	MTX+HCQ + SSZ+LEF	Total
B. Patients with confirmed diagnosis with MTX & other bDMARD / tsDMARD	2,418	5,275	8,352	4,615	1,319	21,978
C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment	51,898	-	-	-	-	51,898

Once the unit costs of the various medications are extrapolated, we get the following costs. These prices have been referenced from the Turkey SSI drug reimbursement list of 2018.

12.1. Cost of treatment for patients in category A (TL) (6)				
Patient Categories	MTX	LEF	HCQ	SSZ
A. Newly diagnosed or still on treatment evaluation with csDMARDs	156	421	312	458

12.2. Cost of treatment for patients in category B and C (TL) (6)					
Patient Categories	No csDMARD	MTX	MTX+ HCQ	MTX+ HCQ+SSZ	MTX+HCQ+ SSZ+LEF
B. Patients with confirmed diagnosis with MTX & other bDMARD / tsDMARD*	17,865	18,021	18,334	18,792	19,213
C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment	0	0	0	0	0

** Average bDMARD cost plus related csDMARD costs*

13.1. Total Cost of treatment for patients in category A (Million TL) (11*12)					
Patient Categories	MTX	LEF	HCQ	SSZ	Total
A. Newly diagnosed or still on treatment evaluation with csDMARDs	11,2	11,7	19,0	12,7	54,6

13.2. Total Cost of treatment for patients in category B and C (Million TL) (11*12)						
Patient Categories	No csDMARD	MTX	MTX+ HCQ	MTX+ HCQ+SSZ	MTX+ HCQ + SSZ+LEF	Total
B. Patients with confirmed diagnosis with MTX & other bDMARD / tsDMARD	43,2	95,0	153,1	86,7	25,3	403,4
C. Patients with confirmed diagnosis of RA, treated in past with any DMARDs but now in remission and not on any active treatment	-	-	-	-	-	-

Grand Total (TL)	458,0

Total annual estimated costs of treatment of RA is about 458 million TL and one can notice the clear difference between the costs of csDMARDs and bDMARDs.

When we consider the approximate number of RA patients receiving treatment every year in Turkey (184,689), the average direct cost of treatment will be 2480 TL.

Assumption references used in cost model are;

(1) TUİK

(2) Tiraje TUNCER et al. (2018) Prevalence of RA and Spondyloarthritis in Turkey

(3) Decision Support Group

(4) HUR-BIO, TReasure ve TURK-BIO Registry Studies, Expert Opinions, IQVIA Analysis

(5) HUR-BIO, TReasure ve TURK-BIO Registry Studies, Expert Opinions

(6) SSI Reimbursement Price List (2018)

10.3. Discussion & Results

A review of the cost effectiveness of RA treatments and the clinical recommendations of EULAR has shown that csDMARDs are cost effective if initiated early on in disease course. If DMARDs fail, therapeutic escalation with Anti-TNF bDMARDs is cost effective when standard-dosing regimens are used. If Anti-TNF bDMARDs fail, non-Anti-TNF rituximab or abatacept is cost effective. There is little economic evidence for switching within TNF inhibitors. MTX and biological agents have been found to be similarly effective as measured by ACR and EULAR response criteria, including clinical remission although folic acid supplementation may have reduced the efficacy of MTX by interfering with its mechanism of action. All studies however, have pointed to a strong performance by MTX in comparison to bDMARDs.

There is a common view as can be seen from a review of all global clinical guidelines that MTX should constitute a part of the first treatment regimen. If MTX cannot be used because of contraindications or intolerance, LEF or SSZ should be started as a part of the first treatment regimen. If the treatment goal cannot be reached with the first treatment regimen, in the absence of poor prognostic factors, other csDMARDs should be initiated. However, if the treatment goal cannot be reached with the first treatment regimen (of csDMARDs monotherapy or combination therapy) and in the presence of poor prognostic factors, a bDMARD or tsDMARD addition should be considered. When starting bDMARDs or tsDMARDs, global guidelines recommend combining them with csDMARDs instead of giving bDMARD or tsDMARD as a monotherapy.

The total annual costs of drug treatment of RA in Turkey was estimated to about 458 million TL after discounting the costs of laboratory investigations done during treatment monitoring and indirect costs. There is also a clear difference in the treatment costs between csDMARDs and bDMARDs. However, the potential savings of indirect costs that bDMARDs offer through slowing the progression of RA disease, justify their use in combination with csDMARD after insufficient response to initial trial of csDMARDs. Hence bDMARDs should be initiated in RA patients after a thorough safety screening, if the treatment target is not achieved with csDMARDs.

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11. ETHICAL PERSPECTIVES

11.1. Introduction

The Ethical Analysis domain considers prevalent social and moral norms and values relevant to the technology in question. It involves an understanding of the consequences of implementing or not implementing a healthcare technology in two respects: with regard to the prevailing societal values and with regard to the norms and values that the technology itself constructs when it is put into use. The moral value that societies attribute to the consequences of implementing a technology is affected by socio-political, cultural, legal, religious and economic differences. However, many ethical considerations are common to all countries and societies.

This domain covers moral and ethical issues related to the consequences of performing the health technology assessment (HTA). These are, for example, questions about the ethical consequences of choosing specific endpoints and about whether there are any ethical problems related to the economic evaluation. There are, however, also various ethical considerations that should be taken into account when choosing what technologies to assess and when planning to conduct the assessment.

11.2. Assessment

The principalism as an approach is adopted for the assessment of Ethical Analysis of DMARDs, wherein we have discussed the basic ethical principles in healthcare such as balance of benefit versus harm; freewill and autonomy of patients in deciding the best treatment options for themselves; and the justice and healthcare equity offered by the constitutional and legal provisions within the country.

This domian consists of six different topics and nineteen issues. We have selected only those topics and issues that are relevant for DMARDs. The information contained herein is obtained mainly from the experts and patients' representatives in Turkey, as such information was not well published in literature.

Table 39. Assessment Areas in Ethical Perspectives of DMARDs

Topic	Issue	Information & Source
Benefit-harm balance	What are the benefits and harms of DMARDs for relatives, other patients, organizations, commercial entities, society, etc.? Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention? Is DMARDs used for individuals that are especially vulnerable?	From prescribing information / summary of product characteristics published by the drug regulatory agencies From the experts and patients' representatives in Turkey
Patient autonomy	Do patients have enough autonomy in treatment decision making? What are the various information and resources available to support patients?	From the experts and patients' representatives in Turkey
Justice and equity	How does implementation or withdrawal of the technology affect the distribution of health care resources? Are there factors that could prevent a group or person from gaining access to the technology?	From the experts and patients' representatives in Turkey

Legislation	Do use of DMARDs affect basic human rights? Do use of DMARDs pose ethical challenges not addressed in laws in the country?	From the experts and patients' representatives in Turkey
Ethical consequences	What are the ethical consequences of the choice of endpoints, cut off values and comparators/controls in the assessment? Are there any ethical problems related to the data or the assumptions in the economic evaluation?	From the experts and patients' representatives in Turkey

11.2.1. Benefits Versus Harm of The DMARDs in RA

Weighing the risks and the benefits for any prescription medicine can be challenging, especially if such medications need to be taken for a long time. RA can affect even individuals who may be at a higher risk of harms and adverse effects such as children, elderly, pregnant and lactating women, patients with pre-existing diseases of immune systems. As such, it is critical to involve patients and their legal guardians to be involved in every treatment plan to enable the patients to be aware of the special risks of the DMARDs and to alert the physicians early enough whenever adverse effects do develop. While such shared decision making may not always be possible for the treating physicians, there remains an ethical obligation on part of the healthcare professionals to educate their patients to all risks and benefits of the DMARDs to the best of their ability and comprehension.

The ethical dimensions of caring for RA patients are heavily influenced by the healthcare environment in a country, provision of universal healthcare, the physical environment and facility in which care is provided, the training, experience and skills of the healthcare professionals, and the availability of the medications for managing RA. These points have discussed in greater detail in later sections, the benefits and risks of the DMARDs for patients are listed in table-40.

Table 40. Risk-Benefit Profiles of DMARDs

Name of DMARD	Characteristics of Risk-Benefit for patients
Synthetic DMARDs	
Methotrexate (MTX)	**Benefits:** Most commonly prescribed drug for RA. As per most of the international and local Turkish treatment recommendations, methotrexate is an anchor drug for newly diagnosed and in early RA patients. Often used methotrexate in combination with other DMARDs to treat arthritis. Any physician can prescribe MTX – from primary care physicians to the subspecialists with minimal treatment monitoring. **Risks:** Methotrexate most commonly causes nausea. Other common side effects include swollen gums, mouth sores and excess tiredness. Women who want to become pregnant should not take methotrexate. Methotrexate can cause an increase in liver enzymes and is therefore not recommended for those who drink alcohol and who are taking drugs that can be hepatotoxic. Methotrexate should not be used in patients with impaired renal function.
Sulfasalazine (SSZ)	**Benefit:** This drug is similar to MTX in its ease of administration and is used for people with RA and other autoimmune conditions. Sulfasalazine can lessen pain and swelling and slow the progression of arthritis

Name of DMARD	Characteristics of Risk-Benefit for patients
	Risks: Sulfasalazine may cause nausea and vomiting. It can cause yellow-orange urine or skin. It is generally safe for pregnancy but should not be taken while breastfeeding. This drug may lower sperm count in men, an effect that gets better once the drug is stopped. Rarely can cause serious skin reactions
Hydroxychloroquine (HCQ)	**Benefit:** Hydroxychloroquine is a relatively safe medicine that is used to treat mild RA. It can be used in combination with other drugs to treat more severe cases. **Risk:** One of the safer DMARDs Hydroxychloroquine has few side effects, but nausea and diarrhea may occur when you first start taking the drug. In very rare cases, vision loss has happened. periodic screening for vision issues with an opthalmologist is recommended
Leflunomide (LEF)	**Benefit:** Leflunomide is used to treat moderate to severe RA, often when methotrexate is not controlling symptoms. Leflunomide is sometimes used to treat psoriatic arthritis. **Risk:** This drug most commonly causes nausea and diarrhea. It can also cause hair loss. It clears from the body slowly; a wash-out procedure may be needed before trying to get pregnant. May cause an increase in blood pressure.
Tofacitinib	**Benefit:** This drug is used for adults with moderate to severe RA whose disease has not responded to methotrexate. It may be used as monotherapy or in combination

Name of DMARD	Characteristics of Risk-Benefit for patients
	with methotrexate or other nonbiologic DMARDs. Its a new generation targeted synthetic (tsDMARDs) **Risks:** Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tofacitinib. The treatment should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections. Administration of tofacitinib results in dose-dependent increase in lipid parameters including total cholesterol, low-density lipoprotein, and high-density lipoprotein
bDMARDs	
Adalimumab (ADA)	**Benefit:** Adalimumab belongs to a class of drugs known as TNF inhibitors. By reducing joint swelling, this medication helps to reduce further joint damage and preserve joint function. **Risks:** Being a biologic and immunomodulatory drug, special precaution is warranted in people with hypersensitivity or allergic tendencies, patients with latent infections such as tuberculosis, patients with hidden or overt hepatitis or are suffering from conditions with diminished immunological strength
Certolizumab (CTZ)	**Benefit:** Certolizumab pegol is a prescription medication used to treat autoimmune conditions. It is called a tumor necrosis factor (TNF) inhibitor because it binds and blocks TNF that causes inflammation. Certolizumab is generally safer for

Name of DMARD	Characteristics of Risk-Benefit for patients
	lactating mothers who have delivered full term as it is not secreted in breast milk being a large protein. Certolizumab is given as a subcutaneous injection under the skin **Risks:** Serious and sometimes fatal side effects have been reported with CTZ, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens (such as Legionella or Listeria). Patients should be closely monitored for the signs and symptoms of infection during and after treatment with CTZ. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CTZ is a member. CTZ is not indicated for use in pediatric patients.
Etanercept (ETA)	**Benefit:** Etanercept is another Anti-TNF bDMARD that blocks the action of TNF implicated in inflammation and join damage. Like other drugs in this class, this drug too reduces the disease symptoms and reduces the progression of the disease. It can be injected subcutaneously and thus can be self-administered by patients with adequate training and supervision. **Risks:** Patients may develop serious infection or sepsis. Reported infections include: 1) Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested and treated for latent TB before and periodically during therapy 2) Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Empiric antifungal therapy should be considered in patients at risk for invasive fungal

Name of DMARD	Characteristics of Risk-Benefit for patients
	infections who develop severe systemic illness, and 3) Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.
Infliximab (INF)	**Benefit:** Infliximab is a "TNF-alpha antagonist", that works by neutralizing TNF-alpha and reducing inflammation. This can lessen the symptoms associated with RA and also help stop further joint damage. **Risks:** Unlike other Anti-TNF bDMARDs, which are given by subcutaneous injections and can be self-administered, infliximab is given by an IV drip and needs to be administered by a healthcare professional. Just like other Anti-TNF bDMARDs, Infliximab also increases the risk of infections that may be latent or acquired after start of the therapy, hence caution is to be exercised among patients with acute or latent infections. In addition, Infliximab is known to decrease the cardiac output and increase blood pressure in many patients without any pre-existing cardiac disease. Caution is hence exercised in patients with pre-existing cardiac diseases
Golimumab (GOL)	**Benefit:** Golimumab targets tumor necrosis factor alpha (TNF-alpha) and helps reduction of inflammation and joint damage. It is used in combination with methotrexate. It can be used in adults who have not responded adequately to other treatments including methotrexate whose disease is moderate to severe, and in patients who have not previously been treated with methotrexate whose disease is severe and progressive; **Risks:** Just like other Anti-TNF bDMARDs, it increases the vulnerability for infections and precautions are to be exercised against any latent or acute infection. Very

Name of DMARD	Characteristics of Risk-Benefit for patients
	rarely, golimumab can cause a condition called drug-induced lupus. The symptoms include a rash, fever and increased joint pain.
Rituximab (RTX)	**Benefit:** Rituximab belongs to a class of biologics known as B-cell kinase inhibitors and acts by reducing the join swelling and pain in the joints in RA patients **Risks:** Rituximab can decrease blood cells, which can cause anemia, reduce immunity levels and increasing vulnerability to infections, or cause easy bruising/bleeding due to reduced platelets. As such patients may experience easy bleeding/bruising from skin wounds, black/tarry stools, vomit that looks like coffee grounds, signs of an infection (such as sore throat that doesn't go away, fever, chills), unusual tiredness, pale skin.
Tocilizumab (TOC)	**Benefit:** Tocilizumab belongs to a class of drugs known as Interleukin-6 (IL-6) blockers. It works by blocking IL-6, a substance made by the body that causes swelling. This medication is used alone or with other medications to treat moderate to severe RA in adults. It helps to reduce pain and swelling due to RA **Risks:** Being a biologic and immunomodulatory drug, special precaution is warranted in pregnant and lactating women, people with hypersensitivity or allergic tendencies, patients with latent infections such as tuberculosis, patients with hidden or overt hepatitis or are suffering from conditions with diminished immunological strength
Abatacept (ABA)	**Benefit:**

Name of DMARD	Characteristics of Risk-Benefit for patients
	Adalimumab belongs to a class of drugs known as T-cell activation inhibitors. By reducing joint swelling, this medication helps to reduce further joint damage and preserve joint function. **Risks:** Being a biologic and immunomodulatory drug, special precaution is warranted in people with hypersensitivity or allergic tendencies, patients with chronic obstructive pulmonary disease-COPD, current/recent/returning infection (such as tuberculosis, hepatitis), immune system disorder (such as HIV infection, bone marrow disorder), diabetes or overt hepatitis or are suffering from conditions with diminished immunological strength.

Keeping in mind the benefits and the risks of DMARDs, patients should be scrutinized in terms of both possible risks of RA and possible risks of DMARDs. Scrutiny of the possible risks of RA covers the expected course of RA in the relevant patient, in other words prognostic assessment as well as in the context of the safety profile of the specific drug. Rheumatology and PTR clinics and hospitals in Turkey have all the laboratory test facilities to enable treatment monitoring.

11.2.2. Measuring Treatment Outcomes And Treatment Goal in RA: Ethical Concerns

The treating physicians need to keep a regular track on the markers for the disease progress and remission. There are several markers including clinical, radiological and biochemical markers. Despite the large amount of evidence available in published literature, there is lack of consensus on having one single universal marker to assess the treatment outcome in RA. These can lead to ethical challenges in either treatment being escalated or delayed unnecessarily. In clinical trials it may be an ACR 20, 50, or 70, or a disease activity score of DAS 28, or some radiographic outcome. Often, these measures are very convenient for use in routine clinical practice. The following parameters summarize the key clinical markers for assessing the disease progress in RA.

ACR Core Set:

- Physician global estimate
- Functional status – health assessment questionnaire (HAQ) multidimensional HAQ

- Pain

ACR Core Set and Disease Activity Scores (DAS)

- Tender joint count
- Swollen joint count
- Acute phase reactant - ESR, CRP
- Patient global estimate

Above are the 7 measures that are the core set that makes up the ACR 20, 50 and 70; and those used in the DAS. The problem with the ACR set is that it measures a percent improvement. DAS measures an absolute level of disease activity, but it has a lot of problems too. There is nothing in the DAS about functional status; it is much too sensitive to change in sedimentation rates; painful joints are overemphasized compared with swollen joints.

DAS28 = 0.56 * square root (tender joint count 28) + 0.28 * square root (swollen joint count 28) + 0.70 * log e (ESR) +0.014 (patient assessment of global status or activity)

The DAS is a complicated mathematical formula but that is not the reason it is not useful to use in clinic. The reason that it is not useful to us in clinic is that most people don't do formal 28 joint counts and even if they do, they don't have sedimentation rates or CRP's done at the time they are seeing the patient. There is also a CRP DAS that can be calculated.

The pharmacovigilance programs in practice when a new bDMARD is launched may necessitate taking certain measures and making examinations which are not necessary for current DMARD, causing costs to increase. Requirement of the majority of the bDMARDs for cold chain may lead to costs in the pharmacy sector during the process of distributing and storing the drugs. New DMARDs and possibly promotions increase disease awareness and ensure that more patients are given treatment; however, DMARDs are not drugs which may be given to the relatives of the patient or other individuals due to awareness, if not necessary. Even though the determination of the cases necessitating new treatment seems to increase drug costs, it will cause necessary patients to receive treatment and decrease social burden of RA. If the NNT (number needed to treat) rate of a new bDMARD is lower than the current bDMARDs and its serious adverse effects are lesser,

total treatment cost will decrease. For this reason, if a new DMARD is to be approved, effectiveness of the drug and its serious adverse event frequency should be considered

11.2.3. Evidence Generation Initiatives on Evaluating DMARDs in Turkey

While there are no obstacles for the ethical implementation of evidence generation initiatives in Turkey, the number of such initiatives especially randomized clinical trials have been limited because of the perceived lack of research time among physicians and current complexities of getting approvals for conducting human research in Turkey. However, in recent times, there have been recently increasing attempts to collect observational data on RA patients. One such prominent survey was the nationwide prevalence studies in undertaken in Turkey by Tiraje Tuncer and coworkers from Akdeniz and Ankara University to estimate the prevalence of RA and spondyloarthritis (SpA). More researchers are starting the multicenter registries to collect prospective data collection on use of bDMARDs.

These are multicenter TReasure (15 sites), TUR-BIO and single-center HUR-BIO databases in Rheumatology. The data of nearly 7000 patients using bDMARD in TReasure and nearly 4000 patients using bDMARD in HUR-BIO is collected prospectively; however, no interventional studies are conducted in these areas.

The TReasure registry, created in 2017, is an observational multicenter cohort that includes inflammatory arthritis patients.

TLAR has input data, analysed, published or at project phase of more than 5,000 rheumatologic patients (RA, SpA, PsA, Systemic Sclerosis, FMF, etc.) in the TLAR-IP register consisting of 41 centers, in the BioSTar biological record register consisting of 10 centers and in the TLAR-Network projects.

Turkey has fallen behind plans to reach its 2023 target of 3600 clinical trials conducted per year. The total number of clinical trials conducted in Turkey for all indications still remains low. Turkey’s global share in industry led clinical trials (for all indications) is currently at 2.9%. However, when considering non-interventional clinical studies and observational studies, RA seems to have been well researched in Turkey. Among non-interventional clinical studies conducted, Turkey's global share in clinical studies completed to date is higher for RA indication (1.9%) than for all clinical studies in total (1.3%). There is clearly a need to increase the number of interventional trials in RA in Turkey.

11.2.4. Patient Vulnerability And Patient Autonomy in Treatment Decisions Using DMARDs

RA can affect even individuals who may be at a higher risk of harms and adverse effects such as children, elderly, pregnant and lactating women, patients with pre-existing diseases of immune systems. As such, it is critical to involve patients and their legal guardians to be involved in every treatment plan to enable the patients to be aware of the special risks of the DMARDs and to alert the physicians early enough whenever adverse effects do develop.

RA is managed in the following sensitive groups as stated below:

a) In pregnant women, Certolizumab and adalimumab are used safely with HCQ and SSZ
b) In young children, it is managed by the family together with pediatric rheumatologists and PTR specialists
c) In persons with mental disabilities or patients, it is managed by persons assigned as guardian, spouse, family and principal physician (rheumatologists and PTR specialists)
d) In the elderly people, it is managed by persons assigned as guardian if there is, spouse, family and principal physician (rheumatologists and PTR specialists)

As per the Patient Rights Directive in Turkey, all patients have guaranteed freedom of deciding on the treatment they receive. The Patient Rights Directive, covers every public and private medical institution, every individual related directly or indirectly to these institutions in terms of providing medical services at every level and under any title besides the ones that have the right to receive medical treatment from aforementioned institutions and persons. This directive covers; utilizing health services according to the principles of justice and equity, right to request information, right to choose and change the medical facility, right to know, chose and change the personnel, right to request determination of priority, right to request being diagnosed, treated and cared appropriate to medical reasons, refuse interventions that are not related to medical necessities, right to receive medical attention, right to receive general information, right to examine records, right to request record correction, right of privacy, right to not being exposed to any medical procedure without informed consent, right to keep records confidential, right to refuse or discontinue treatment, right to have informed consent prior to organ or tissue transplantation or other medical research, right of the volunteers to be protected and informed, right to security, right to practice the religious duties and receive religious services, right to request respect to humanitarian values and right to have visitors and attendants.

A guide concerning the use of bDMARD on pregnant women has been discussed by Turkish Society for Rheumatology (TRD) with its sub-commissions and the guide is about to be finalized. Furthermore, there are recommendations of FDA and EMA about the issue and also EULAR recommendations which have been recently published. Within the framework of these recommendations, decision is taken by the physician and the patient considering benefits/harms balance. There are no arrangements concerning the persons with mental disabilities. Assent of the parents is obtained for children.

As required by the pharmacovigilance laws in Turkey, a standard informed consent is taken from all patients and they / their guardians are informed about the possible side effects prior to the use of bDMARDs. This consent and approval process should be completed in order to collect drugs from the pharmacies. This consent form is obtained from the patients at each visit. Possible side effects are explained in this form; possible effects are also described in detail by the physicians.

There is no data stipulating that DMARDs affect cognitive and executive functions.

Medical Statute of Deontology (Bylaw) was adopted and published by the Turkish Medical Association. The statute includes patient rights and responsibilities of the dentists and explains issues like respect to the privacy of patients, patients' right to choose their doctor, clarification of diagnosis and treatment, confidentiality, withdrawal of the doctor from patient treatment. Medical Statute of Deontology was insufficient in terms of patient rights despite it included some terms about the subject. In addition, this statute was recomposed and adopted under the name of "Rules on Medicine and Professional Ethics" by the Turkish Medical Association at the 47th Grand Congress organized in Ankara in 1998.

The most important step taken in terms of patient rights in Turkey; under the influence of human rights conventions that Turkey is a party to and the agreements on patient rights at the international level, was "The Patient Rights Directive (HHY) ", adopted on August 1, 1998.

There has not been any regulation as to the ways of applying this directive which was issued in 1998, until 2003 in Turkey. To ensure the application of the Patient Rights Directive issued in 1998 under the frame of Health Reform Program, "Directive on Patient Rights Application in Health Facilities (HHUY)" had been adopted in 2003. With this directive it was aimed to ensure patients and their attendant relatives can utilize their rights, be informed at every level, be protected against violations and be actually able to use legal precautions if necessary.

11.2.5. Health Equality And Access to Healthcare in Turkey

By Universal Health Insurance Law (2012), all Turkish citizens are formally covered by general health insurance. Also, Turkish Constitution Article 10 titled "Equality Against Laws" states that "Everyone is equal against laws regardless of language, ethnicity, colour, gender, political views, philosophical belief, religion, religious sect, and alike. No exceptions can be given to any person, family, group or class. State and government authorities must act in accordance with the principle of equality against laws in all of their operations."

In spirit of these provisions, no patients diagnosed with RA or undergoing medical evaluation for RA is denied any care in public health institutions in Turkey.

A large number of full-fledged university and state hospitals are available in all geographical regions. However, physical access to healthcare may still be challenging for some patients living in remote locations, especially in extreme weather conditions and to private healthcare institutions.

11.2.6. Legal Systems And Other System Level Supports For Patients in Turkey

There are robust systems of collecting pharmacovigilance data in Turkey and reporting all adverse effects resulting from medical interventions.

In Turkey, pharmacovigilance activities started in 1985 with the establishment of the “Turkish Adverse Drug Reaction Monitoring and Evaluation Center” (TADMER) under the General Directorate of Pharmaceuticals and Pharmacy. In 1987, TADMER joined the WHO Programme as an official member. In 2005, first pharmacovigilance regulation, “Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use”, became effective. With this regulation, TADMER started to conduct pharmacovigilance activities under the name “Turkish Pharmacovigilance Center” (TUFAM), in order to stress the term “Pharmacovigilance”. In the regulation, major responsibilities of TUFAM were defined as: monitoring national ADR reports and drug safety alerts worldwide, communicating drug safety alerts to healthcare professionals, educating physicians and pharmacists on pharmacovigilance, conducting risk minimization methods, and assessing conformity of risk management plans and periodic safety update reports. Taking this first regulation as reference, responsibilities of Authorization Holders, Pharmacovigilance Inspections and Structure of Risk Management Systems were addressed in detail in the guidelines published in 2005, 2009 and 2011, respectively. In 2012, the General Directorate of Pharmaceuticals and Pharmacy became an agency called the Turkish Medicines and

Medical Devices Agency. With this structural change, a Risk Management Unit was formed to take over risk minimization activities. Since then, TUFAM has been concentrating on monitoring and assessing national ADR reports (20).

National ADR reports reach TUFAM from two major sources: healthcare professionals and marketing authorization holders (MAHs). Healthcare professionals can notify spontaneous reports to the TUFAM either directly or by means of the pharmacovigilance contact points (PvCPs) within the health organization that they are employed in. PvCPs are physicians or pharmacists who are responsible for encouraging the notification of ADRs, collecting and communicating information to TUFAM, and carrying out training and awareness activities at hospitals they work in. According to regulation, a PvCP should be assigned to work at university hospitals, training and research hospitals, and private hospitals with a bed capacity of 50 or more. This regulation was later expanded to cover all hospitals. This method is different from many countries, and has the intention of communicating information faster between TUFAM and health-care professionals (20).

MAHs are responsible for keeping the records of all suspected ADRs and notifying serious ADRs occurring in Turkey to the TUFAM within 15 days. They collect both spontaneous reports and solicited reports from patient support programmes where they receive and collect information relating to the use of their medicinal products. In Turkey, MAHs are also responsible for screening national and international literature for ADRs regarding the local population and forwarding a copy to TUFAM (20).

Spontaneous and solicited ADR reports reaching TUFAM from healthcare professionals and MAHs are sent to the VigiBase as ICSRs. In this way TUFAM contributes to the integration of world data on ADRs as intended by the WHO programme. In 2014, national pharmacovigilance regulation was revised in the context of harmonization with EU directives. With these new regulations, patient reports also started to be accepted and sent to the VigiBase by TUFAM. Additionally national ADRs mentioned in the literature started to be sent to the Vigibase if they complied with the requirements of an ICSR (20).

In addition to the system to record data on drug safety and pharmacovigilance, the legal system in Turkey also has provisions to safeguard the interests of patients.

11.2.7. Patient Rights in Turkey

The Patient Rights are granted with Patient Rights Practices Circular no. 2014/30 in Turkey. Patient rights in accordance with this circular have been detailed in legal aspect domain.

The Patient Rights Boards is a unit that evaluates, decides, submits proposals for and determines remedial actions on the applications received from private healthcare institutions and organisations, public hospitals, oral health centres, family health centres and public health centres.

The patients benefit from the healthcare services and their relatives may apply in many different ways against all violation of rights during the first application to hospital or diagnosis, treatment, hospital stay and patient follow-up. All applications to be made by patients or patient relatives regarding the healthcare service provider can be made online via institution's website, directly to the Patient Communication Unit or Provincial Directorate of Health. Complaint, dispute settlement, opinion, suggestion and appreciation applications can be made to patient application notification system (HBSS).

Notwithstanding the above provisions for patient rights, there are few challenges within the Turkish legal system, which may have a bearing on the treatment of DMARDs for RA. The lack of these laws can bring to fore certain situations which may put the patients in a vulnerable situation.

11.2.8. Lack of a Law Specific to Medicine Manufacturers' Liability

Turkey does not have a law specific to the liability (particularly the manufacturer's liability) for medicines. The liability of the manufacturer for drugs are generally subject to the Law on the Protection of Consumers, Code of Obligations and other general laws, where applicable.

In some other countries, however, there are laws specific to medicines, which also regulate the manufacturer's liability (e.g. the German Medicine Law, Arzneimittelgesetz).

Therefore, generally speaking, the patients may use the Law on the Protection of Consumers and the secondary regulations on consumer protection as a legal remedy. There are also discussions on whether Article 71 of the Code of Obligations, which regulate the objective liability of those who carry out dangerous activities, may apply to the medicine manufacturers.

However, due to the complexity of medicinal preparations and the high risk posed due to the use of medicines, these general laws may not always give fair results. Therefore, some academics suggest a specific law regulating the medicine manufacturers' liability. It is generally suggested that such a law must regulate, among other issues, the conditions of proof of the causality link

between the medicine and the patients' damages and conditions of medicine manufacturers' objective liability.

11.2.9. Lack of Class Action

Class action, which is a type of civil lawsuit filed or defended by an individual acting on behalf of a group, does not exist in Turkey. Therefore, if high number of victims suffer from the same type of damages caused by a single party, each victim is required to file separate civil lawsuits for indemnification.

Although Turkish Law on Civil Procedure, Art. 113 provides for a "collective lawsuit", this only enables associations to file lawsuits for the determination of their members' or other relevant persons' rights in case if a violation. Still, each individual suffering from a certain violation is required to file separate lawsuits for damage claims.

Each patient being required to file a lawsuit individually creates an obstacle for satisfactory management of mass sufferings from product defects or adverse events.

11.2.10. Lengthy Legal Procedures And Lack of Fast-Track Dispute Resolution Mechanisms

Lawsuits for manufacturers' or HCPs' liability generally takes years to be resolved by the courts. Turkey has a consumer arbitration mechanism, which give quicker results. The consumer arbitration mechanism, however, applies only for damage claims below 8.480 TL (approx. EUR 1.400). As the patients' damages are much higher in many cases, the fast-track arbitration mechanism does not apply and the patients must go through lengthy court procedures.

11.3. Discussion & Results

To summarize, there are some ethical challenges surrounding the use of DMARDs for treatment of RA but these challenges are common to rheumatology and PTR as a specialty and clinical practice at large. The challenges of diagnosis, patient selection, initiation, monitoring, continuation and supportive care in RA using DMARDs are also seen globally and are not just unique to Turkish healthcare systems. Within DMARDs, bDMARDs generally necessaite additional precautions and monitoring by the healthcare professionals. csDMARDs may be safer than bDMARDs and are good choices for treatment initiation, their usage in long run presents challenge of treatment resistance and disease progression. In order to slow the disease and even potentially halt the

progression of the disease, it is now established that a combination of csDMARDs and selective bDMARDs regimen offer better clinical outcomes.

Turkey ensures universal access to healthcare to all its citizens and everyone diagnosed with RA has similar access to the best quality care regardless of the person's socio-economic-political background. All the DMARDs are made available to patients across the disease spectrum of RA with more administrative procedures for bDMARDs. There are good systems to collect and report information on adverse effects and there are good systems to safeguard patients' rights. There are however, certain limitations within the legal system that may not adequately complement the other support systems.

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12. ORGANIZATIONAL ASPECTS

12.1. Introduction

The domain of Organisational Aspects considers the ways in which different kinds of resources (e.g. material artefacts, human skills and knowledge, money, attitudes, work culture) need to be mobilised and organised when implementing a technology, and the consequences they may further on produce in the organisation and the health care system as a whole. Organisational issues include e.g. work processes and patient/participant flow, quality and sustainability assurance, centralisation, communication and co-operation, managerial structure, and acceptance of a technology.

There are three levels on which to consider organisational aspects: The first is intra-organisational (e.g. how information about a new technology is provided to the patients in the organisation), the second is inter-organisational (e.g. how the communication between different organisations occur), and lastly there is the health care system level (e.g. how to set national objectives). There are various stakeholders besides staff and patients/participants, at various levels, e.g. payers, providers and suppliers. These groups usually have different aims for and expectations of the technology.

The elements which constitute an organisation have been defined in many ways through different approaches; for example, the physical structure, social relations, technology and organisational culture. The structure of an organisation defines its assignment of tasks, reporting systems and the mechanisms of interaction and coordination. In addition, there are other elements of a society and its culture that influence an organisation and its function. There are also different types of organisations, e.g. the profit centre organisation, the matrix organisation and the network organisation.

12.2. Assessment

This domain includes 5 topics with each topic containing about 3-6 issues. Not all the topics are relevant for DMARDs and hence have been selected only those that are within the context of the DMARDs. The assessment of the DMARDs and the organizational aspects in DMARDs is based on the interviews with physician experts from Turkey – 3 of whom are rheumatology specialists and 2 people are representatives of the patients groups. We have included the following topics and issues in the evaluation.

Table 41. Areas of Assessment in Organizational Aspects of DMARDs

Topic	Issue	Information & Source
Health delivery process	How do DMARDs affect current process and structure of health care in Turkey for RA patients? Is there a demand for DMARDs? Who will use the DMARDs? What kind of process ensures proper education and training of staff in the use of DMARDs? What are the available means for quality assurance for the effectiveness of DMARDs and what are the monitoring systems for the safety of DMARDs?	From the experts and patients' representatives in Turkey
Structure of healthcare system	Impact of de-centralisation or centralisation needs on the prescription and use of DMARDs? What are the processes ensuring access to DMARDs for patients?	From the experts and patients' representatives in Turkey

	Are there any costs involved to set-up special systems for the prescription and use of DMARD?	
Management	Who decides which people are eligible for the use of DMARDs and on what basis? What are the management problems and opportunities?	From the experts and patients' representatives in Turkey
Culture	What is or will be the acceptance of DMARDs among people? How are other interest groups taken into consideration during the planning/implementation of DMARDs for RA in Turkey?	From the experts and patients' representatives in Turkey

In Turkey, there may be some delays in diagnosis in patients with joint complaints associated with RA. There is also some time delays between diagnosis and initiation of treatment with DMARDs. There is however, no special need for processes and infrastructure for the diagnosis and treatment of RA.

The treatment with synthetic DMARDs is based on a screening x-ray of chest, baseline liver and renal function tests and hepatitis markers. If DAS28 score is more than 5.1 after initial trial of synthetic DMARDs, bDMARDs or tsDMARDs are added to the initial therapy. Thus, the patient will have completed 10-12 months from the time of initiation of treatment with MTX.

All patients initiated on DMARDs especially bDMARDs are advised with regard to precautions on active lifestyle, exercise program, diet and work. They are also advised on follow-up during treatment for tests and other investigations once in 3 to 6 months.

Additionally, prior to initiation of treatment with bDMARDs, Pulmonary Diseases and / or Infectious Diseases specialist opinions are requested for screening patients for any latent tuberculosis and viral hepatitis.

Key persons deciding to use DMARDs are authorized persons of Health Application Communique (SUT). SSI also determines the criteria for using drugs by establishing commissions. Commissions are consisted of rheumatology, physical medicine and rehabilitation lecturers of the universities. There are certain documented criteria (TRASD and TRD guides), but decisions are taken by commissions made up of lecturers and authorized persons of legislation.

Use of supplementary detection methods in detecting eligible patients for the drug: For example patients with bad prognosis criteria: patients with seropositive RA or rheumatoid vasculitis (RV), patients with extra-articular involvement, presence of early erosive disease, consistently high ESR and CRP, and DAS28 >5.1

Criteria for patient in high risk group such as elderly and children: Patients who have difficulty in walking and cannot use their hands due to problems in their hands and feet joints; children with low percentile values and growth and development retardation; the elderly with the risk of falling and osteoporotic fracture

To assess tuberculosis risk before and during the bDMARDs, screening tests such as PPD screening test and Quantiferon TB test are used within the Tuberculosis Control Dispensary.

Patients are advised to receive adult vaccinations to protect them from any major infectious diseases prior to the start of the bDMARDs. This process of screening patients with the various specialists is done on an outpatient basis. However, in the event of any disease or treatment related complications, patients may need hospitalization and specialized inpatient care.

The pre-treatment review of patients is particularly intense for patients about to be initiated on bDMARDs. Storage of the bDMARDs is an important consideration, especially in remote and rural areas. bDMARDs need storage in cold chain in refrigerators with steady electricity supply. Patients are trained in the administration of bDMARDs by intramuscular or subcutaneous

injections by the nurse network and related clinics organized by the pharmaceuticals industry. They also ascertain full understanding by the patients by asking patients to demonstrate injection techniques. However, for those bDMARDs that are to be administered by the intravenous bolus or infusion route, the patients are asked to report to the clinic and hospitals. The nurses will then manage the administration of the drugs under the supervision of the physicians. However, such services often put additional burden on the hospital nursing services. Rheumatology clinics are obliged to establish infusion departments for this reason.

So, we can see that prescription, use and monitoring the treatment of RA patients with DMARDs can be done within the available healthcare infrastructure and manpower although bDMARDs may need care from specialised centers.

DMARDs are widely accepted and used as a standard for the treatment of the RA patients in accordance to the published guidelines in Turkey. Rheumatologists and PTR specialists are the main specialists in the management of RA patients. The care for RA patients is initially offered by primary care physicians and specialists in physical medicine and rehabilitation in Turkey. However, in matters of prescribing DMARDs for RA, in particular bDMARDs and tsDMARDs are generally preferred and prescribed by rheumatologists. The main reasons underlying this dilemma are; insufficient awareness of clinical guidelines, adverse event concerns with bDMARDs and lack of adequate knowledge and awareness of their management.

Often bDMARDs are under-prescribed by many physicians in Turkey, the main reasons being low awareness about the effectiveness of bDMARDs, patient preference for non-biologic treatments, preconcieved notions by the treating physicians and patients.

There are some limitations in patient education and involvement of family members in treatment decisions. Patients have expressed that they are often not well educated by the treating physicians about the drugs and their side effects and the overall plan of treatment. This may pose challenges in the adherence to treatment and also avoid myths and misconceptions about treatment. The specialists treating RA patients however, opine that considering the complexities of treatment in DMARDs, it is not often feasible to educate patients on all aspects of care. Besides, the specialists often are burdened with a lot of workload and it may not be possible for them to spend quality time on patient education away from their busy clinical practice. It is in this context that nurse educators and primary care physicians can be play a vital role in patient education by supporting patients

during their treatment with DMARDs. Nurse support programs may be organized by contracted institutions (i.e. Eczacıbaşı) in order for them to show practices due to current clinic burden. There are also channels for creating awareness among patients about DMARDs. Compared to bDMARDs, tsDMARDs are often taken orally just like any other medication. Patients should be informed to carefully monitor the side effects of tsDMARDs used orally. It is in this context, patient education outside of hospital environment becomes essential. All necessary information on DMARDs are being offered through call centers supported by pharmaceutical industry and patient associations. Today, information channels and communication strategies are uniform for all groups of the population. Patient associations are slowly on the rise in Turkey and they often play a great role in bridging the gap between patients and healthcare providers. However, there is a need for greater empowerment and resourcing of such associations.

As can be seen, there are well established systems for post-marketing surveillance and quality assurance. These systems are currently being used for tracking and monitoring drug quality and adverse drug reactions arising from DMARDs as well.

In Turkey, the first organized system for pharmacovigilance began in 1985. A fully structured adverse drug reaction (ADR)-reporting system was established with the publication of the first pharmacovigilance regulation in 2005. Subsequent regulation published in 2014 brought further improvements to the system.

In Turkey, pharmacovigilance activities started in 1985 with the establishment of the "Turkish Adverse Drug Reaction Monitoring and Evaluation Center" (TADMER) under the General Directorate of Pharmaceuticals and Pharmacy. In 1987, TADMER joined the WHO Programme as an official member. In 2005, first pharmacovigilance regulation, "Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use", became effective. With this regulation, TADMER conducts pharmacovigilance activities under the name "Turkish Pharmacovigilance Center" (TUFAM), in order to stress the term "Pharmacovigilance". In the regulation, major responsibilities of TUFAM were defined as: monitoring national ADR reports and drug safety alerts worldwide, communicating drug safety alerts to healthcare professionals, educating physicians and pharmacists on pharmacovigilance, conducting risk minimization methods, and assessing conformity of risk management plans and periodic safety update reports. Taking this first regulation as reference, responsibilities of Authorization Holders,

Pharmacovigilance Inspections and Structure of Risk Management Systems were addressed in detail in the guidelines published in 2005, 2009 and 2011, respectively. In 2012, the General Directorate of Pharmaceuticals and Pharmacy became an agency called the Turkish Medicines and Medical Devices Agency. With this structural change, a Risk Management Unit was formed to take over risk minimization activities. Since then, TUFAM has been concentrating on monitoring and assessing national ADR reports.

National ADR reports reach TUFAM from two major sources: healthcare professionals and marketing authorization holders (MAHs). Healthcare professionals can notify spontaneous reports to the TUFAM either directly or by means of the pharmacovigilance contact points (PvCPs) within the health organization that they are employed in. PvCPs are physicians or pharmacists who are responsible for encouraging the notification of ADRs, collecting and communicating information to TUFAM, and carrying out training and awareness activities at hospitals they work in. According to regulation, a PvCP should be assigned to work at university hospitals, training and research hospitals, and private hospitals with a bed capacity of 50 or more. This regulation was later expanded to cover all hospitals. This method is different from many countries, and has the intention of communicating information faster between TUFAM and health-care professionals.

MAHs are responsible for keeping the records of all suspected ADRs and notifying serious ADRs occurring in Turkey to the TUFAM within 15 days. They collect both spontaneous reports and solicited reports from patient support programmes where they receive and collect information relating to the use of their medicinal products. In Turkey, MAHs are also responsible for screening national and international literature for ADRs regarding the local population and forwarding a copy to TUFAM.

Spontaneous and solicited ADR reports reaching TUFAM from healthcare professionals and MAHs are sent to the VigiBase as ICSRs. In this way TUFAM contributes to the integration of world data on ADRs as intended by the WHO programme. In 2014, national pharmacovigilance regulation was revised in the context of harmonization with EU directives. With these new regulations, patient reports also started to be accepted and sent to the VigiBase by TUFAM. Additionally national ADRs mentioned in the literature started to be sent to the Vigibase if they complied with the requirements of an ICSR.

The treatment with bDMARDs is centralized in Turkey and is often rationed involving several administrative and clinical formalities. RA patients getting care in the public hospitals full either free treatment or reimbursement for the treatment. Early treatment of RA with csDMARDs is fully reimbursed in Turkey with proper documentation of disease progression. Disease activity scores for 28 joints (DAS28) are the key indicator to assess the response to the treatment. Treatment usually proceeds with the addition of a 2nd csDMARD or combination with a short trial of corticosteroids before starting a TNF-inhibitor. Addition of a bDMARD also needs to be documented by the relevant specialist for the treatment to be fully reimbursed by general health insurance. These drugs are reimbursed by Social Security Institution based on HCP committee reports issued in secondary and tertiary health care institutions.

In adult patients with RA bDMARDs are covered free of costs if the following condition are met:

1. At least three different DMARDs, one of which is methotrexate, have been used for at least three consecutive months each;
2. The disease activity was not be controlled (Disease Activity Score (DAS) 28 > 5.1), the drug is initiated based on a 3-month HCP committee report
3. If the DAS 28 score has decreased by more than 0.6 points after starting bDMARDs in the evaluation made 3 months after drug initiation, treatment with bDMARDs is continued for 3 more months, provided that this progress is specified in the updated HCP committee report. If the DAS 28 score decreases by more than 1.2 points at the end of 6 months, patients' treatment with bDMARDs can be continued, once again after documentation in the updated HCP committee report. Further continuation of bDMARD is determined on the DAS 28 criteria, which is examined every 6 months, while clearly documenting and noting the changes in the DAS 28 scores before each extension. If, despite the treatment with bDMARDs for 6 months, there is not more than 1.2 point decrease in patient's DAS 28 score in comparison to the initial DAS 28 score, then the treatment is terminated.

Additions/Exceptions to the above reimbursement condition for bDMARDS are:

4. Anti-TNF drugs can be prescribed based on an HCP committee report of maximum 6 months, issued by a committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist

from university hospitals or training and research hospitals, by any one of these specialists or by internists or pediatricians.

5. Patients who have had a disease relapse after a long period of time (longer than 3 months) free from DMARDs, they are required again to meet initiation criteria. In cases where two different Anti-TNF and/or two different bDMARDs are used together for two different diagnoses, they are not reimbursed by the Institution.

6. Tofacitinib can be prescribed based on an HCP committee report of maximum 6 months, issued by a committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists or by internists.

7. For Tocilizumab, all prescribing conditions are the same as Anti-TNF drugs and Tofacitinib, except initial prescription condition: In adult patients with RA, who have used at least three different disease-modifying anti-rheumatic drugs, one of which is methotrexate, or an Anti-TNF treatment for at least three consecutive months, but the disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1), the drug is prescribed based on a 3-month health report issued by an HCP committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists.

8. For Rituximab, in combination with methotrexate, in adult patients with active RA whose disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1) despite one or more Anti-TNF treatment(s) or who are not eligible for TNF inhibitor use or who have intolerance for TNF inhibitors, it is prescribed by rheumatology or clinical immunology or physical medicine and rehabilitation specialists based on an HCP committee report which indicates this condition. For the HCP committee report; in healthcare institutions where a rheumatology specialist is present, the HCP committee must include at least one rheumatology specialist; in university hospitals and training and research hospitals, the HCP committee must include at least one rheumatology or clinical immunology or physical medicine and rehabilitation specialist.

9. For Abatacept, in adult patients with active RA, if at least three different disease-modifying anti-rheumatic drugs, one of which is methotrexate, have been used for at least three consecutive months each, but the disease activity could not be controlled (Disease Activity Score (DAS) 28 > 5.1) despite at least one Anti-TNF treatment, it is prescribed with methotrexate based on a 3-month health report issued by an HCP committee which includes a rheumatology specialist from any health care institution or a clinical immunology or physical medicine and rehabilitation specialist from university hospitals or training and research hospitals, by any one of these specialists.

It is to be noted that most of the tsDMARDs can be prescribed by a majority of the physicians.

10. Methotrexate can be given in outpatient and inpatient treatment, based on health report (specialist report / HCP committee report).
11. Sulfasalazine and Hydroxychloroquine can be prescribed by all HCPs.
12. Leflunomide is prescribed by any one of internists, pediatricians or physiotherapy and rehabilitation specialists, based on a 1-year specialist report indicating this condition and issued by such specialists.

The key stakeholders involved in determining the prescription and use of DMARDs in RA are the patients suffering from RA, the physicians giving the treatment, care givers (usually family members of patients), pharmaceutical industry, social security system, healthcare professionals and NGOs. However patients does not participate much in drug evaluation process. It is noted that often patients are only included in the drug risk discussions but sufficient information is not provided to them about risks of the disease and positive effects of the DMARDs. This often leads to biased accumulation of information. It is important that professional and patient associations need a uniform understanding of reliable and unbiased information on both disease and DMARDs.

12.3. Discussion & Results

There is considerable knowledge and expertise available among the healthcare community in Turkey for care of RA patients. However, often patients feel that they are not involved in treatment decisions especially during advance disease and more complicated treatments. Patients feel that they need better information about the safety profile of DMARDs and how they can manage the side effects of the medications. Lack of such information often reflects in poor compliance to

treatments and treatment failure.There is a perception among the patient representatives that there are well established systems and processes to ensure the quality and safety of DMARDs before they are prescribed to patients. DMARDs by themselves do not require additional cost or infrastructure to deliver. Physicians caring for the patients with RA are followed established guidelines to screen patients for potential risk factors before administering DMARDs. After start of the therapy, DMARDs will need regular monitoring for adverse effects and disease progression. Currently, there are no shortage of facilities or expertise within Turkey for treatment monitoring and there is no additional burden put on other healthcare services. Since the DMARDs are administered either in oral form or through intravenous forms, most often patients themselves are capable of taking the medications after they have been thoroughly briefed. The system of pharmacovigilance in Turkey is well established to ensure a continuous monitoring of all adverse events arising from DMARDs. There are well established processes to determine the most appropriate price of the DMARDs to ensure equal access to DMARDs. However, biologic DMARDs have to be administered after a thorough evaluation and only after following specific procedures because of their higher costs. The administration of bDMARDs is more centralized and typically needs to be prescribed and treatment monitored by a specialist rheumatologist. This can sometime increase the costs of care, given the limited availability of specialist rheumatologists in rural and peripheral areas of the country and that such patients often have to travel to bigger cities for their treatment.

There is also a perceived need among patients and their representatives to improving patient education and involvement of patients and their care givers in the treatment decisions. This is more true for bDMARDs, which have higher treatment complications as well as often require special conditions for use and administration such as cold storage, knowledge of intravenous treatment, etc.

However, at an overall level, the healthcare systems in Turkey are fully evolved and well established for the use and implementation of DMARDs for the care of RA patients.

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13. PATIENTS AND SOCIAL ASPECTS

13.1. Introduction

The Patients and Social Aspects domain takes patients or individuals in whose care a health technology is used as a point of reference in an HTA. Patients Aspects relate to issues relevant to patients, individuals and caregivers. Patient refers to a person who receives (or has received) and uses (or used) health technologies and health services in the healthcare sector. The term individual is sometimes used synonymously with 'patient', but it can also refer to a healthy individual, who receives health technologies, e.g. a person taking part in a screening programme. The term caregivers (sometimes referred to as carers) refers to family, friends and other persons from the patient's/individual's social network, who provide care to the patient and are in other ways involved during the course of the disease. It excludes those paid to give care, such as healthcare professionals. Social Aspects are related to social groups, that is specific groupings of patients or individuals that may be of specific interest in an HTA, such as older people, people living in remote communities, people with learning disabilities, ethnic minorities, immigrants etc.

Patients, caregivers or individuals can provide unique perspectives about experiences, attitudes, preferences, values and expectations concerning health, illness, service delivery and treatments that can inform HTA. Patients, caregivers and individuals will have a range of perspectives and an HTA should seek to gather as much evidence as possible to understand these wide ranging views. There may be some social groups that are particularly important to consider for a specific health technology or for which there is a policy imperative for special consideration (such as those with disabilities) or in which the value of the technology may be different (such as ethnic minorities) and these may need to be specified. Hence social groups are also important consideration in HTA.

A technology may be implemented in a hospital or at home. However, implications for patients may extend far beyond the original setting of the technology. Patients and caregivers attribute specific meaning and significance to health technologies, to which they may attach feelings of hope, fear, perhaps uncertainty, as well as societal values. The assessment which looks at patients, individuals, caregivers and social groups is thus interested in all the above mentioned aspects. Since the focus of this domain is the patients and caregivers the views of citizens (that is citizen using health services but not having the condition under study) is not included in the Patients and Social Aspects domain, but is covered in the Ethical and Legal domain of the Core Model.

13.2. Assessment

This domain includes 3 topics and 8 issues. Again, not all the topics are relevant for DMARDs and hence we have selected only those that are within the context of the DMARDs.

Table 42. Assessment Areas in Patients And Social Aspects of DMARDs

Topic	Issue	Information & Source
Patients' perspectives	What are the experiences of living with the condition? What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology? How do patients perceive the technology under assessment? What is the burden on care-givers? In What way is the quality assurance and monitoring system of the new technology organised?	From the experts and patients' representatives in Turkey
Social group aspects	Are there groups of patients who currently don't have good access to available therapies? Are there factors that could prevent a group or person from gaining access to the technology?	From the experts and patients' representatives in Turkey

Communication aspects	How are treatment choices explained to patients? What specific issues may need to be communicated to patients to improve adherence?	From the experts and patients' representatives in Turkey

13.2.1. Social Burden of Disease And Access to Care

Patients diagnosed with RA live with constant pain that limits their daily activities. RA particularly affects fingers and toes, it affects everything all aspects of a patient – medical, psychological, and social, in other words all aspects of life we call "human". Morning pains and tiredness are reasons for a bad start to a day. Difficulty in self-care and daily housework is evident. Most of the complaints are difficulty in holding glasses due to swollen hands in the morning; difficulty in raising due to painful wrists; difficulty in sitting on and standing up the toilet bowl due to knees hurting and difficulty in walking in the morning due to inflammation in the toes. Patients often refrain from their social commitments because of the pains. Such isolation may often decrease their self-confidence and increase their fear of dependence upon others for basic needs. Painful episodes lead to loss of productivity, loss of wages and periods of unemployment putting financial burden on the individual. Given such severe implications from the disease, it is only but natural that patients expect DMARDs to eliminate the symptoms of RA without creating any side effects and protect the life quality. In this respect, it is significant to remove the pain and loss of functionality in RA. Physical symptoms which are more distressing, if relieved, also tend to improve the emotional pain too.

After the confirmation of diagnosis of RA, when physicians inform the patients that they may have to take medications for "a lifetime", it often brings a sense of helplessness and hopelessness among the patients. This feeling is often difficult to overcome and it takes serious efforts by the treating physician to counsel. Although DMARDs have mild or moderate side effects, nausea of methotrexate is an unforgettable memory for most of the patients even though the drug is discontinued. The fact that DMARDs suppress the immune system more or less occupies a significant place in the memories of the patients and exploited by those favouring treatment of RA

by traditional herbal treatments and against DMARDs. DMARDs must continue being used also after the complaints of the patient are relieved. Patients easily forget the painful times at the beginning and think that the drug they are using is not efficient. As the effects of DMARDs continue for 1.5-4 months after the drug is discontinued, some of the patients think that they have been using the drug redundantly when the drug is temporarily discontinued. Using the DMARDs as injection/infusion is harder than oral intake. Hepatic toxicity is one of the major risks of these drugs.

As RA particularly affects middle-aged group, it is not immediately a disabling condition and can be often managed with self-care. However, considering the mental and social impact of the disease, the support of family, friend and workplace colleagues is necessary particularly during periods of increased disease activity. The more the family members and relatives are informed about the disease and drugs, the better they can adapt the expectations of the patients.

There are no differences among individuals with respect to access to DMARDs in Turkey. However, there are regional differences in terms of accessing rheumatologists due to their small number. PTR specialists trained in the rheumatology section of the PTR curriculum in TUKMOS can manage the DMARD treatment process. bDMARDs may be prescribed only by rheumatologists and PTR specialists. bDMARDs are considerably expensive drugs; however, SSI reimburses 100% of the drug costs for RA patients whom are issued report by the hospital's health committee. There is review of the disease progression every 3 months to determine continuation of the treatment and addition of other DMARDs.

13.2.2. Communication Aspects And Impact on Adherence to Treatment

RA patients are given information about DMARDs when such drugs are necessary. Patient knowledge increased as education level increased.

For chronic diseases such as RA, sufficient information is very important for increasing patient compliance with treatment and willingness to take preventive precautions. Therefore, patient education is an integral part of RA management. Several studies have demonstrated increasing knowledge through patient education decreases RA disabilities.

A study conducted by Bozbas and Gurer (2018) among RA patients in Turkey found that Turkish patients' have inadequate knowledge about the disease, and did not have sufficient information about the relationship between RA and exercise, as a result, many Turkish patients in this study

did not regularly exercise (14). There were some more findings from this study which shed more light on the importance of good communications in the treatment process and what determines the knowledge levels of patients. It was also found that the level of patient knowledge decreased with age. Knowledge was positively influenced by education level and socioeconomic status. Knowledge levels of patients who had a family history of RA were higher compared to those who did not. Furthermore, the duration of disease also influenced the knowledge levels wherein patients with short duration of disease tend to be more receptive to receiving education about the disease and treatment more than patients with longer duration of disease. There was no difference between awareness levels of those patients who used conventional DMARDs and bDMARDs.

However, this period is not long under the conditions of hospitals. It is not also practical to explain them to the patients one by one. Therefore, such information should be given via patient hospital or patient meetings. Patient associations should be active in this area. As indicated above, training may be given outside the hospitals if SSI accepts patient associations as its partner with respect to training of the patients and use its resources allocated to such training via patient associations. Today, patient training events are insufficient with respect to DMARDs.

13.3. Discussion & Results

RA which is mainly a disease of old age has been noted in ancient as well as from the beginning of modern medical literature. However, the correct categorization of the disease happened only after invention of molecular diagnostic techniques, which further paved way for innovations in treatments.

The ultimate measure of success of any health technology is the impact it has on the social and economic life of patients using it. The invention of DMARDs has been a turning point in the historical management of RA and have since then helped to successfully manage RA. These medications, especially the newer generation bDMARDs have helped to significantly reduce the suffering from RA. We have not noticed any significant social or economic barriers faced by RA patients while accessing DMARDs in Turkey.

In Turkey, there is no distinction or discrimination between individuals generally for access to medicines and this is no different when it concerns the access to DMARDs for treating RA. Everyone has equal access to medicines. Equality and access to quality healthcare is assured to the

citizens within the Turkish Constitution. The social security insurance provides coverage for most patients within Turkey and included medicines that are already approved for market authorization within Turkey as well as medicines that are not yet approved for marketing in Turkey. This effectively means that RA patients can have access to all the relevant and quality medicines without having to worry about their availability or affordability.

Patient are informed about DMARD when DMARD are initiated. Notwithstanding the strong provisions within the healthcare system for equitable access to care, there remain concerns with regard to effective communications between physicians and patients. Studies have demonstrated that the knowledge and awareness levels in patients on RA and about DMARDs generally is low, which may have an adverse impact on the ultimate adherence to treatment and outcomes. There is a need to further revisit and strengthen the communication strategies to ensure other physicians, nurses and family members of the RA patients are also adequately engaged in the care continuum. This will also need more involvement of private sector pharmaceutical and patient associations in the healthcare delivery process.

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14. LEGAL ASPECTS

14.1. Introduction

The objective of the Legal Aspects domain is to assist the decision makers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of implementing a health technology. Rules and regulations have been established to protect the patient's rights and societal interests. The rules and regulations may be a part of patient rights legislation, data protection legislation, or health care personnel's provisions, rights and duties in general. The market access authorisation or -regulation processes have not been the direct focus of HTA earlier, but this may be subject to change in the future.

14.2. Assessment

This domain has 7 topics and about 15 issues. Only the relevant ones are included here

Table 43. Assessment Areas in Legal Aspects of DMARDs

Topic	Issue	Information & Source
Autonomy of patient	What kind of legal requirements are there for providing appropriate information to the user or patient and how should this be addressed when implementing the technology? Who is allowed to give consent to minors and incompetent persons?	Relevant legislations enacted in Turkey and inputs from experts
Privacy of patient	Is there a possibility that the use of DMARDs produces additional information that is not directly related to the current care of the patient and may violate their right to respect for privacy?	Relevant legislations enacted in Turkey and inputs from experts

	What do laws/binding rules require with regard to informing relatives about the results? What do laws/binding rules require with regard to appropriate measures for securing patient data and how should this be addressed when implementing DMARDs?	
Equality in health care	What do laws/binding rules require with regard to appropriate processes or resources which would guarantee equal access to DMARDs?	Relevant legislations enacted in Turkey and inputs from experts
Authorisation and safety	What do laws/binding rules require with regard to safety of DMARDs and how should this be addressed when implementing DMARDs?	Relevant legislations enacted in Turkey and inputs from experts
Ownership and liability	What should be known about the intellectual property rights and potential licensing fees?	Relevant legislations enacted in Turkey and inputs from experts

14.2.1. Autonomy of Patient & Patient Rights

a. Patient Rights in Ancient Medicine

The topic of patients' rights although is seeing a relatively new start in Modern Turkey, it has its basis in the code of conduct laid within the Hammurabi's Code of Laws. For example, in Hammurabi's law, if the physician killed a patient for his own misconduct, his hands would be cut off (1).

Compliance with the rules of medicine written in Ancient Egyptian texts meant that physicians could practice medicine with skill competence and without fear of persecution. In Roman Law, the physician could be held accountable for negligence and inexperience (2).

b. Patient Rights in Modern Medicine

Thinking and consideration for patients' rights grew fast after the United Nations adopted the Universal Declaration of Human Rights in 1948 and included the rights of patients in the 3rd General Assembly of the World Physicians Association in the 'International Medicine Code of Medicine' adopted in London in October-1949 (3). In the United States of America (USA), in 1969, within the framework of the revision of the standards related to hospitals, the subjects such as confidentiality, information, informed consent (consent), and equal and humane treatment of patients were discussed. In 1973, the American Association of Hospitals published the Declaration of the Patient Rights. This declaration is regarded as the first modern approach in the world on patient rights. The European Union (EU) refers to the fundamental rights of the patients within the chapter 'EU Charter of Fundamental Rights EUROPA, Article 35, Section 3 and 4 of Part 1 of the Charter of Fundamental Rights of the European Union, signed on 7 December 2000 in Nice, France. This charter concerned health and patient rights, so that for the first time the EU has emphasized patient rights at an organizational and continental level (3).

In today's legislation, it is seen that laws and international conventions have changed within the process in line with the developing technology and medical science and that human and patient rights are becoming more important with each passing day. The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine ("Human Rights and Biomedicine Convention") is an international instrument aiming to prohibit the misuse of innovations in biomedicine and to protect human dignity. The Convention was opened for signature on 4 April 1997 in Oviedo, Spain and is thus otherwise known as the Oviedo Convention. The International treaty is a manifestation of the effort on the part of the Council of Europe to keep pace with developments in the field of biomedicine; it is notably the first multilateral binding instrument entirely devoted to life sciences (4,5,6).

The Convention entered into force on 1 December 1999 and remains the first binding text on patient rights in Turkey (7,8,9).

c. Patients' Rights in Turkish Constitution And Laws

The rights of patients as specified within the Turkish Constitution are summarized below (10)

- The right of the patient to request information on his/her own health,
- The right of the patient to choose and change the health institution,

- The right of the patient to recognize, select and change the staff,
- The right of the patient to request the order of priority,
- The right to diagnosis, treatment and care of the patient according to medical requirements,
- The right of the patient to prohibit information;
- The right not to be kept under medical supervision without the consent of the patient,
- The right of the patient to refuse and stop treatment,
- The right to consent and consent of the patient for medical treatment,
- The right to respect for the privacy of the patient,
- The right to patient safety,
- The patient's application, complaint and right of proceedings

The most important consideration from a legal perspective is that patients should enough mental understanding about his/her health condition and to the treatment that is being offered to him / her. This understanding is absolutely essential for the patient to freely exercise his/her right to appropriate treatment as well as the right to refuse or stop treatment if they are not convinced about the benefit they will derive from the treatment. The basis of such an understanding is a fully functional and mature mental faculty.

The Turkish Civil Codes 9-14 provides guidance on who qualify as having legal capacity as specified below (11, 12):

Turkish Civil Code 9: *The person having legal capacity may possess any right by his/her own will and may undertake any obligation.*

Turkish Civil Code 10: *Every adult person possessing distinguishing power and not in the state of disability is deemed to possess full legal capacity.*

Turkish Civil Code 11: *Adultness begins with 18 years of age.*

Turkish Civil Code 12: *Infant completing the age of fifteen may become adult by his/her own will or under parent's consent subject to court decision*.

Turkish Civil Code 13: *According to this law, every person who is not minor, or mentally defective or suffering from mental illness, or intoxicated, or beyond self-control by similar reasons, is deemed to possess capacity of judgment.*

Turkish Civil Code 14: *Infants and persons who are in a state of disability or lack of the capacity of act do not have legal capacity.*

Legal capacity has been further explained in detail below:

- Under Turkish Civil Code, legal capacity means a person's ability to possess any right by his/her own will and to undertake any obligation thereof. Legal capacity can be defined as the ability to understand the purpose, results, scope and effects of the actions of individuals and to take decisions accordingly.. Adults having distinguishing power and not in the state of disability is deemed to possess full legal capacity.
- Adultness begins with completing age of 18.A person may be accepted as an adult below the age of 18 years only in the following three circumstances:
  - ✓ First: If a person reached the age of 17 years and is married with the consent of the legal representative,
  - ✓ Second: If a person completed age of 16 years and allowed to get married by a court in the event of extraordinary circumstances and reasons of high importance. In this case, if possible, court will hear the mother, father or legal guardian before the court decision.
  - ✓ Third: If a person completed age of 15 years, accepted adult with a court verdict pursuant to her/his will and the consent of the parent.

  In the above situations, the persons are considered as having legal capacity to exercise distinguishing power.

  - Distinguishing power means having self-control due to not being minor, or mentally defective or intoxicated or not suffering from mental illness, or similar reasons.
  - Incompetency means to be placed under guardianship by the court due to mental illness or mental defectiveness, extravagance, addiction to alcohol or drugs, inappropriate way of living, maladministration of the assets, imprisonment, or if a person demands and proves that he/she is not capable of conducting his/her businesses properly due to elderliness, disability, inexperience or serious disease.

According to the above legal provisions, any person having legal capacity can make a decision on the treatment or technology to be applied to him/herself. It is important to note that medical interventions, which are intended for medical research only, cannot be applied to minors, and

therefore such a treatment or technology to be applied should be in the best interest of the patient, even with the permission of the parent. Regarding this situation, which has been accepted and signed by the Patient's Rights Regulation in Turkey, there are clear regulations on Human Rights and Biomedicine Convention.

Regulation on Patients' Rights Article 35: Medical interventions for the purpose of medical research cannot be applied to underaged and non-deprived persons without clarifying its benefits. The matter of benefit from the medical intervention is subjective and will need to be decided by the minors and by the parents or legal guardians of majors who lack of distinguishing power. In cases where no consent is given by the legal representative, the second paragraph of Article 24 shall apply.

Human Rights and Biomedicine Convention Article 6:

1. A person who is not capable of consenting to medical treatment may, in accordance with Articles 17 and 20 mentioned later, then the medical treatment of such individuals will be done only if there is a clear and immediate benefit from the treatment
2. A minor who does not have the legal capacity to consent to an intervention may be offered such a medical intervention only with the permission of his/her legal representative or the competent authority, person or institution designated by law. The idea of the minor should be taken into account as a decisive factor increasing in proportion to the age and the degree of maturity
3. If an adult is not legally capable of consenting to an intervention due his/her mental illness, illness or similar reasons, such an intervention may be offered only with the permission of a legal representative or a competent authority, person or institution designated by law to represent such a person. Such a legal representative will participate in the treatment decisions as much as possible
4. The information referred to in Article 5 shall also be given to the representative, the competent authority, the person or the institution referred to in paragraphs 2 and 3 above in similar circumstances
5. The permission referred to in paragraphs 2 and 3 above may be withdrawn at any time if it is more appropriate to the interest of the person concerned.

14.2.2. Informed Consent For Medical Treatments in Turkey

The Human Rights and Biomedicine Convention Article 7 covers this aspect:

Medical interventions can be offered in persons who cannot provide an informed consent because of severe mental illness who is not capable of providing a valid consent and if the medical intervention is aimed to treat his mental illness or where not providing such a treatment will pose a serious danger to his/her health.

In order for any medical intervention to be in accordance with the law, the patient must have consent. However, the patient should also be able to understand what he consents to and knowingly consent to the results. For this reason, the patient must have the capacity to think and act, before allowing the treatment or technology to be tested on him/her. It is called alternative informed consent. Such a consent is obtained by educating the patient in such a way that the patient has adequately understood both the disease and the treatment in terms of benefits, risks and alternatives.

The basis of the mandatory informed consent before any medical intervention is mentioned explicitly in the Turkish Constitution article 17/2 which states that the physical integrity of the person shall not be touched, except in the case of medical obligations and law.

The Turkish Constitution remains the sole basis for all legal and other statutory provisions on patients' rights and for this reason, any law, international treaty, decree, statute or regulation in Turkish law cannot be against the Constitution.

Human Rights and Biomedicine Convention Article.5: Any intervention in the field of health may be made only after the person concerned has given free and informed consent to this intervention. This person should be given appropriate information in advance on the purpose and nature of the intervention and its consequences and hazards. The person concerned may at any time, freely withdraw his consent.

The matter of informed consent is further guided by a decision taken by the Turkish Supreme Court in 1977 wherein there is mention of consent by consensus. This decision underscored the importance of making available sufficient information, time allowed to process this information, free will and voluntary decision-making capacity for the patients to be an integral element in any decision-making process. While securing informed consent by inclusion of all the above

considerations is not always practical (consider medical emergencies where time is of essence and the person may not always be in mentally stable condition to provide consent), the courts often highlight the importance of patient education and that either the treatment or the treatment provider should not do more harm to the patient's health.

14.2.3. Privacy of Patients And Data Protection Laws in Turkey

Physician–patient privilege is a legal concept, related to medical confidentiality, that protects communications between a patient and his or her doctor and the personal information collected by the physician from being used against the patient in court. It is a part of the rules of evidence in many common law jurisdictions. Almost every jurisdiction that recognizes physician–patient privilege not to testify in court, either by statute or through case law, limits the privilege to knowledge acquired during the provision of medical services. In some jurisdictions, conversations between a patient and physician may be privileged in both criminal and civil courts.

The exception is the mandatory provisions of the law. For example, it is imperative that a patient carrying one of the infectious diseases mentioned in the law be required to be notified and should be notified as soon as the disease is detected. At this stage, it does not matter whether the patient does not want this information to be reported.

The confidentiality of the patient's personal information is evaluated within the context of the patient's privacy. It is essential that any medical intervention applied to the patient is carried out in an environment which offers adequate privacy to the patient. If the information that is obtained as a result of the medical intervention applied to the patient should be documented and any other institution, legal / legal representative, attendant or physician should be contacted, all measures should be taken to safeguard the confidentiality of data to persons and institutions who are not in need for this information. The protection of personal data is of high social and economic importance at the international level due to globalization and increasing data traffic between countries. Keeping patients' information in secure digital environments together can also allow sharing of non-personal information about the patients' health condition and treatments for the purpose of improving research without having to share personal identifiable information which is not related to the patient's treatment. For this reason, efforts to harmonize the countries' data protection legal infrastructure have increased in recent years. and international conventions have been prepared. International regulations on the protection of personal data are as follows:

- The European Union's directive 24 October 1995 on the Protection of Real Persons in the Processing of Personal Data and the Free Movement of these Data.
- The EU General Data Protection Directive adopted in 2016 and the EU Charter of Fundamental Rights (13,14,15).
- In addition, the matter of patient privacy is highlighted in the various regulations on patient rights mentioned below.

Patient Rights Regulation Article 15 states

"Following information shall be provided to the patient in an appropriate environment with respect to patient privacy:

a) Possible causes and course of disease

b) By whom, where and how medical intervention will be performed and estimated time,

c) Other diagnose and treatment options and benefits and risks of such options and possible impacts on the patient's health

d) Possible benefit and risks in the event of rejection

e) Important specifications of the drugs to be used

f) Life style recommendations critical to health

g) The way to reach medical treatment in the same issue when necessary

Patient Rights Regulation Article 18/3 States

"It is essential to inform the patient himself. In the event that the patient requests that someone else, not the patient, to be informed, only those who are required to be informed shall be informed provided that such request is recorded in writing with the signature of the person."

Patient Rights Regulation Article 20 States

"Except as required by the provisions of the relevant legislation and / or the measures to be taken by the competent authorities; the person may request that he / she, his / her relatives or no one is informed about his / her health. In this case, the decision of the person shall be obtained in writing. The patient may change his / her request at any time and request information."

Patient Rights Regulation Article 21 States

"It is essential to respect the privacy of the patient. The patient may explicitly demand protection of privacy. All medical intervention shall be performed by respecting the privacy of the patient.

The right to privacy and to demand it consists as follows:

- To conduct the medical evaluations related to patient's healthcare in confidentiality
- To carry out examination, diagnosis, treatment and other procedures requiring direct contact with the patient in confidentiality

Patient Rights Regulation Article 23 States

The information obtained due to the providing of health services cannot be disclosured in any way except as permitted by law.

Patient Rights Regulation Article 24/1, 24/2 and 24/7 elaborate the consent process during medical interventions:

Medical interventions require consent of the patient. If the patient is minor or incompetent, permission is taken from his / her parents or guardian. This requirement does not apply if the patient has no parent or guardian or they are not present, or the patient has no ability of expression.

Even if the consent of the legal representative is sufficient, the participation of the patients, who are minor or incompetent, to the decision about his / her treatment must be ensured, to the extent possible, by informing the patient in a way that they can understand and listening to them. (…)

In the presence of an emergency situation where the patient is in a life-critical condition or has a risk of loss of an organ or dysfunction of an organ, is unconscious and his / her consent cannot be obtained, medical intervention is not subject to consent. In this case, the medical intervention shall be made and the case shall be recorded. In this case, however, if possible, the relative or legal representative of the patient who is present shall be informed; if no such person is present, the relative or legal representative of the patient must be informed after the medical intervention. However, the consent of the patient must be sought after he / she becomes conscious

Medical Deontology Regulation Article 4 States

"Doctors or dentists shall not disclose, except otherwise required by law, the information obtained with the occasion of its profession or art."

14.2.4. Data protection laws in Turkey

In Turkish regulations, this is covered within the Law on Patient Rights and the Protection of Personal Data. Violation of the provisions of the protection of personal data also took place as a criminal offense under the Turkish Penal Code (12,16,17,18,19).

Personal data definition is made as follows in EU General Data Protection Regulation.

Personal data is any information that enables a person to be identified individually. This may be a single piece of information, as well as a number of interrelated information. A person's name, address, identification number, date of birth, photograph, registration number of the vehicle if any, credit card numbers, fingerprints, IP address, health reports are examples that can be given to personal data.

On 7 April 2016, a new law on the protection of personal data came into force in Turkey, Data Protection Law 6698 (Data Protection Law). It is the first law of its kind, regulating the protection of personal data, and also introducing many new obligations that persons or entities dealing with personal data (data controllers) must comply with.

Until 2016, the protection of personal data, except for certain regulated sectors, was regulated by a single provision in the Turkish Constitution and a few provisions in the Turkish Penal Code. None of those provisions were adequate in responding to the needs of increasingly complex technology and the amount of personal data processed and transferred each day. In comparison to the previous applicable legislation, the Data Protection Law is a modern law aiming to respond to the requirements of the constantly increasing volume of personal data that is collected and processed.

This Data Protection Law is a step towards harmonising the Turkish legislation with EU legislation, and it was prepared based on Directive 95/46/EC on data protection (Data Protection Directive). This new Data Protection Law though is similar to the earlier Data Protection Directive, it is not a complete replica and, in relation to the Turkish Data Protection Law, the differences between them may be seen as deficiencies rather than improvements.

Furthermore, the EU has introduced new legislation on the protection of personal data in the form of Regulation (EU) 679/2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation

(GDPR)), and is repealing the Data Protection Directive. As a result, the Data Protection Law is now further away from its EU counterpart, yet still closer than where Turkey would have been had it not introduced a law on the protection of personal data.

In 2017, Turkey saw a lot of important activities in terms of personal data:

The Personal Data Protection Board (Board) was established. A number of guidelines were issued in relation to the various concepts set out in the Data Protection Law. Three regulations (that is, secondary legislation under Turkish law) were prepared by the Board and came into force in 2017. The three regulations issued so far are as follows:

1. Regulation on Data Controllers' Registry;
2. Regulation on Erasure, Destruction and Anonymisation of Personal Data; and
3. Regulation on Working Principles of the Data Protection Board.

Discuss briefly the different aspects of this new legislation focusing on the provisions for protection of personal data in Turkey. The obligations discussed apply to both data controllers inside and outside of Turkey when processing the personal data of the residents in Turkey.

14.2.5. Important Concepts & Definitions in The Turkish Data Protection Law

One of the most important developments brought about by the Data Protection Law is that it provides official and generally applicable definitions for some of the most important concepts related to the protection of personal data. The concepts and their related definitions are as follows:

14.2.6. Personal Data

This is defined as any type of information that relates to an identified or identifiable individual. Before the Data Protection Law was enacted, there was discussion as to whether information related to legal entities can be categorised as personal data. The new definition of personal data put an end to that discussion by stating that only individuals (natural persons) can have personal data.

a. Sensitive personal Data

This is limited to only the types of data as listed in the definition. Sensitive data has been defined as data relating to:

- Race

- Ethnic origin
- Political beliefs
- Philosophical beliefs
- Religion, denomination or other faiths
- Clothing and attire
- Membership of an association, charity or union
- Health status
- Sexual life
- Criminal convictions and security measures
- Biometric and genetic data

b. Explicit Consent

This is defined as consent that relates to a specified issue, declared by free will and based on information.

c. Processing of Personal Data

This is defined as any type of action made using personal data.

Data Controller

This is defined as the real or legal person that determines the objectives and tools of processing of the personal data, and is responsible for the establishment and management of a data recording system.

d. Data Processor

This is the real or legal entity that processes the personal data, with the authority bestowed by the data controller, and in the name of the data controller.

e. Processing Personal Data

Legal Ground for Processing Non-Sensitive Personal Data

The Data Protection Law provides that the general rule for the processing of personal data is that such data can only be processed only with the explicit consent of the data subject.

The definition provides that not all kinds of consent will suffice under the Data Protection Law. The data subject must know for what he is providing consent, and the consent must be explicit.

For example, consent obtained in English from non-English speakers in Turkey would not be considered to be explicit consent.

f. Concerns About The Explicit Consent

After clarifying that obtaining consent is the general rule for processing of personal data, the Data Protection Law provides additional legal grounds that allow the data controller to process personal data without the explicit consent of the data subject. This raises doubts as to whether the explicit consent is the preferred legal ground for processing personal data. However, taking into consideration the fact that the Turkish Constitution does not discriminate between explicit consent and any other legal ground for processing personal data, the structure adopted by the Data Protection Law must be accepted.

g. Additional Legal Grounds That Do Not Require Explicit Consent

Personal data can be processed without the explicit consent of the data subject in the following circumstances:

- If clearly proposed under laws
- If mandatory for the protection of life or to prevent the physical injury of a person, in cases where that person cannot express consent or whose consent is legally invalid due to physical disabilities
- If necessary for and directly related to the establishment or performance of a contract, and limited with the personal data related to the parties to the contract
- If mandatory for a data controller to fulfil its legal obligations
- If the data is made manifestly public by the data subject
- If mandatory for the establishment, exercise or protection of certain rights
- If processing the data is mandatory for the legitimate interests of the data controller, provided that the fundamental rights and freedoms of the data subject or any related person are not compromised.

h. Legal Grounds For Processing of Sensitive Personal Data

All sensitive personal data can only be processed only with the explicit consent of the data subject.

In terms of additional legal grounds for processing such data, the Data Protection Law divides sensitive personal data into two categories:

1. Personal data on health or sexual life
2. "Other" sensitive personal data.

Personal data related to health or sexual life is protected more strictly than other sensitive data, as the scope of the additional legal grounds for processing is very limited. In addition to the requirement to obtain the explicit consent of the data subject, personal data related to health or sexual data can only be processed by persons under an obligation of confidentiality, or by authorised institutions and establishments, for the purposes of:

- Protection of public health.
- Protective medicine.
- Medical diagnosis.
- Treatment and care services.
- Planning and management of health care and financing

For other types of sensitive personal data, these can only be processed if such processing is allowed under Turkish laws.

Additionally, the Data Protection Law provides that for the processing of sensitive personal data, "sufficient measures" as determined by the Board must be adopted.

However, it is necessary to highlight that the tight regulations and legislations that limit processing health data can create challenges for healthcare research and other sectors.

i. Data Transfer to a Third Party

Sensitive and non-sensitive personal data can be transferred to third parties if the explicit consent of the data subject is obtained or if one of the additional legal grounds mentioned above is applicable for such transfer (see above, Additional legal grounds that do not require consent).

Responsibilities of data controllers or people who collect such data in relation to safe custody of personal data from patients

1. Obligation to Erase, Destroy or Anonymise The Data

If the reason(s) for processing the data are eliminated, any related personal data must be deleted, destroyed or anonymised automatically by the data controller or on request by a related person (Article 7, Data Protection Law). Therefore, data controllers must establish an infrastructure where the reasons for processing data can be monitored and assessed regularly. To address this, the Board has issued Regulation on Erasure, Destruction and Anonymisation of Personal Data. Under the Regulation, every data controller must prepare and put into force an internal policy for the erasure, destruction and anonymisation of personal data. This internal policy should create a regular monitoring system of all of the personal data kept by the data controller. The regular monitoring should be made at intervals of six months or less. At each monitoring session, the data controller must determine whether the legal grounds for keeping the personal data still exist. If there is any personal data for which there is no legal ground for keeping, the relevant personal data must be erased, destroyed or anonymised.

2. Obligation to Inform The Patients

Under the new Data Protection Law, data controllers are obliged to inform the data subject when they process their personal data. Within the framework of this obligation, the data controller must inform the data subject of the:

- Identity of the data controller and its representative (if any).
- Purpose of processing the data.
- Legal grounds for collecting and processing the personal data.
- Method for collecting the personal data.
- Rights of data subjects provided under Article 11 of the Data Protection Law (see below).

Data controllers who do not fulfil the obligation to inform data subjects can be subject to an administrative fine of between 5,000 TL and 100,000 TL. Additionally, data controllers must establish necessary communication and monitoring systems for the exercise of rights granted to related persons in accordance with Article 11 of the Data Protection Law.

3. Data Safety Obligations

Data controllers are obliged to adopt all kinds of technical and administrative measures to (Article 12, Data Protection Law) including but not limited to:

- Prevent the illegal processing of data.
- Prevent unauthorised access to data.
- Provide safekeeping of personal data.

A data controller that authorises a third party to process personal data will be jointly responsible together with the data processor in relation to the adoption of these administrative and safety measures. If the measures are not adopted, the data controllers will be liable for an administrative fine of between 15,000 TL and 1 million TL.

In the case of a data breach, the data controller must notify the unauthorised access to both the related data subject and the Institution of Protection of Personal Data as soon as possible.

4. Obligations Related to Complaint Applications

Under the Data Protection Law, data subjects can file complaint applications in relation to data controllers and to compel them to carry out their obligations under the Data Protection Law. The application must be in writing or in any other means, as to be determined by the Institution, to the data controller (Article 13, Data Protection Law). The Data Protection Law states that these applications must be concluded within a maximum period of 30 days. Following the assessment of the application by the data controller, the response (whether positive or negative) will be delivered in writing or through electronic medium.

5. Data Officers Registry

An obligation to register in the Data Controllers Registry has been introduced for data controllers (Article 16, Data Protection Law). However, although the Data Protection Law has introduced this new obligation, the details of how this obligation will be implemented were not clear until the end of 2017. On 30 December 2017, the Board issued a Regulation on Data Controllers' Registry, which provided the details of the obligations that the data controllers must comply with in terms of the Data Controllers' Registry. With this Regulation, it became apparent that the obligation to

register with the Data Controllers' Registry was not a simple notification to an online registrar but a set of obligations with a detailed preparation process.

6. Data Inventory

The first and most important obligation regarding the Data Controllers' Registry is that a data controller must prepare a personal data inventory before registering. The inventory will then be accessible online through the website of the Data Controllers' Registry.

Every data controller must make a thorough review on its activities, determine where it uses personal data in any way and make a list of the following issues for each personal data process:

- The purpose of processing activity.
- The category of the personal data.
- The recipient group.
- The data subject group.
- The maximum retention period.
- Whether or not the personal data is to be transferred abroad.
- The precautions taken for data security.

The second important obligation related to the Data Controllers' registry is that the data controllers must appoint either a contact person or an authorised representative based on whether the data controller is based inside or outside of Turkey.

The data controllers' residing in Turkey must appoint an individual as a contact person. It is important to note that the Turkish subsidiaries of foreign companies fall under this category, if such subsidiaries process personal data (however minimal their workforce in Turkey is). This individual's name and contact details will be published online and they will be responsible for establishing the communication between the data subjects and the data controllers.

The data controllers residing outside Turkey must appoint a representative. The representative can be either a legal entity or an individual. The appointment of the representative must be made with a resolution of the data controller, which needs to be notarised and apostilled (or otherwise

legalised). The representative will act as a point of contact for the data controller in relation to its dealings with the Board, the Data Protection Authority and the data subjects.

Data controllers that do not fulfil the obligation to register with the Data Controllers Registry will be sentenced to an administrative fine of between 20, 000 TL and 1 million TL.

7. Rights of The Data Subjects

Article 11 of the Data Protection Law provides certain rights to data subjects, which data controllers must abide by. A data subject has the following rights:

1. To know whether or not their personal data is processed
2. To know how their data is processed
3. To know what the purpose of the processing is, and whether or not the data is being processed in accordance with these purposes
4. To know of any third parties located inside or outside Turkey to whom their personal data is transferred
5. To request the correction of incomplete or inaccurate information
6. To request erasure of their personal data in case the legal ground for processing the relevant personal data does not exist anymore
7. To ensure that their request for the correction and erasure of their personal data are notified to the third parties to whom their personal data has been transferred (see above, Responsibilities of data controllers related to personal data, Obligation to erase, destroy or anonymise the data)
8. To object to any negative results produced through a fully automated processing of their personal data
9. To request compensation if they suffer damage due to processing of their personal data that is contrary to the law

14.2.7. Equality in Healthcare

In Turkey, there is no distinction or discrimination between individuals generally for access to medicines and this is no different when it concerns the access to DMARDs for treating RA.

Everyone has equal access to medicines. As shown in earlier section, equality and access to quality healthcare is assured to the citizens within the Turkish Constitution.

If a certain medicine does not yet have a marketing authorization or not available in Turkey, it can also be procured from abroad. Any medicine that is not available in Turkey and if required to be procured from abroad, must be prescribed by a licensed physician and its supply must be approved by the Ministry of Health. Then, the patient must apply to the Turkish Pharmacists Union for its procurement from abroad. Turkish Ministry of Health has a list of approved medicines for supply from abroad ("Abroad Drug List"), for which individual permissions from the Ministry of Health is not required. Therefore, supply of medicines from abroad is easier if a medicine already exists in the Ministry of Health's said list. This situation may be relevant for certain newer DMARDs such as biologics and targeted synthetic DMARDs.

Recently, Turkish Parliament has passed a new law removing the Turkish Pharmacists Association's characteristic of being an only institution over supply of medicines which did not have a marketing authorization in Turkey. Instead the Parliament authorized the Social Security Institution, institutions approved by Social Security Institution and Turkish Pharmacists Union to procure medicines from abroad.

This is hoped to further reduce any discrimination between individuals in terms of access to medicines.

In terms of equal access to medicines generally, the coverage of the Turkish social security system may need to be visited. social security system reimburses only some medicines, and does not reimburse some others.

By November 2018, Turkish Social Security covers 86,5% of the Turkish population. Even if the DMARDS benefit from reimbursement by the social security system, the remaining 14,5% of Turkish population, being outside the social security coverage, are required to pay from their pocket for the medicines and thus their access may be limited unless they have a private health insurance or any other form of financial protection for their health to cover for these treatments.

14.2.8. Safety of DMARDs And Legal Provisions

The Patient Rights Boards is a unit that evaluates, decides, submits proposals for and determines remedial actions on the applications received from private healthcare institutions and

organisations, public hospitals, oral health centres, family health centres and public health centres (Patient Rights Regulation). In order to carry out the operations within the scope of the Regulation, more than one board may be established at the places deemed appropriate by the Provincial Directorate of Health. The Board consists of the chairman, trade union representative, the representative of the institution, the representative of the association and a citizen. A member, having at least a bachelor's degree, having experience or education on patient's rights, preferably having administrative position, especially chairman of the Provincial Directorate of Health or a patient rights coordinator appointed by the chairman or vice chairman of health presides the board. The other board members are (if applicable) the workplace representative of the union in which the complainee personnel is a member, an institution representative appointed by the provincial top manager of the institution where the complainee personnel is employed, (if complainee personnel is working at a private health institution) a representative appointed by the institution's responsible manager, (if complainee personnel is working at a military hospital) a representative appointed by the military hospital head doctor, a representative from the patient rights association, (if there is no patient's rights association or a representative is not stated) a representative from the consumer associations, a citizen appointed by the governor (Patient Rights Practices Circular no. 2014/30).

The Patient Rights units are established in this regard. patient communication unit manager will be appointed especially among social services specialists having education on patient rights, psychologist, graduates of communication faculty or persons holding at least bachelor's degree from the faculties providing communication, public relations courses upon proposal of the healthcare organisation, and (if applicable) approval of the supreme institution where the health institution is administratively affiliated and approval of the healthcare manager, and governorate. They may be dismissed following the same procedure. Persons not having the education of patient rights cannot be appointed as patient communication unit manager. However, if there are no educated personnel in the healthcare institution, an appropriate unit manager may be appointed. Manager must take the education within 3 months.

Patient communication unit managers having patient rights or trainer certificates are not required to take the education again. Patient communication unit manager may be discharged upon her/his own will, appointment, resignation, termination of the agreement, leave of employment, proposal on workplace change at an investigation/examination report. If the manager takes a leave for more

than three months, continuously, in one time, she/he will be replaced. If official leaves and medical reports takes less than 3 months, a manager may be appointed, to be limited to this period, by the institution's/organization's manager, among the personal having qualifications appropriate to be a unit manager.

The patients benefit from the healthcare services and their relatives may apply in many different ways against all violation of rights during the first application to hospital or diagnosis, treatment, hospital stay and patient follow-up (19). All applications to be made by patients or patient relatives regarding the healthcare service provider can be made online via institution's website, directly to the Patient Communication Unit or Provincial Directorate of Health. Complaint, dispute settlement, opinion, suggestion and appreciation applications can be made to patient application notification system (HBSS). This application is processed by the relevant healthcare facility patient communication unit. In case of direct application to the patient communication unit by the patient or his / her relative, the application is received in writing with the submission of the ID card. The applicant will be informed about the process. The process is initiated upon registration of the applications made to provincial directorate and regarding the healthcare institutions included in HBBS by patient rights.

14.2.9. Perceived Limitations of Laws And Need to Strengthen

Notwithstanding the above provisions for patient rights, the experts whom we spoke to noted few challenges within the Turkish legal system, which may have a bearing on the treatment of DMARDs for RA. The lack of these laws can bring to fore certain situations which may put the patients in a vulnerable situation.

a. Lack of a Law Specific to Medicine Manufacturers' Liability

Turkey does not have a law specific to the liability (particularly the manufacturer's liability) for medicines. The liability of the manufacturer for drugs are generally subject to the Law on the Protection of Consumers, Code of Obligations and other general laws, where applicable (20).

In some other countries, however, there are laws specific to medicines, which also regulate the manufacturer's liability (e.g. the German Medicine Law, Arzneimittelgesetz).

Therefore, generally speaking, the patients may use the Law on the Protection of Consumers and the secondary regulations on consumer protection as a legal remedy. There are also discussions on

whether Article 71 of the Code of Obligations, which regulate the objective liability of those who carry out dangerous activities, may apply to the medicine manufacturers.

However, due to the complexity of medicinal preparations and the high risk posed due to the use of medicines, these general laws may not always give fair results. Therefore, some academics suggest a specific law regulating the medicine manufacturers' liability. It is generally suggested that such a law must regulate, among other issues, the conditions of proof of the causality link between the medicine and the patients' damages and conditions of medicine manufacturers' objective liability.

b. Lack of Class Action

Class action, which is a type of civil lawsuit filed or defended by an individual acting on behalf of a group, does not exist in Turkey. Therefore, if high number of victims suffer from the same type of damages caused by a single party, each victim is required to file separate civil lawsuits for indemnification.

Although Law on Civil Procedure, Art. 113 provides for a "collective lawsuit", this only enables associations to file lawsuits for the determination of their members' or other relevant persons' rights in case if a violation. Still, each individual suffering from a certain violation is required to file separate lawsuits for damage claims.

Each patient being required to file a lawsuit individually creates an obstacle for satisfactory management of mass sufferings from product defects or adverse events.

c. Lengthy legal procedures and lack of fast-track dispute resolution mechanisms

Lawsuits for manufacturers' or health care professional's (HCP) liability generally takes years to be resolved by the courts. Turkey has a consumer arbitration mechanism, which give quicker results. The consumer arbitration mechanism, however, applies only for damage claims below 8.480 TL (approx. 1.400 EUR). As the patients' damages are much higher in many cases, application to consumer arbitration committee is not possible and the patients must go through lengthy court procedures.

d. Ownership And Liability And Protection For Intellectual Property Rights For Pharma Companies in Turkey

Turkey is a party to the following international agreements regarding patents:

- WIPO Paris Convention for the Protection of Industrial Property 1883 (including the London, Washington, The Hague, and Stockholm texts. The Lisbon text is signed but has yet to be ratified)
- European Patent Convention 1973
- Patent Cooperation Treaty 1970
- WIPO Strasbourg Agreement Concerning the International Patent Classification 1971
- WTO Agreement on Trade-Related Aspects of Intellectual Property Rights 1994 (TRIPS)

As per the prevailing laws in Turkey, all pharmaceutical product formulas are protected by patents. All new patents will be applied to the Turkish Patent and Trademark Institute. The Institute's website provides information on the fees and regulations for the application procedure in both Turkish and English (21).

It is also possible for a pharma company to apply for international or European patents to the World Intellectual Property Organization (WIPO) (under the Patent Cooperation Treaty) or the European Patent Office (EPO) and then extend the application to cover Turkey as a region under international treaties that Turkey is a party to. This route also grants patent protection in Turkey as soon as a patent is granted. This is generally the preferred route for international pharmaceutical patent owners to extend their patent protection into Turkey.

A typical patent application takes between 2 and 6 years to be processed and approved. Once granted, the patent protection lasts 20 years from the date of filing the application. The subject of the patent will become public property following expiry of the patent protection period. Turkish law does not allow for the renewal of a patent. Patent holders must pay annual fees to maintain patent protection, and patent protection will lapse if the annual fees are not paid. Turkish law does not allow for the extension of patent protection, and supplementary protection certificates are not granted or applied in Turkey. The owner of a patent can revoke a patent by giving up his/her patent rights by applying to the Turkish Patent and Trademark Institute.

Courts can revoke a patent if one of the following conditions is proven:

1. The subject of the patent does not meet the patentability criteria

2. The subject matter of the invention is not described in a sufficiently explicit and comprehensive way to enable a person skilled in the technical field to use/apply the invention
3. The subject of the patent does not fall within the scope of the patent application
4. The patent holder does not have the right to request the patent
5. The scope of protection granted by the patent is exceeded

e. Protection For Patent Holders And What Constitutes Infringement

The following acts constitute patent infringement (Article 141, Industrial Property Code):

- Imitating the invention product by producing the product partly or fully without the consent of the patent holder.
- Selling, distributing, commercialising, importing, possessing for commercial purposes, or using by applying products or making an offer to enter into agreements concerning products known or that should be known to be produced through imitation that cause patent infringement.
- Using the patented process or selling, distributing, commercialising, importing, or possessing for commercial purposes the output of the patented process that is known or should be known to be used without the permission of the patent holder, or using by applying such output or making an offer to enter into agreements concerning such outputs.
- Seizing the patent rights.
- Extending the scope of the rights granted through a licence or a compulsory licence, or transferring such rights to third parties without the permission of the patent holder.

A patent holder or applicant can file an infringement lawsuit in specialised IP courts in Istanbul, Ankara, and Izmir, and in civil courts of first instance in other cities. The claimant can claim the following remedies:

- A ruling on the existence of infringement
- Prevention of a possible infringement
- Cessation of the acts causing the infringement granted through the patent

- Termination of the infringement and reimbursement for material and immaterial damages
- Confiscation of the products that caused the infringement or gave rise to the penalty and confiscation of tools, such as devices or machines used solely to produce these infringing products, to the extent that this will not prevent the production of products other than the ones constituting the infringement.
- Ownership of the confiscated products and devices
- Preliminary measures to prevent infringement at the expense of the infringer, such as changing the shapes of confiscated products and devices, erasing the trade marks on them, or destroying them if necessary to prevent the infringement
- Complete or partial announcement of the infringement decision in daily newspapers or through other means, or notification of the infringement to interested parties

f. IP Laws And Barriers to Low-Cost Generic Medicines in Turkey

Patent protection prevents the entry of generics into the market if the patent protection period is in effect. However, patent protection does not cover marketing authorisation applications or other activities to obtain a marketing authorisation under Article 85/3-(c) of the Industrial Property Code (known as the Turkish Bolar exception). Therefore, it is not possible to prevent generic marketing authorisation applications or other activities by generic manufacturers for the purposes of filing such applications.

Because of these restrictions, the only available route is to apply data exclusivity provisions. Under the Regulation on Licensing of Human Medicinal Products, the data exclusivity period is six years from the date on which a product received marketing authorisation for the first time in the Turkish-EU Customs Union area. It is only applied to products that received marketing authorisation after 1 January 2005 (and for products authorised for the first time after 1 January 2001 and for which no generic application was filed until 1 January 2005). On the other hand, if the patent protection period expires earlier, the data exclusivity period will be regarded as expired at the same time. Since, patent applications made earlier than a marketing authorization application; data exclusivity periods may not be useful in practice if the patent protection period is limited. During this term,

no abridged application can be made by using clinical data obtained from the clinical trials performed during the marketing authorisation application of the original pharmaceutical.

There is no marketing exclusivity in Turkey. Generic companies can make abridged applications for obtaining marketing authorisation once the data exclusivity period ends (21).

14.3. Discussion & Results

Modern medicine and scientific evidence has established that DMARDs are the standard treatment for RA, which is a debilitating medical condition resulting in significant physical, mental, social and economic burden to people and the country. The acquisition, storage, provision of DMARDs for treating RA does not pose social, ethical and legal challenges that are not already existing within the broader healthcare delivery context of a country. The healthcare systems in the form of physicians, hospitals and information systems are ensuring that RA patients have access to all information about the disease and the DMARDs.

DMARDs are also equally accepted by patients and healthcare providers alike and the legal and regulatory systems in Turkey provide adequate safeguard to both patients to accessing the care as well as for the healthcare providers to continue extending care for the patients.

The Turkish constitution as well as the social insurance sector has well established systems to ensure equitable access to all RA patients to quality healthcare without any discrimination. There will be however emerging challenges in confidentiality of the data resulting increasing healthcare networks and data sharing practices to inform the research.

The newly enacted Data Protection Law is a step in the right direction and has strong provisions to the rights of the patients but may have further scope for refinements to allow use of data in the larger interest of healthcare research and improving healthcare.

The legal system in Turkey is mature and has made provisions to encourage pharma companies to increase their R&D by having strong intellectual property laws to protect the rights of the patent holders and also subscribing to prominent international legislations. It is also noteworthy that these laws are well balanced to ensure access to high quality medicines and prevent unwanted strategies by drug companies. This is particularly relevant in the context of entry of effective biosimilars, which have comparable efficacy but cost a fraction of the cost of the originator.

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15. CONCLUSION

15.1. Recommendations For Clinical Practice

- Regardless of the disease activity levels, using a "treat-to-target strategy" than a non-targetd approach is noted to achieve better clinical outcomes. The ideal target for treatment with DMARD was noted to be lowering disease activity or to achieve clinical remission.
- For newly diagnosed DMARD naïve patients with early, symptomatic RA, the treatment is guided by the disease activity. MTX continues to be the anchor ('first') drug for patients with RA both as monotherapy as well as in combination with other drugs. Moreover, MTX appears to reduce comorbidities and mortality in RA.
- However, for patients with contraindication to methotrexate, other csDMARDs such as leflunomide or sulfasalazine may be started, with a provision for addition of short-term glucocorticoids.
- Although the initiation of treatment could be with a csDMARD monotherapy, there are many studies that have shown to achieve better disease activity reduction with subsequent trials with combination of other csDMARDs. The decision to combine monotherapy with other csDMARDs should be on the basis of presence or absence of prognostically unfavourable factors (such as continued high disease activity, high serum marker levels, early join damage, etc).
- Combination therapies improve response rates in some patients previously receiving monotherapy. If treatment target is not achieved with initial trial of csDMARD monotherapy or combination of csDMARDs, addition of a bDMARD should be considered after a thorough review of the safety parameters. Among the bDMARDs, there is no difference in outcomes, irrespective of their target and the ultimate choice of bDMARDs to be used in combination with csDMARDs, will need to be on the basis of safety and cost considerations.
- Head to head comparisons between the bDMARDs did not provide any conclusive findings. Although attempts have been made to come to a statistical conclusion for this comparison, but the heterogeneity of the sample could not be ignored. Head to head studies with direct comparisons are warranted to arrive to a conclusive juncture in this regard.

- The combination of methotrexate with biologic after the failure of csDMARDs (monotherapy and combination) yielded better clinical outcomes as compared to bDMARDs monotherapies. This was invariably the case with all the biologic subgroups. A similar finding was observed in terms of the tsDMARDs where combination with methotrexate had better outcomes. However, there are still some unrequited areas around the safety of these drugs.
- Use of tsDMARDs did provide clinical benefits for people who had shown an inadequate response to csDMARDs and biologics, including Anti-TNF. However, these studies were underpowered in terms of their sample size and there is a requirement of studies that follow scientifically robust methodologies.
- Based on this systematic literature review and the DELPHI exercise, can be summarized that to come up with appropriate technology suitable for Turkish context, the drug recommendations would not be different from the available international guidelines. csDMARDs still remain the first line of treatment. However, for the second line of treatment, biologics appear to be the most favorable options.

15.2. Recommendations For Policymakers

- Based on the results of the search conducted on the ULAKBIM database, we did not find studies that met our inclusion criteria. Considering the dearth of the local evidence on, the government must encourage robust scientific studies aiming to compare the clinical efficacy of the treatment options for RA.
- Research initiatives should also be targeted at understanding of the patient acceptability of the various health technologies.
- Inclusion of effective treatment options of the health system into existing national guidelines in the light of international studies. Considering that the there are frequent updates in the area of treatment of RA, we recommend a closer review of such changes in newer treatment options in the international treatment guidelines. They can be then included as necessary within the Turkish National treatment guidelines. It is necessary to conduct a systematic assessment of any newer treatment option within the local context before such treatments are formally recommended within the National guidelines
- Regular evaluation of issues related to the availability of these treatment options and the mechanisms of implementation. After review and inclusion of any newer treatment option

within the Turkish National treatment guidelines, it is necessary for policy makers to determine how these newer treatment options will be acquired and made available to the general public. This could mean a thorough review of the supply-distribution and reimbursement mechanism of the health systems

- Determining and implementing a strategy on the acceptability of these treatments by patient group. In addition to ensuring sufficient availability of any newer treatment options, efforts will also have to be made to educate the patients on safety and efficacy of these treatments. It is noteworthy that no treatment option will succeed without proper adherence and compliance to treatment by the patients. We have found that patient education and support to the patients during therapy with DMARDs needs improvement in Turkey
- Cost-efffectiveness analysis of bDMARDs provide mixed findings. Most studies have found bDMARDs as cost-effective option but only in combination with csDMARDs after initial trial and failure of csDMARDs. Some studies observe that the higher risk of adverse effects and the higher costs of bDMARDs as unacceptable to the benefits they offer. However, both International and Turkish National guidelines do recommend bDMARDs after a thorough screening of patients and only after initial trial of csDMARDs
- The process of procurement needs to be streamlined with a focus on purchase of biosimilar drugs that are needed to serve a large group of population suffering from RA. Therefore, we feel that there is a need to develop policies to favour early imitation of bDMARDs, in the segment that has the highest burden of RA.
- Further, there is a need to develop systems that collect structured patient data at a national level to drive resource allocation, policies, choice of medicines.

15.3. Limitations of This Review

- Due to the scope of this assessment, findings are limited to a systematic literature review and did not extend it to a meta-analysis, due to which not have a difference in the effect sizes of each of these selected treatments.
- We could not verify many critical determinants of clinical outcomes in RA in the literature. These included patients' acceptance to treatment and treatment adherence. There is scarce information available on the impact of these factors on the overall outcome in chronic conditions such as RA.

15.4. Gaps Noted in The Current Evidence in Turkey And Way Forward

This assessment is a comprehensive study which provides a detailed assessment and presents a landscape of the clinical and cost-effective ness of the available treatment options for RA. However, there remain some information gaps that are required to be answered with the appropriate understanding of the local context. Though there is a dearth of clinical studies from Turkey to support a comprehensive health technology assessment for DMARDs in RA, we attempted to select evidence from countries that have similar demographic profiles. Going beyond the clinical and the cost-effectiveness indicators it would be important to couple these finding with appropriate understanding of:

1) Preparedness of the health system to bring the clinically and cost-effective treatment into the national guidelines
2) Issues related to the availability and delivery mechanism of these treatment options.
3) Issues around the acceptability of these treatment by the patient groups

APPENDIX

Appendix 1 – Questionnaires For Delphi Exercise

First Round of the Delphi Exercise

Name:	
Job Title:	
Organization:	
Telephone number:	
Date:	_____ /_____ /_____

A. Epidemiological Burden of RA (RA) in Turkey

The global prevalence of RA was estimated to be around 1% (Cross et al., 2014)

1. What according to you is the estimated prevalence of RA in Turkey?

My Upper Estimate is: _____%
My Best Estimate is: _____%
My Lower Estimate is: _____%
Not enough data, available: _____%

2. What is the estimated prevalence of RA, among **women** in Turkey?

My Upper Estimate is: _____%
My Best Estimate is: _____%
My Lower Estimate is: _____%
Not enough data, available: _____%

3. What is the estimated prevalence of RA, among **men** in Turkey?

My Upper Estimate is: _____%

My Best Estimate is: _____%

My Lower Estimate is: _____%

Not enough data, available: _____%

B. Drug Prescription

1. Are there any national or international guidelines that are followed for clinical management of RA in Turkey?

Please provide us your comments here or provide us references of any actual data or studies to support your estimates

C. Clinical Scenarios

Please provide responses to the following questions based on your clinical experience or evidence-based knowledge.

First line treatment for RA

1. What is your preference as the first line of treatment for patients with RA?

Please ✓ your preferred treatment option

Conventional Synthetic DMARD (csDMARDs) _____

- Methotrexate
- Hydroxychloroquine
- Sulfasalazine
- Leflunomide

Biologic DMARD (bDMARDs)

Adalimumab
Certolizumab
Etanercept
Infliximab
Golimumab
Abatacept
Rituximab
Tocilizumab

Targeted Synthetic DMARD (tsDMARD)

- Tofacitinib

2. In your experience, is there any particular csDMARD (methotrexate, hydroxychloroquine, leflunomide, or sulfasalazine) that is more clinically effective from the others csDMARD?

3. What is your preference as a first line treatment between a csDMARDs combination therapy or a csDMARDs monotherapy?

4. Are there any specific csDMARDs combinations that you prefer as a first line treatment?

5. In case of failure of a csDMARD monotherapy as the first line of treatment, would you prefer switching the patient to a second monotherapy regimen or use combination therapy with two or more csDMARDs?

Biologics and tsDMARD

6. Do you think that a particular Anti-TNF (adalimumab, certolizumab, etanercept, golimumab, or infliximab) or non-Anti-TNF (abatacept, rituximab, or tocilizumab) bDMARD is more effective than other biological agents?

7. Which out of the two bDMARD (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, or tocilizumab) monotherapy or bDMARD combined with methotrexate do you think is clinically effective?

8. Would you prefer a second bDMARD scheme in case of failure of the first bDMARD?

9. Do you think that tsDMARD (tofacitinib) is more effective than bDMARD (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, or tocilizumab)?

Please provide us your comments here or provide us references of any actual data or studies to support your estimates

D. Cost of Treatment

1. What do you think would be the estimated monthly direct cost of treatment (drugs only) for RA patients being treated with the following drugs?

Drug Type	**My Upper Estimate**	**My Best Estimate**	**My Lower Estimate**
csDMARD			
• Methotrexate			
• Hydroxychloroquine			
• Sulfasalazine			
• Leflunomide			
bDMARD			
Adalimumab			
Certolizumab			
Etanercept			
Infliximab			

Drug Type	My Upper Estimate	My Best Estimate	My Lower Estimate
Golimumab			
Abatacept			
Rituximab			
Tocilizumab			
tsDMARD			
Tofacitinib			

Please provide us your comments here or provide us references of any actual data or studies to support your estimates on the cost of the treatment

E. Prescription And Drug Procurement System

1. What percentage of patients with RA receive treatment in public / government hospitals / clinics?

(please give just a percentage, for example 40% or 50%, or anything that you think is appropriate)

2. What percentage of patients with RA receive treatment in private hospitals / clinics? ***(please give just a percentage, for example 40% or 50%, or anything that you think is appropriate)***

3. Do hospitals follow an established drug formulary for the treatment of RA in Turkey? If yes, are these public/government hospitals/clinics or even private hospitals/clinics also follow a fixed drug formulary?

4. Are these formularies developed based on the clinical data? How frequently are these formularies updated?

5. Are biosimilar or biologic DMARDs procured and prescribed as a part of this formulary system?

F. Overall Safety

Please rank the following drugs/combinations in descending order of over safety on a scale of 1-5

(with 1 being the safest and 5 being least safe). You can even assign similar rank to two or more drugs in case you think there is no difference in the overall safety.

Please circle the rank you think is appropriate

Drug Type	**Overall Safety Ranking**				
csDMARD					
• Methotrexate	**1**	**2**	**3**	**4**	**5**
• Hydroxychloroquine	**1**	**2**	**3**	**4**	**5**
• Sulfasalazine	**1**	**2**	**3**	**4**	**5**
• Leflunomide	**1**	**2**	**3**	**4**	**5**
bDMARD					
• Adalimumab	**1**	**2**	**3**	**4**	**5**
• Certolizumab	**1**	**2**	**3**	**4**	**5**
• Etanercept	**1**	**2**	**3**	**4**	**5**
• Infliximab	**1**	**2**	**3**	**4**	**5**
• Golimumab	**1**	**2**	**3**	**4**	**5**
• Abatacept	**1**	**2**	**3**	**4**	**5**
• Rituximab	**1**	**2**	**3**	**4**	**5**
• Tocilizumab	**1**	**2**	**3**	**4**	**5**
tsDMARD					
• Tofacitinib	**1**	**2**	**3**	**4**	**5**
Combinations					
• csDMARDs combination with other csDMARDs	**1**	**2**	**3**	**4**	**5**
• csDMARDs combination with bDMARDs	**1**	**2**	**3**	**4**	**5**
• bDMARDs combination with other bDMARDs	**1**	**2**	**3**	**4**	**5**

Please provide us your comments here or provide us references of any actual data or studies to support your estimates

G. Patient Acceptability

From your clinical experience, please rank the following drugs/combinations in descending order of patient acceptability on a scale of 1-5 (with 1 being the most acceptable by your patients and 5 being least accepted by your patients).

You can give the same rank to two or more drugs in case you think there is no difference in the patient acceptability.

Please circle the rank you think is appropriate

Drug Type	**Patient acceptability ranking**				
csDMARD					
• Methotrexate	**1**	**2**	**3**	**4**	**5**
• Hydroxychloroquine	**1**	**2**	**3**	**4**	**5**
• Sulfasalazine	**1**	**2**	**3**	**4**	**5**
• Leflunomide	**1**	**2**	**3**	**4**	**5**
bDMARD					
• Adalimumab	**1**	**2**	**3**	**4**	**5**
• Certolizumab	**1**	**2**	**3**	**4**	**5**
• Etanercept	**1**	**2**	**3**	**4**	**5**
• Infliximab	**1**	**2**	**3**	**4**	**5**
• Golimumab	**1**	**2**	**3**	**4**	**5**
• Abatacept	**1**	**2**	**3**	**4**	**5**
• Rituximab	**1**	**2**	**3**	**4**	**5**

Drug Type	Patient acceptability ranking				
• Tocilizumab	**1**	**2**	**3**	**4**	**5**
tsDMARD					
• Tofacitinib	**1**	**2**	**3**	**4**	**5**
Combinations					
• csDMARDs combination with other csDMARDs	**1**	**2**	**3**	**4**	**5**
• csDMARDs combination with bDMARDs	**1**	**2**	**3**	**4**	**5**
• bDMARDs combination with other bDMARDs	**1**	**2**	**3**	**4**	**5**

Please provide us your comments here or provide us references of any actual data or studies to support your estimates

H. Prescription of Biosimilar Drugs

1. Do you prescribe biosimilar biologics to RA patients in your routine clinical practice? What are your views / opinions about the clinical effectiveness, cost effectiveness and patient acceptability of these biosimilar biologics?

Please provide us your comments here or provide us references of any actual data or studies to support your estimates

I. Research For Evidence-Based Practice

1. How have you been using the existing clinical research evidence from Turkey, in your routine clinical practice for management of RA patients, specifically in terms of comparative effectiveness of different drugs?

2. Do you think the local research is sufficient for facilitating contextualized and evidence-based practice for clinical management of RA in Turkey?

3. What are the possible research questions with regard to RA treatment options, that you would want to answer through scientific studies in Turkey?

Second Round of the Delphi Exercise

A. Epidemiological Burden of RA (RA)

1. What according to you is the best estimate of the prevalence of RA in Turkey?
   a) 0.35%
   b) 0.5%
   c) 1%

2. What is the estimated prevalence of RA, among women in Turkey?
   d) 0.5%
   e) 0.8%
   f) 1.2%

3. What is the estimated prevalence of RA, among men in Turkey?
   g) 0.15%
   h) 0.3%
   i) 0.55%

B. Drug Prescription

4. Which of the following guidelines do you use as a reference for clinical management of RA in Turkey?
   a) Turkish League Against Rheumatism (TLAR) guidelines
   b) Turkish Rheumatology Association (TRA) guidelines
   c) International ACR and EULAR guidelines

5. Would you agree that the other rheumatologists in Turkey are using Turkish League Against Rheumatism (TLAR) guidelines for clinical management of RA?
   d) Yes
   e) No
   f) Don’t Know/Can’t Say

6. Would you agree that the other rheumatologists in Turkey are using Turkish Rheumatology Association (TRA) guidelines for clinical management of RA?
   g) Yes
   h) No
   i) Don't Know/Can't Say

C. Clinical Scenarios

Please provide responses to the following questions based on your clinical experience or evidence-based knowledge.

7. What is your preference as the first line of treatment for patients with RA?

Conventional Synthetic DMARD (csDMARDs)

- Methotrexate ☐
- Hydroxychloroquine ☐
- Sulfasalazine ☐
- Leflunomide ☐

Biologic DMARD (bDMARDs)

- Adalimumab ☐

8. Which of the following is your preferred first line treatment csDMARDs combination, in case of failure of csDMARD monotherapy failure?
   a) Methotrexate + Hydroxychloroquine
   b) Methotrexate + Sulfasalazine
   c) Leflunomide + Sulfasalazine
   d) Methotrexate + Hydroxychloroquine + Sulfasalazine

9. Which of the following statement would you consider to be 'TRUE' about Rituximab?
   a) Rituximab has shown better effectiveness than other biological agents

b) Rituximab has similar effectiveness as the other Anti-TNF

c) Rituximab has similar effectiveness as the other non-Anti-TNF

d) Can't say, requires more clinical evidence and data

10. Which of the following statement would you consider to be 'TRUE' about Tocilizumab?
    a) Tocilizumab monotherapy is more effective than Methotrexate + bDMARD combination
    b) Tocilizumab monotherapy is as effective as Methotrexate + bDMARD combination
    c) Tocilizumab monotherapy is less effective than Methotrexate + bDMARD combination

11. Which of the following statement would you consider to be 'TRUE' about tsDMARD (tofacitinib)?
    a) tsDMARD (tofacitinib) is more effective than bDMARD or MTX in combination with other bDMARD
    b) tsDMARD (tofacitinib) is less effective than bDMARD or MTX in combination with other bDMARD
    c) tsDMARD (tofacitinib) is as effective as bDMARD or MTX in combination with other bDMARD
    d) Can't say, requires more clinical evidence and data

D. Cost of Treatment

Based on the Phase 1 of this exercise we have provided the estimated monthly direct cost of treatment (drugs only) for RA patients being treated with the following drugs? Do you agree with the estimate? if not, please provide a new estimated monthly cost

Drug Type	**Estimate monthly cost**	**Agree (Yes/No)**	**If No, provide new estimate**
csDMARD			
• Methotrexate (Oral)	**20 TL**		
• Hydroxychloroquine	**20 TL**		
• Sulfasalazine	**25 TL**		

Drug Type	Estimate monthly cost	Agree (Yes/No)	If No, provide new estimate
• Leflunomide	**40 TL**		
bDMARD			
• Adalimumab	**2200 TL**		
• Certolizumab	**2150 TL**		
• Etanercept	**2250 TL**		
• Infliximab	**1800 TL**		
• Golimumab	**2400 TL**		
• Abatacept	**2400 TL**		
• Rituximab	**1500 TL**		
• Tocilizumab	**1800 TL**		
TsDMARD			
• Tofacitinib	**2000 TL**		

Appendix 2: Conflict of Interest Declarations

HEALTH TECHNOLOGY ASSESSMENT DEPARTMENT

Conflict of interest Notification Form (Declaration of Neutrality)

During the advisory service of the "Health Technology Assessment of Rheumatoid Arthritis" project, with respect to the subject work for;

- During the evaluation process of the project, any financial and/or moral support that may affect the decision negatively, receive/not receive from any natural or legal person who produces, imports, distributes and/or provides medicine, medical device or other product that has direct or indirect connection,
- Potential conflict of interest; scientific and/or medical committee membership or consultancy, expertise, working status at present, shareholding and similar situations,
- There is/is not any relationship based on interest during the data collection, interpretation of results and report writing of HTA,

must be clearly indicated and signed.

☐ **There is NO potential** for any financial contribution, relationship based on interest or any other (potential) conflict of interest, that is need to know about **neutrality of our contribution to our report/HTA report**

…… …… ……

Name, Surname Date Signiture

☐ **There is potential** for financial contribution, relationship based on interest or other (potential) conflict of interest, that is need to know about **neutrality of our contribution to our report/HTA report**
(Please explain what kind of conflict of interest might negatively affect your neutrality)

……
……

…… …… ……

Name, Surname Date Signiture

Appendix 3: AMSTAR Instrument

The methodological quality of the included reviews will be assessed by two authors independently using the 'assessment of multiple systematic reviews' (AMSTAR) instrument. The AMSTAR instrument assesses the quality of systematic reviews using the following criteria:

1. Was an a priori design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Appendix 4: The Cochrane Collaboration's Tool for Assessing Risk of Bias in RCTs

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		

Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix 5: HTA Core Model and Domains

The HTA Core Model divides HTA information into standardised items referred to as assessment elements – items of information that are relevant for the HTA. Each assessment element contains a question that one should consider including and answering within a specific assessment project. Furthermore, those elements most likely to be useful for international sharing of information are defined as core elements. There are total of 9 domains in the HTA model, which have been used to draft this report:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Patients and Social aspects (SOC)
9. Legal

Appendix 6: Search Strategy for Systematic Review

Search Strategy for Systematic Reviews (SRs), Randomized Controlled Trials (RCTs), Controlled Trials (CT, Phase IV), Controlled Trials (CT, Phase III) and Health Technology Assessments (HTA) from PubMed

Search	Query	Items found	Search article type
#1	Search "Arthritis, Rheumatoid"[Mesh]	105015	
#2	Search Arthritis Rheumatoid[Title]	54	
#3	Search Arthritis, Rheumatoid	137409	
#4	Search Rheumatoid Arthritis[Title/Abstract]	95457	
#5	Search Methotrexate[Title/Abstract]	37742	
#6	Search METOART[Title/Abstract]	0	
#7	Search METOJECT[Title/Abstract]	4	
#8	Search EMTHEXATE S[Title/Abstract]	1073839	
#9	Search METHOTREXAT EBEWE[Title/Abstract]	1	
#10	Search METHOTREXATE KOCAK[Title/Abstract]	0	
#11	Search TREXAN[Title/Abstract]	10	
#12	Search METOART CON[Title/Abstract]	24274	
#13	Search MEXTU[Title/Abstract]	0	
#14	Search ZEXATE[Title/Abstract]	0	
#15	Search sulfasalazine[Title/Abstract]	2960	
#16	Search hydroxychloroquine[Title/Abstract]	3236	
#17	Search leflunomide[Title/Abstract]	1954	
#18	Search B-cell kinase inhibitor[Title/Abstract]	741	

Search	Query	Items found	Search article type
#19	Search RITUXIMAB[Title/Abstract]	17064	
#20	Search MABTHERA[Title/Abstract]	167	
#21	Search JAK inhibitor[Title/Abstract]	652	
#22	Search TOFACITINIB[Title/Abstract]	665	
#23	Search XELJANZ[Title/Abstract]	17	
#24	Search Interleukin-6 inhibitor[Title/Abstract]	20	
#25	Search TOCILIZUMAB[Title/Abstract]	2053	
#26	Search ACTEMRA[Title/Abstract]	31	
#27	Search T-cell-activation inhibitor[Title/Abstract]	11	
#28	Search ABATACEPT[Title/Abstract]	1211	
#29	Search ORENCIA[Title/Abstract]	36	
#30	Search TNF inhibitor[Title/Abstract]	589	
#31	Search ADALIMUMAB[Title/Abstract]	5404	
#32	Search HUMIRA[Title/Abstract]	197	
#33	Search ETANERCEPT[Title/Abstract]	6055	
#34	Search ENBREL[Title/Abstract]	281	
#35	Search INFLIXIMAB[Title/Abstract]	10543	
#36	Search REMICADE[Title/Abstract]	314	
#37	Search REMSIMA[Title/Abstract]	47	
#38	Search GOLIMUMAB[Title/Abstract]	776	
#39	Search SIMPONI[Title/Abstract]	22	
#40	Search CERTOLIZUMAB PEGOL[Title/Abstract]	572	

Search	Query	Items found	Search article type
#41	Search CIMZIA[Title/Abstract]	30	
#42	Search ((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract]	137409	
#43	Search (((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract]	1132318	
#44	Search ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract]	859	
#45	Search ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract])	663	

Search	Query	Items found	Search article type
	OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract]		
#46	Search ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract]	699	
#47	Search ((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract]	17779	
#48	Search ((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract]	1189	
#49	Search ((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract]	2063	
#50	Search ((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract]	1226	
#51	Search (ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract]	5435	

Search	Query	Items found	Search article type
#52	Search (ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract]	6133	
#53	Search ((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract]	10599	
#54	Search (GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract]	777	
#55	Search (CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]	581	
#56	Search (((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract])	17424	
#57	Search ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract])	1165430	

Search	Query	Items found	Search article type
	OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract]))		

Search	Query	Items found	Search article type
	AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))		
#58	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((((Methotrexate[Title/Abstract]) OR	15396	Without country filter

Search	Query	Items found	Search type	article
	METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE			

Search	Query	Items found	Search article type
	S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract])))		
#59	Search ((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France	7030782	
#60	Search (((((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT	3959	With Country filter

Search	Query	Items found	Search article type
	EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France)		
#61	Search (((((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract])	218	With Filter: Systematic Reviews

Search	Query	Items found	Search article type
	OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND ((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Systematic Reviews		
#62	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE	207	Filter: Full text systematic reviews

Search	Query	Items found	Search article type
	KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Systematic Reviews; Full text		

Search	Query	Items found	Search article type
#63	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR	184	Filters: Systematic Reviews; Full text; Humans

Search	Query	Items found	Search article type
	MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR		

Search	Query	Items found	Search article type
	(((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Systematic Reviews; Full text; Humans		
#64	Search (((((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR	5	Filters: Systematic Reviews; Full text; Humans; Adolescent: 13-18 years

Search	Query	Items found	Search article type
	MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Systematic Reviews; Full text; Humans; Adolescent: 13-18 years		
#65	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE	45	Filters: Systematic Reviews; Full text; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search article type
	KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract])))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France)		

Search	Query	Items found	Search article type
	Filters: Systematic Reviews; Full text; Humans; Adolescent: 13-18 years; Adult: 19+ years		
#66	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE	45	Filters: Systematic Reviews; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search article type
	KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR		

Search	Query	Items found	Search article type
	((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Systematic Reviews; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years		
#67	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE	262	Filters: Randomized Controlled Trial; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search article type
	S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract])))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Randomized Controlled Trial; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years		
#68	Search (((((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND	8	Filters: Clinical Trial, Phase IV; Full text;

Search	Query	Items found	Search article type
	((((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR		Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search type	article
	METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR			

Search	Query	Items found	Search article type
	SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Clinical Trial, Phase IV; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years		
#69	Search (((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR	66	Filters: Clinical Trial, Phase III; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search article type
	((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATES[Title/Abstract]) OR METHOTREXATEBEWE[Title/Abstract]) OR METHOTREXATEKOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR		

Search	Query	Items found	Search article type
	ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France) Filters: Clinical Trial, Phase III; Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years		
#70	Search Health Technology Assessment[Title/Abstract]	3734	
#71	Search HTA	4728	
#72	Search HTA[Title/Abstract]	2592	

Search	Query	Items found	Search article type
#73	Search ((HTA) OR HTA[Title/Abstract]) OR Health Technology Assessment[Title/Abstract]	6665	
#74	#60 AND #73	14	Total HTA Articles
#75	Search (((((((("Arthritis, Rheumatoid"[Mesh]) OR Arthritis Rheumatoid[Title]) OR Arthritis, Rheumatoid) OR Rheumatoid Arthritis[Title/Abstract])) AND ((((((((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND sulfasalazine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR	4	Filters: Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years

Search	Query	Items found	Search article type
	METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND hydroxychloroquine[Title/Abstract])) OR ((((((((((Methotrexate[Title/Abstract]) OR METOART[Title/Abstract]) OR METOJECT[Title/Abstract]) OR EMTHEXATE S[Title/Abstract]) OR METHOTREXAT EBEWE[Title/Abstract]) OR METHOTREXATE KOCAK[Title/Abstract]) OR TREXAN[Title/Abstract]) OR METOART CON[Title/Abstract]) OR MEXTU[Title/Abstract]) OR ZEXATE[Title/Abstract])) AND leflunomide[Title/Abstract])) OR (((B-cell kinase inhibitor[Title/Abstract]) OR RITUXIMAB[Title/Abstract]) OR MABTHERA[Title/Abstract])) OR (((JAK inhibitor[Title/Abstract]) OR TOFACITINIB[Title/Abstract]) OR XELJANZ[Title/Abstract])) OR (((Interleukin-6 inhibitor[Title/Abstract]) OR TOCILIZUMAB[Title/Abstract]) OR ACTEMRA[Title/Abstract])) OR (((T-cell-activation inhibitor[Title/Abstract]) OR ABATACEPT[Title/Abstract]) OR ORENCIA[Title/Abstract])) OR ((((((TNF		

Search	Query	Items found	Search type	article
	inhibitor[Title/Abstract]) OR ((ADALIMUMAB[Title/Abstract]) OR HUMIRA[Title/Abstract])) OR ((ETANERCEPT[Title/Abstract]) OR ENBREL[Title/Abstract])) OR (((INFLIXIMAB[Title/Abstract]) OR REMICADE[Title/Abstract]) OR REMSIMA[Title/Abstract])) OR ((GOLIMUMAB[Title/Abstract]) OR SIMPONI[Title/Abstract])) OR ((CERTOLIZUMAB PEGOL[Title/Abstract]) OR CIMZIA[Title/Abstract]))))) AND (((((((Turkey) OR United States) OR United Kingdom) OR Germany) OR Italy) OR Russia) OR France))) AND (((HTA) OR HTA[Title/Abstract]) OR Health Technology Assessment[Title/Abstract]) Filters: Full text; Publication date from 1998/01/01 to 2018/12/31; Humans; Adolescent: 13-18 years; Adult: 19+ years			

SEARCH STRATEGY FOR EXISTING HEALTH TECHNOLOGY ASSESSMENTS (HTAS) AND SYSTEMATIC REVIEWS (SRS) FROM CENTRE FOR REVIEW AND DISSEMINATION, UNIVERSITY OF YORK AND NHS NATIONAL INSTITUTE FOR HEALTH RESEARCH

Line	Search	Hits
1	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES WITH QUALIFIERS DT, PC IN DARE, NHSEED, HTA	309

Line	Search	Hits
2	((ZEXATE OR MEXTU OR METOART CON OR TREXAN OR METHOTREXATE KOCAK OR METHOTREXAT EBEWE OR EMTHEXATE S OR METOJECT OR METOART OR Methotrexate): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	105
3	((Methotrexate OR METOART OR METOJECT OR EMTHEXATE S OR METHOTREXAT EBEWE OR METHOTREXATE KOCAK OR TREXAN OR METOART CON OR MEXTU OR ZEXATE):TI AND (sulfasalazine):TI) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	1
4	((Methotrexate OR METOART OR METOJECT OR EMTHEXATE S OR METHOTREXAT EBEWE OR METHOTREXATE KOCAK OR TREXAN OR METOART CON OR MEXTU OR ZEXATE):TI AND (hydroxychloroquine):TI) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	0
5	((Methotrexate OR METOART OR METOJECT OR EMTHEXATE S OR METHOTREXAT EBEWE OR METHOTREXATE KOCAK OR TREXAN OR METOART CON OR MEXTU OR ZEXATE): TI AND (leflunomide): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review: ZDT and Abstract: ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT)	2

Line	Search	Hits
	OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	
6	((B-cell kinase inhibitor OR RITUXIMAB OR MABTHERA): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review: ZDT and Abstract: ZPS) OR (Cochrane review: ZDT) OR (Cochrane related review record: ZDT) OR (Economic evaluation: ZDT and Bibliographic: ZPS) OR (Economic evaluation: ZDT and Abstract: ZPS) OR Full publication record: ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	146
7	((JAK inhibitor OR TOFACITINIB OR XELJANZ): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review: ZDT and Abstract: ZPS) OR (Cochrane review: ZDT) OR (Cochrane related review record: ZDT) OR (Economic evaluation: ZDT and Bibliographic: ZPS) OR (Economic evaluation: ZDT and Abstract: ZPS) OR Full publication record: ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	15
8	((Interleukin-6 inhibitor OR TOCILIZUMAB OR ACTEMRA): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review: ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	26
9	((T-cell-activation inhibitor OR ABATACEPT OR ORENCIA): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review: ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	30

Line	Search	Hits
10	((TNF inhibitor OR ADALIMUMAB OR HUMIRA OR ETANERCEPT OR ENBREL OR INFLIXIMAB OR REMICADE OR REMSIMA OR GOLIMUMAB OR SIMPONI OR CERTOLIZUMAB PEGOL OR CIMZIA): TI) and ((Systematic review: ZDT and Bibliographic: ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 1998 TO 2018	274
11	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	560
12	#1 AND #11	123

Search Strategy for Reviews, Trials, Technology Assessments, Economic Evaluations and other reviews from Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register, HTA database, NHS Economic Evaluation Database and Cochrane collaboration

Search	Search terms	Hits
#1	"Arthritis, Rheumatoid"	4867
#2	Arthritis Rheumatoid	10921
#3	Rheumatoid Arthritis	10921
#4	#1 or #2 or #3	10921
#5	MeSH descriptor: [Methotrexate] explode all trees	3094
#6	#5 or METOART or METOJECT or EMTHEXATE S or METHOTREXAT EBEWE or METHOTREXATE KOCAK or TREXAN or METOART CON or MEXTU or ZEXATE	3109

#7	sulfasalazine	839
#8	#6 and #7	147
#9	hydroxychloroquine	682
#10	#6 and #9	95
#11	leflunomide	451
#12	#6 and #11	57
#13	B-cell kinase inhibitor	187
#14	#13 or RITUXIMAB or MABTHERA	3234
#15	JAK inhibitor	381
#16	#15 or TOFACITINIB or XELJANZ	666
#17	Interleukin-6 inhibitor	852
#18	#17 or TOCILIZUMAB or ACTEMRA	1350
#19	T-cell-activation inhibitor	87
#20	#19 or ABATACEPT or ORENCIA	599
#21	TNF inhibitor	1095
#22	ADALIMUMAB or HUMIRA	1930
#23	ETANERCEPT or ENBREL	1611
#24	INFLIXIMAB or REMICADE or REMSIMA	1974
#25	GOLIMUMAB or SIMPONI	488
#26	CERTOLIZUMAB PEGOL or CIMZIA	378
#27	#21 or #22 or #23 or #24 or #25 or #26	5534
#28	#6 or #8 or #10 or #12 or #14 or #16 or #18 or #20 or #27	12907
#29	#4 and #28	3208

#30	Turkey or United States or United Kingdom or Germany or Italy or Russia or France	337030
#31	#29 and #30 Publication Year from 1998 to 2018	1672

SEARCH STRATEGY FOR CLINICAL TRIALS ON CLINICAL TRIAL.GOV

Search	Search terms	Hits
#1	METHOTREXATE OR METOART OR METOJECT OR EMTHEXATE S OR METHOTREXAT EBEWE OR METHOTREXATE KOCAK OR TREXAN OR METOART CON OR MEXTU OR ZEXATE OR SULFASALAZINE OR HYDROXYCHLOROQUINE OR LEFLUNOMIDE OR B CELL KINASE INHIBITOR OR RITUXIMAB OR MABTHERA OR JAK | Available, Completed Studies | Interventional Studies | Rheumatic Arthritis | Methotrexate or DMARDs | Adult | Phase 3, 4 | NIH, U.S. Fed, Industry, Other | Start date from 01/01/1998 to 07/12/2020 Applied Filters: Available, Completed, Interventional, Adult (18–65), Phase 3, Phase 4, Funding: NIH, Funding: U.S. Federal, Funding: Industry Funding: Other	38

SEARCH STRATEGY FOR JBI DATABASE OF SYSTEMATIC REVIEWS AND IMPLEMENTATION REPORTS

Search	Search terms	Studies
#1	Rheumatoid Arthritis; METHOTREXATE OR METOART OR METOJECT OR EMTHEXATE S OR METHOTREXAT EBEWE OR	9

	METHOTREXATE KOCAK OR TREXAN OR METOART CON OR MEXTU OR ZEXATE OR SULFASALAZINE OR HYDROXYCHLOROQUINE OR LEFLUNOMIDE OR B CELL KINASE INHIBITOR OR RITUXIMAB OR MABTHERA OR JAK INHIBITOR OR TOFACITINIB OR XELJANZ OR INTERLEUKIN 6 INHIBITOR OR TOCILIZUMAB OR ACTEMRA OR T CELL ACTIVATION INHIBITOR OR ABATACEPT OR ORENCIA OR TNF INHIBITOR OR ADALIMUMAB OR HUMIRA OR ETANERCEPT OR ENBREL OR INFLIXIMAB OR REMICADE OR REMSIMA OR GOLIMUMAB OR SIMPONI OR CERTOLIZUMAB PEGOL OR CIMZIA

SEARCH STRATEGY FOR INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH (ISPOR)

Search	Search terms	Studies
#1	Keyword: None Disease: Rheumatoid Arthritis Topic: Clinical Outcomes Studies (COS) Subtopic: All Meeting: All	52
#2	Keyword: None Disease: Rheumatoid Arthritis Topic: Cost Studies (CS) Subtopic: All Meeting: All	297
#3	Keyword: None	4

Disease: Rheumatoid Arthritis

Topic: Health Care Use & Policy Studies (HP)

Subtopic: Health Technology Assessment Programs (HTA)

Meeting: All

Appendix 7 Table 1. Characteristics of clinical trials included

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
Methotrexate +Sulfasalazine					
10364900	Finland, France, Germany	205	MTX + PBO	69	52
			MTX + SSZ	68	
			SSZ + PBO	68	
16926184	UK	165	MTX + SSZ	56	78
			SSZ	55	
			MTX	54	
Methotrexate + Sulfasalazine + Hydroxychloroquine					
12115219	USA	171	MTX + HCQ	58	104

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
			MTX + SSZ	55	
			MTX + SSZ	58	
Leflunomide					
12416973	USA and Canada	263	MTX + PBO	133	24
			MTX + LEF	130	
10888712	Europe and South Africa	999	MTX + PBO	498	52
			LEF + PBO	501	
10573044	USA and Canada	364	MTX + PBO	182	52
			LEF + PBO	182	
Adalimumab					
26138593	International	120	MTX	61	24
			ADA + MTX	59	
22739990	Germany	172	MTX + PBO	85	48
			ADA + MTX	87	
22562973	International	1032	MTX + PBO	517	26
			ADA + MTX	515	
16385520	Australia, Europe, North America	799	MTX	257	104
			ADA	274	
			ADA + MTX	268	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
15146409	USA and Canada	407	MTX + PBO	200	52
			ADA + MTX	207	
12528101	USA and Canada	135	MTX + PBO	62	24
			ADA + MTX	73	
18821658	USA	148	MTX + PBO	75	24
			ADA + MTX	73	
19369462	UK	526	MTX	166	104
			ADA + MTX	199	
			ADA	161	
22915617	International	638	ADA + MTX	229	104
			ADA	205	
			MTX	204	
Certolizumab					
26533965	International	868	MTX + PBO	213	52
			CTZ + MTX	655	
22344576	USA and Europe	247	CTZ + MTX	126	24
			MTX + PBO	121	
19015207	USA and Europe	373	MTX + PBO	127	24
			CTZ + MTX	246	
19909548	USA	589	CTZ + MTX	390	52

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
			MTX + PBO	199	
Etanercept					
24618266	UK	110	MTX + PBO	55	52
			ETN + MTX	55	
15001324	Europe	682	MTX	228	52
			ETN + MTX	231	
			ETN	223	
11096165	North America	424	MTX + PBO	217	52
			ETN	207	
20937671	International	499	MTX + PBO	249	52
			RTX + MTX	250	
20187135	UK	202	ETN + MTX	108	104
			MTX	94	
18794178	International	254	ETN	103	104
			ETN + SSZ	101	
			SSZ	50	
Golimumab					
23861303	International	637	MTX + PBO	160	52
			GOL + PBO	159	
			GOL + MTX	318	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
22661646	International	592	MTX + PBO	197	24
			GOL + MTX	395	
19066176	International	444	MTX + PBO	133	24
			GOL + PBO	133	
			GOL + MTX	178	
18383539	International	172	MTX + PBO	35	16
			GOL + MTX	137	
20131276	International	643	MTX + PBO	129	48
			GOL	257	
			GOL + MTX	257	
19644849	UK	637	MTX + PBO	160	24
			GOL + PBO	159	
			GOL + MTX	318	
25005327	UK	319	MTX + PBO	160	52
			GOL + MTX	159	
Infliximab					
16572442	International	724	MTX + PBO	363	22
			IFX + MTX	361	
15641102	UK	20	MTX + PBO	10	54
			IFX + MTX	10	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
15529377	International	645	MTX + PBO	298	54
			IFX + MTX	373	
11096166	North America, Europe	169	MTX + PBO	88	54
			IFX + MTX	86	
10622295	USA	169	MTX + PBO	88	52
			IFX + MTX	81	
Rituximab					
22012969	International	499	MTX + PBO	249	104
			RTX + MTX	250	
20488885	International	342	MTX + PBO	172	24
			RTX + MTX	170	
16649186	International	341	MTX + PBO	149	24
			RTX + MTX	192	
15201414	Australia, Canada, Israel, Europe	121	MTX + PBO	40	24
			RTX + PBO	40	
			RTX + MTX	40	
16947627	USA	520	MTX + PBO	209	24
			RTX + PBO	311	
17062648	USA	120	MTX + PBO	40	48

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
			RTX	40	
			RTX + MTX	40	
16947627	USA	517	MTX + PBO	209	24
			RTX + MTX	301	
Tocilizumab					
18625622	UK	328	MTX + PBO	158	24
			TCZ + MTX	170	
22562983	International	553	TCZ + MTX	277	24
			TCZ + PBO	276	
21360490	International	791	MTX + PBO	393	52
			TCZ + MTX	398	
19297346	International	524	MTX + PBO	259	24
			TCZ + PBO	265	
18358926	International	409	MTX + PBO	204	24
			TCZ + MTX	205	
16947782	Europe	151	MTX + PBO	49	16
			TCZ + MTX	50	
			TCZ	52	
22972745	USA	523	TCZ + MTX	360	24
			TCZ	163	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
Abatacept					
22915624	Europe	50	MTX + PBO	23	16
			ABA + MTX	27	
19124524	International	509	MTX + PBO	253	52
			ABA + MTX	256	
16785473	USA	652	MTX + PBO	219	52
			ABA + MTX	433	
16052582	International	234	MTX + PBO	119	52
			ABA + MTX	115	
25367713	USA	351	ABA + MTX	119	78
			ABA	116	
			MTX	116	
		256	ABA + MTX	91	NR
			ABA	81	
			MTX	84	
18383390	USA	539	ABA + MTX	378	104
			MTX + PBO	161	
Tofacitinib					
27002108	International	109	MTX + PBO	37	52
			TOFA	36	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
			TOFA + MTX	36	
23348607	International	395	MTX + PBO	79	24
			TOFA + MTX	316	
22006202	International	149	MTX + PBO	69	24
			TOFA + MTX	71	
25186034	International	200	MTX + PBO	66	12
			TOFA + MTX	134	
27734232	USA	134	MTX + PBO	40	26
			TOFA + MTX	94	
DOI: 10.1056/NEJMoa1310476	International	559	MTX	186	104
			TOFA	373	
Conventional synthetic + biologics					
23755969	North America	353	MTX + SSZ+HCQ	178	24;
			ETN + MTX	175	
22508468	USA	376	ETN + MTX	244	102
			MTX+SSZ+HCQ	132	

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
28388820	USA	289	MTX + SSZ + HCQ	145	48
			ETN + MTX	144	
	UK	205	MTX + SSZ + LEF	104	52
			Anti-TNF	101	
20082236	Italy	120	Anti-TNF + MTX	60	24
			Anti-TNF + LEF	60	
Head to head biologics					
18055472	International	431	MTX + PBO	110	28
			IFX + MTX	165	
			ABA + MTX	156	
21360491	USA	51	Anti-TNF + MTX + PBO	18	24
			Anti-TNF + RTX + MTX	33	
16935912	USA	121	ABA + ETN	85	52
			ETN + PBO	36	
18821691	USA	1220	DMARDs + PBO	415	24

Study PubMed ID	Country	Total sample	Arms	Participants/Arm	Study duration (weeks)
			TCZ + DMARDs	805	
21949007	USA	614	TCZ + DMARDs	409	24
			DMARDs + PBO	205	
27654603	France	292	NON-TNFI	146	24
			Alternate Anti-TNF	146	
23148339	UK	120	ADA + MTX	60	52
			ETN + MTX	60	
26473625	US	646	ABA + MTX	318	104
			ADA + MTX	328	
24442884	International	1111	RTX	604	26
			Alternate Anti-TNF	507	
28629665	International	1146	TCZ	384	52
			TCZ + MTX	376	
			ADA + MTX	386	
		295	RTX	144	52
			Anti-TNF	151	

Appendix 7 Table 2. Patient characteristics in included clinical trials

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
Methotrexate + Sulfasalazine							
10364900	0.2	NR	1.3	9.8	0	0	7.5-15
16926184	1	3.8	NR	NR	100 %	100%	17
Methotrexate + Sulfasalazine + Hydroxychloroquine							
12115219	6.9	NR	NR	21.4	54	NR	7.5-17.5
Leflunomide							
12416973	11.6	NR	1.5	18	100	100	16.4
10888712	3.7	NR	1	16.1	NR	67	12.6
10573044	6.8	NR	0.8	13.7	0	43	12
Adalimumab							
26138593	6.3	6.2	1.7	18.2	100	100	16.9

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
22739990	0.1	6.2	1.4	10.4	0	0	15
22562973	0.4	6	1.6	18	0	10	20
16385520	0.7	6.3	1.5	21.6	0	86	16.6
15146409	10.9	NR	1.46	19.2	100	100	16.6
12528101	12.1	NR	1.6	16.9	100	100	16.7
18821658	NR	5.9	1.3	10	NR	NR	16.2
19369462	0.7	6.3	1.6	21	100%	100%	17
22915617	0.7	6.3	1.6	21.8	NR	38%	NR
Certolizumab							
26533965	NR	6.8	1.6	NR	0	0	21.4
22344576	9.6	6.2	1.4	22.5	100	100	16.7
19015207	5.9	6.8	1.6	21.2	100	100	12.4

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
19909548	NR	6.9	1.7	NR	100 %	100%	more than 10
Etanercept							
24618266	0.6	4.1	1	NR	0	0	25
15001324	6.6	NR	1.7	22.6	43	NR	17
11096165	1	NR	NR	24	0	43	19
20937671	0.92	7	1.7	20.8	NR	70%	NR
20187135	8.6	2.8	0.6	2.7	NR	NR	NR
18794178	NR	NR	NR	NR	NR	NR	NR
Golimumab							
23861303	3.54	5.7	1.5	15.4	0	51	19.1
22661646	6.9	6	1.6	14.9	100	100	15-25
19066176	5.7	6.1	1.3	12.4	100	100	15
18383539	7.8	6.4	1.6	15	100	100	10

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
20131276	8	NR	1.5	15.6	49%	69%	15
19644849	3	6.3	1.5	15.3	NR	52%	19.1
25005327	3.2	5.1	1.5	15.4	57%	57%	15
Infliximab							
16572442	7.3	NR	1.5	15	100	100	15
15641102	0.6	NR	1.3	NR	0	0	17
15529377	0.8	NR	1.5	21.4	0	20	15.3
11096166	11.5	NR	1.7	21.5	100	100	16.5
10622295	8.8	NR	1.6	22	100%	100%	15
Rituximab							
22012969	0.9	7	1.7	20.8	0	69	7.5-20
20488885	7	6.5	NR	20.2	100	100	16.4

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
16649186	10.1	6.7	1.7	21.6	100	100	15.2
15201414	10.6	6.8	1.9	21	100	100	10
16947627	11.9	6.8	1.9	23.1	100	100	60.5
17062648	10.8	6.8	1.9	19.4	100 %	100%	more than 10
16947627	11.8		1.9	23.2	100 %	100%	16.7
Tocilizumab							
18625622	0.7	6.8	1.7	18.9	0	NR	15.8
22562983	8.2	6.3	1.4	14.8	100	100	16
21360490	9.1	6.5	1.5	17	100	100	15.2
19297346	6.3	6.8	1.6	19.1	33	43	15.5
18358926	7.6	6.8	1.6	20.1	100	100	14.7
16947782	0.8	6.5	NR	11.4	100	100	15.5

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
22972745	12.3	5.7	NR	18.4	100%	100%	NR
Abatacept							
22915624	2.2	5.3	NR	10	100	100	17.1
9124524	0.5	6.3	1.7	22.4	2	3	18.5
16785473	8.6	6.8	1.7	21.6	100	100	16
16052582	9.3	5.5	1	21.6	99	99	15.4
25367713	0.56	5.4	1.4	11.1	30%	NR	15
	NR	5.4	1.4	11.2	NR	NR	NR
18383390	8.5	6.4	1.7	22	100%	100%	NR
Tofacitinib							
27002108	0.7	6.3	1.5	14.8	0	0	15
23348607	9	6.3	1.4	14.1	100	100	25

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
22006202	9.4	5.2	1.3	14.9	100	100	16.5
25186034	13	NR	1.55	NR	100 %	100%	15
27734232	8.7	6.2	1.3	16.6	NR	NR	21
DOI: 10.1056/NEJMoa1310476	2.8	6.5	1.5	16.5	NR	NR	15
Conventional synthetic + biologics							
23755969	5.2	5.8	1.4	11.2	100	100	19.6
22508468	0.4	5.8	1	12.4	24	25	20
28388820	6	3.6	0.8	5	100 %	100%	NR
	5.2	6.2	1.8	11	100 %	100%	NR
20082236	4.5	7.6	1.7	17.9	NR	NR	15

Study PubMed ID	RA duration (years)	DAS28	HAQ-DI	SJC	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)
Head to head biologics							
18055472	7.8	6.8	1.8	20.6	100	100	16.4
21360491	10.4	6.6	1.4	15.9	100%	100%	17
16935912	12.9	NR	0.9	19.8	100%	100%	15
18821691	9.8	6.6	NR	19.2	100%	100%	14.7
21949007	8.62	6.53	NR	19.7	NR	70%	17.1
27654603	10	5.1	1.3	5	77%	77%	15
23148339	6	5.7	NR	9	70%	70%	NR
26473625	1.8	5.5	1.5	NR	100%	100%	NR
24442884	8.3	4.9	1.4	7	52%	54%	13.7
28629665	6	6.5	1.6	11.1	36%	43%	15
	7.4	NR	1.7	9	100%	100%	NR

Appendix 7 Table 3. Clinical outcomes reported in trials: ACR 50

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
Methotrexate +Sulfasalazine			
10364900	MTX + PBO	69	59%
	MTX + SSZ	68	65%***
	SSZ + PBO	68	59%
16926184	MTX + SSZ	56	11%***
	SSZ	55	6%
	MTX	54	7%
Methotrexate + Sulfasalazine + Hydroxychloroquine			
12115219	MTX + HCQ	58	40%
	MTX + SSZ	55	55%***
	MTX + SSZ	58	29%
Leflunomide			
12416973	MTX + PBO	133	6%
	MTX + LEF	130	26%***
10573044	MTX + PBO	182	18%***
	LEF + PBO	182	13%
Adalimumab			

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
26138593	MTX	61	12%
	ADA + MTX	59	51%***
22739990	MTX + PBO	85	51%
	ADA + MTX	87	53%***
22562973	MTX + PBO	517	34%
	ADA + MTX	515	52%***
16385520	MTX	257	43%
	ADA	274	37%
	ADA + MTX	268	59%***
15146409	MTX + PBO	200	10%
	ADA + MTX	207	42%***
12528101	MTX + PBO	62	8%
	ADA + MTX	73	42%
18821658	MTX + PBO	75	45%
	ADA + MTX	73	56%***
19369462	MTX	166	31%
	ADA + MTX	199	53%
	ADA	161	60%***
Certolizumab			
26533965	MTX + PBO	213	53%
	CTZ + MTX	655	62%***
22344576	CTZ + MTX	126	18%***

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
	MTX + PBO	121	6%
19015207	MTX + PBO	127	3%
	CTZ + MTX	246	33%***
Etanercept			
24618266	MTX + PBO	55	22%
	ETN + MTX	55	26%***
15001324	MTX	228	40%
	ETN + MTX	231	69%***
	ETN	223	42%
11096165	MTX + PBO	217	30%
	ETN	207	43%***
20937671	MTX + PBO	249	42%
	RTX + MTX	250	65%***
20187135	ETN + MTX	108	70%***
	MTX	94	46%
18794178	ETN	103	49%
	ETN + SSZ	101	59%***
	SSZ	50	10%
Golimumab			
23861303	MTX + PBO	160	36%
	GOL + PBO	159	38%
	GOL + MTX	318	45%***

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
22661646	MTX + PBO	197	13%
	GOL + MTX	395	35%***
19066176	MTX + PBO	133	14%
	GOL + PBO	133	20%
	GOL + MTX	178	34%***
18383539	MTX + PBO	35	6%
	GOL + MTX	137	31%***
20131276	MTX + PBO	129	32%
	GOL	257	18%
	GOL + MTX	257	39%***
19644849	MTX + PBO	160	31%***
	GOL + PBO	159	35%
	GOL + MTX	318	41%***
25005327	MTX + PBO	160	36%
	GOL + MTX	159	48%***
Infliximab			
16572442	MTX + PBO	363	10%
	IFX + MTX	361	34%***
15641102	MTX + PBO	10	0%
	IFX + MTX	10	60%***
15529377	MTX + PBO	298	32%
	IFX + MTX	373	50%***

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
11096166	MTX + PBO	88	10%
	IFX + MTX	86	38%***
10622295	MTX + PBO	88	20%
	IFX + MTX	81	58%***
Rituximab			
22012969	MTX + PBO	249	42%
	RTX + MTX	250	65%***
20488885	MTX + PBO	172	9%
	RTX + MTX	170	26%***
16649186	MTX + PBO	149	13%
	RTX + MTX	192	34%***
15201414	MTX + PBO	40	5%
	RTX + PBO	40	15%
	RTX + MTX	40	35%***
16947627	MTX + PBO	209	5%
	RTX + PBO	311	27%***
17062648	MTX + PBO	40	5%
	RTX	40	13%
	RTX + MTX	40	35%***
16947627	MTX + PBO	209	8%
	RTX + MTX	301	28%***
Tocilizumab			

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
18625622	MTX + PBO	158	4%
	TCZ + MTX	170	29%***
22562983	TCZ + MTX	277	46%***
	TCZ + PBO	276	40%
21360490	MTX + PBO	393	9%
	TCZ + MTX	398	35%***
19297346	MTX + PBO	259	34%
	TCZ + PBO	265	44%***
18358926	MTX + PBO	204	11%
	TCZ + MTX	205	44%***
16947782	MTX + PBO	49	29%
	TCZ + MTX	50	53%***
	TCZ	52	41%
22972745	TCZ + MTX	360	27%***
	TCZ	163	24%
Abatacept			
19124524	MTX + PBO	253	42%
	ABA + MTX	256	57%***
16785473	MTX + PBO	219	18%
	ABA + MTX	433	47%***
16052582	MTX + PBO	119	20%
	ABA + MTX	115	42%***

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
18383390	ABA + MTX	378	54%***
	MTX + PBO	161	32%
Tofacitinib			
27002108	MTX + PBO	37	8%
	TOFA	36	8%***
	TOFA + MTX	36	8%
23348607	MTX + PBO	79	8%***
	TOFA + MTX	316	44%***
22006202	MTX + PBO	69	25%
	TOFA + MTX	71	40%***
27734232	MTX + PBO	40	8%
	TOFA + MTX	94	37%***
DOI: 10.1056/NEJMoa1310476	MTX	186	28%
	TOFA	373	49%***
Conventional synthetic + biologics			
23755969	MTX + SSZ+HCQ	178	26%
	ETN + MTX	175	36%***
22508468	ETN + MTX	244	38%***
	MTX+SSZ+HCQ	132	28%
20082236	Anti-TNF + MTX	60	51%***

Study PubMed ID	Arms	Participants/Arm	Events ACR 50 response
	Anti-TNF + LEF	60	47%
Head to head biologics			
18055472	MTX + PBO	110	20%
	IFX + MTX	165	32%
	ABA + MTX	156	48%***
21360491	Anti-TNF + MTX + PBO	18	6%
	Anti-TNF + RTX + MTX	33	12%***
16935912	ABA + ETN	85	28%***
	ETN + PBO	36	17%
18821691	DMARDs + PBO	415	9%
	TCZ + DMARDs	805	38%***
21949007	TCZ + DMARDs	409	19%***
	DMARDs + PBO	205	12%
26473625	ABA + MTX	318	No difference*
	ADA + MTX	328	No difference*
28629665	TCZ	384	35%
	TCZ + MTX	376	44%***
	ADA + MTX	386	43%
	RTX	144	41%
	Anti-TNF	151	45%***

Appendix 7 Table 4. Clinical outcomes reported in trials: DAS 28 (Remission)

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
Methotrexate +Sulfasalazine			
10364900	MTX + PBO	69	12%
	MTX + SSZ	68	16%***
	SSZ + PBO	68	11%
16926184	MTX + SSZ	56	5%***
	SSZ	55	2%
	MTX	54	2%
Adalimumab			
26138593	MTX	61	12%
	ADA + MTX	59	24%***
22739990	MTX + PBO	85	37%
	ADA + MTX	87	42%***
22562973	MTX + PBO	517	17%
	ADA + MTX	515	34%***
16385520	MTX	257	27%
	ADA	274	25%
	ADA + MTX	268	29%***
18821658	MTX + PBO	75	4%

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
	ADA + MTX	73	48%***
19369462	MTX	166	20%
	ADA + MTX	199	30%
	ADA	161	32%***
Certolizumab			
26533965	MTX + PBO	213	36%
	CTZ + MTX	655	48%***
22344576	CTZ + MTX	126	9%***
	MTX + PBO	121	3%
19015207	MTX + PBO	127	1%
	CTZ + MTX	246	9%***
Etanercept			
24618266	MTX + PBO	55	37%
	ETN + MTX	55	47%***
15001324	MTX	228	13%
	ETN + MTX	231	35%***
	ETN	223	16%
20937671	MTX + PBO	249	13%
	RTX + MTX	250	31%***
20187135	ETN + MTX	108	57%***
	MTX	94	35%
Golimumab			

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
23861303	MTX + PBO	160	35%
	GOL + PBO	159	31%
	GOL + MTX	318	45%***
22661646	MTX + PBO	197	3%
	GOL + MTX	395	6%***
19066176	MTX + PBO	133	6%
	GOL + PBO	133	12%
	GOL + MTX	178	21%***
18383539	MTX + PBO	35	6%
	GOL + MTX	137	26%***
20131276	MTX + PBO	129	15%
	GOL	257	18%
	GOL + MTX	257	38%***
19644849	MTX + PBO	160	28%
	GOL + PBO	159	25%
	GOL + MTX	318	38%***
25005327	MTX + PBO	160	29%
	GOL + MTX	159	39%***
Infliximab			
16572442	MTX + PBO	363	14%
	IFX + MTX	361	32%***
15641102	MTX + PBO	10	20%

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
	IFX + MTX	10	70%***
15529377	MTX + PBO	298	15%
	IFX + MTX	373	31%***
Rituximab			
22012969	MTX + PBO	249	13%
	RTX + MTX	250	31%***
20488885	MTX + PBO	172	2%
	RTX + MTX	170	5%***
16649186	MTX + PBO	149	11%
	RTX + MTX	192	18%***
15201414	MTX + PBO	40	50%
	RTX + PBO	40	85%***
	RTX + MTX	40	83%
16947627	MTX + PBO	209	0%
	RTX + PBO	311	3%
16947627	MTX + PBO	209	3%
	RTX + MTX	301	18%***
Tocilizumab			
18625622	MTX + PBO	158	2%
	TCZ + MTX	170	30%***
22562983	TCZ + MTX	277	40%***
	TCZ + PBO	276	35%

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
21360490	MTX + PBO	393	47%***
	TCZ + MTX	398	8%
19297346	MTX + PBO	259	12%
	TCZ + PBO	265	34%***
18358926	MTX + PBO	204	1%
	TCZ + MTX	205	27%***
16947782	MTX + PBO	49	8%
	TCZ + MTX	50	34%***
	TCZ	52	17%
22972745	TCZ + MTX	360	25%***
	TCZ	163	19%
Abatacept			
22915624	MTX + PBO	23	14%
	ABA + MTX	27	50%***
19124524	MTX + PBO	253	23%
	ABA + MTX	256	41%***
16052582	MTX + PBO	119	8%
	ABA + MTX	115	32%***
25367713	ABA + MTX	119	37%***
	ABA	116	27%
	MTX	116	22%
18383390	ABA + MTX	378	56%***

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
	MTX + PBO	161	31%
Tofacitinib			
27002108	MTX + PBO	37	6%
	TOFA	36	7%
	TOFA + MTX	36	8%***
23348607	MTX + PBO	79	2%
	TOFA + MTX	316	16%***
22006202	MTX + PBO	69	15%
	TOFA + MTX	71	31%***
DOI: 10.1056/NEJMoa1310476	MTX	186	10%
	TOFA	373	21%***
Conventional synthetic + biologics			
23755969	MTX + SSZ + HCQ	178	21%
	ETN + MTX	175	25%***
22508468	ETN + MTX	244	57%
	MTX + SSZ + HCQ	132	59%***
28388820	MTX + SSZ + HCQ	145	No difference*
	ETN + MTX	144	No difference*

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
	MTX + SSZ + LEF	104	36%
	Anti-TNF	101	44%***
20082236	Anti-TNF + MTX	60	20%***
	Anti-TNF + LEF	60	15%
Head to head biologics			
18055472	MTX + PBO	110	3%
	IFX + MTX	165	13%***
	ABA + MTX	156	11%
21360491	Anti-TNF + MTX + PBO	18	6%
	Anti-TNF + RTX + MTX	33	18%***
18821691	DMARDs + PBO	415	3%
	TCZ + DMARDs	805	30%
21949007	TCZ + DMARDs	409	38%***
	DMARDs + PBO	205	3%
27654603	NON-TNFI	146	20%***

Study PubMed ID	Arms	Participants/Arm	Remission (DAS28)
	Alternate Anti-TNF	146	10%
23148339	ADA + MTX	60	2%
	ETN + MTX	60	2%
26473625	ABA + MTX	318	15%***
	ADA + MTX	328	11%
24442884	RTX	604	11%***
	Alternate Anti-TNF	507	8%
28629665	TCZ	384	23%
	TCZ + MTX	376	27%
	ADA + MTX	386	33%***
	RTX	144	23%***
	Anti-TNF	151	21%

Appendix 7 Table 5. Radiological progression reported in trials

Study PubMed ID	Arms	Participants/Arm	Radiological progression mean change % progressed
Methotrexate +Sulfasalazine			

10364900	MTX + PBO	69	4.5
	MTX + SSZ	68	3.5***
	SSZ + PBO	68	4.6
Leflunomide			
10573044	MTX + PBO	182	3.3***
	LEF + PBO	182	3.5
Adalimumab			
22739990	MTX + PBO	85	3.0
	ADA + MTX	87	2.9***
22562973	MTX + PBO	517	1.0
	ADA + MTX	515	0.2***
16385520	MTX	257	10.4
	ADA	274	5.5
	ADA + MTX	268	1.9***
15146409	MTX + PBO	200	2.7
	ADA + MTX	207	0.1***
19369462	MTX	166	4.1
	ADA + MTX	199	1***
	ADA	161	4
22915617	ADA + MTX	229	18%***
	ADA	205	40%
	MTX	204	40%
Certolizumab			

26533965	MTX + PBO	213	1.8
	CTZ + MTX	655	0.2***
19015207	MTX + PBO	127	1.2
	CTZ + MTX	246	-0.4***
Etanercept			
24618266	MTX + PBO	55	0.9*
	ETN + MTX	55	0.9*
15001324	MTX	228	2.8
	ETN + MTX	231	-0.5***
	ETN	223	0.5
11096165	MTX + PBO	217	1.6
	ETN	207	1.0***
20937671	MTX + PBO	249	1.1
	RTX + MTX	250	0.4***
20187135	ETN + MTX	108	10%***
	MTX	94	33%
18794178	ETN	103	2.8
	ETN + SSZ	101	2.6***
	SSZ	50	4.5
Golimumab			
23861303	MTX + PBO	160	1.4
	GOL + MTX	318	0.4***
22661646	MTX + PBO	197	1.1

	GOL + MTX	395	0.0***
19066176	MTX + PBO	133	0.6*
	GOL + MTX	178	0.6*
25005327	MTX + PBO	160	57.50%
	GOL + MTX	159	64.20%***
Infliximab			
15529377	MTX + PBO	298	3.7
	IFX + MTX	373	0.5***
11096166	MTX + PBO	88	7
	IFX + MTX	86	-0.7***
Rituximab			
22012969	MTX + PBO	249	1.1
	RTX + MTX	250	0.4***
16947627	MTX + PBO	209	1.2
	RTX + PBO	311	0.6***
16947627	MTX + PBO	209	1.2
	RTX + MTX	301	0.6***
Tocilizumab			
22562983	TCZ + MTX	277	0.1***
	TCZ + PBO	276	0.2
21360490	MTX + PBO	393	1.1
	TCZ + MTX	398	0.3***
Abatacept			

22915624	MTX + PBO	23	0.4
	ABA + MTX	27	-0.3***
19124524	MTX + PBO	253	1.1
	ABA + MTX	256	0.6***
16785473	MTX + PBO	219	2.3
	ABA + MTX	433	1.2***
	ABA + MTX	91	Better***
	ABA	81	
	MTX	84	
18383390	ABA + MTX	378	1.1***
	MTX + PBO	161	3.1
Tofacitinib			
27002108	MTX + PBO	37	1.4
	TOFA	36	-0.2***
	TOFA + MTX	36	0.9
23348607	MTX + PBO	79	0.9
	TOFA + MTX	316	0.1***
27734232	MTX + PBO	40	64.90%
	TOFA + MTX	94	85.40%***
DOI: 10.1056/NEJMoa1310476	MTX	186	35.10%***
	TOFA	373	20.10%
Conventional synthetic + biologics			
23755969	MTX + SSZ + HCQ	178	0.5

	ETN + MTX	175	0.3***
22508468	ETN + MTX	244	0.6***
	MTX + SSZ + HCQ	132	2.7
Head to head biologics			
26473625	ABA + MTX	318	38%
	ADA + MTX	328	37%***

Appendix 7 Table 6. Adverse events reported in the trials

Study PubMed ID	Arms	Participants/Arm	Adverse events
Methotrexate +Sulfasalazine			
10364900	MTX + PBO	69	3***
	MTX + SSZ	68	8
	SSZ + PBO	68	6
Leflunomide			
12416973	MTX + PBO	133	9***
	MTX + LEF	130	16
10573044	MTX + PBO	182	22
	LEF + PBO	182	10***
Adalimumab			
26138593	MTX	61	2***

Study PubMed ID	Arms	Participants/Arm	Adverse events
	ADA + MTX	59	3
22739990	MTX + PBO	85	4
	ADA + MTX	87	3***
22562973	MTX + PBO	517	32***
	ADA + MTX	515	37
16385520	MTX	257	16***
	ADA	274	21
	ADA + MTX	268	18
15146409	MTX + PBO	200	1***
	ADA + MTX	207	16
12528101	MTX + PBO	62	0***
	ADA + MTX	73	3
18821658	MTX + PBO	75	11***
	ADA + MTX	73	13
Certolizumab			
22344576	CTZ + MTX	126	16
	MTX + PBO	121	12***
19015207	MTX + PBO	127	4***
	CTZ + MTX	246	18
Etanercept			
24618266	MTX + PBO	55	3***
	ETN + MTX	55	15

Study PubMed ID	Arms	Participants/Arm	Adverse events
15001324	MTX	228	10
	ETN + MTX	231	10
	ETN	223	10
11096165	MTX + PBO	217	16***
	ETN	207	77
20187135	ETN + MTX	108	8***
	MTX	94	12
18794178	ETN	103	34
	ETN + SSZ	101	21
	SSZ	50	2***
Golimumab			
23861303	MTX + PBO	160	22
	GOL + MTX	318	44
22661646	MTX + PBO	197	4***
	GOL + MTX	395	19
19066176	MTX + PBO	133	5***
	GOL + PBO	133	8
	GOL + MTX	178	22
18383539	MTX + PBO	35	3***
	GOL + MTX	137	11
20131276	MTX + PBO	129	2***
	GOL	257	10

Study PubMed ID	Arms	Participants/Arm	Adverse events
	GOL + MTX	257	10
19644849	MTX + PBO	160	16
	GOL + PBO	159	11***
	GOL + MTX	318	24
Infliximab			
16572442	MTX + PBO	363	6***
	IFX + MTX	361	24
15641102	MTX + PBO	10	0***
	IFX + MTX	10	1
15529377	MTX + PBO	298	32***
	IFX + MTX	373	51
11096166	MTX + PBO	88	18
	IFX + MTX	86	16
10622295	MTX + PBO	88	14
	IFX + MTX	81	10***
Rituximab			
22012969	MTX + PBO	249	26
	RTX + MTX	250	24***
20488885	MTX + PBO	172	3***
	RTX + MTX	170	7
16649186	MTX + PBO	149	0***
	RTX + MTX	192	6

Study PubMed ID	Arms	Participants/Arm	Adverse events
15201414	MTX + PBO	40	4
	RTX + PBO	40	4
	RTX + MTX	40	4
16947627	MTX + PBO	209	23
	RTX + PBO	311	18***
16947627	MTX + PBO	209	49***
	RTX + MTX	301	53
Tocilizumab			
18625622	MTX + PBO	158	31
	TCZ + MTX	170	24***
22562983	TCZ + MTX	277	17
	TCZ + PBO	276	16***
21360490	MTX + PBO	393	44***
	TCZ + MTX	398	50
19297346	MTX + PBO	259	8***
	TCZ + PBO	265	11***
18358926	MTX + PBO	204	33
	TCZ + MTX	205	29
16947782	MTX + PBO	49	4***
	TCZ + MTX	50	6
	TCZ	52	5
22972745	TCZ + MTX	360	11

Study PubMed ID	Arms	Participants/Arm	Adverse events
	TCZ	163	9***
Abatacept			
22915624	MTX + PBO	23	6***
	ABA + MTX	27	8
19124524	MTX + PBO	253	20
	ABA + MTX	256	20
16785473	MTX + PBO	219	5***
	ABA + MTX	433	19
16052582	MTX + PBO	119	2
	ABA + MTX	115	2
25367713	ABA + MTX	119	8
	ABA	116	14
	MTX	116	9***
18383390	ABA + MTX	378	68***
	MTX + PBO	161	149
Tofacitinib			
27002108	MTX + PBO	37	1***
	TOFA	36	5
	TOFA + MTX	36	4
23348607	MTX + PBO	79	5***
	TOFA + MTX	316	49
22006202	MTX + PBO	69	8

Study PubMed ID	Arms	Participants/Arm	Adverse events
	TOFA + MTX	71	5***
DOI: 10.1056/NEJMoa1310476	MTX	186	22
	TOFA	373	40***
Conventional synthetic + biologics			
23755969	MTX + SSZ + HCQ	178	25***
	ETN + MTX	175	26
22508468	ETN + MTX	244	18
	MTX + SSZ + HCQ	132	12***
	MTX + SSZ + LEF	104	10***
	Anti-TNF	101	18
Head to head biologic			
18055472	MTX + PBO	110	3***
	IFX + MTX	165	8
	ABA + MTX	156	3
21360491	Anti-TNF + MTX + PBO	18	0***
	Anti-TNF + RTX + MTX	33	2
16935912	ABA + ETN	85	14
	ETN + PBO	36	1***
18821691	DMARDs + PBO	415	54
	TCZ + DMARDs	805	18***

Study PubMed ID	Arms	Participants/Arm	Adverse events
21949007	TCZ + DMARDs	409	35
	DMARDs + PBO	205	13***
27654603	NON-TNFI	146	16
	Alternate Anti-TNF	146	8***
23148339	ADA + MTX	60	1***
	ETN + MTX	60	2
24442884	RTX	604	82
	Alternate Anti-TNF	507	56***
28629665	TCZ	384	35
	TCZ + MTX	376	27
	ADA + MTX	386	24***
	RTX	144	15
	Anti-TNF	151	12***

Appendix 7 Table 7. HAQ-DI scores reported in trials

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
Methotrexate +Sulfasalazine			
10364900	MTX + PBO	69	-0.73***
	MTX + SSZ	68	-0.7
	SSZ + PBO	68	-0.74
16926184	MTX + SSZ	56	-0.5***
	SSZ	55	-0.25
	MTX	54	-0.19
Leflunomide			
10888712	MTX + PBO	498	-0.5***
	LEF + PBO	501	-0.45
10573044	MTX + PBO	182	-0.2
	LEF + PBO	182	-0.3***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
Adalimumab			
26138593	MTX	61	44.30%
	ADA + MTX	59	71.20%***
22739990	MTX + PBO	85	0.66***
	ADA + MTX	87	0.61
22562973	MTX + PBO	517	0.9***
	ADA + MTX	515	0.7
16385520	MTX	257	63%
	ADA	274	58%
	ADA + MTX	268	72%***
15146409	MTX + PBO	200	-0.25***
	ADA + MTX	207	-0.05
12528101	MTX + PBO	62	-0.27

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
	ADA + MTX	73	-0.59***
18821658	MTX + PBO	75	-0.4
	ADA + MTX	73	-0.7***
Certolizumab			
26533965	MTX + PBO	213	-0.8
	CTZ + MTX	655	-1***
22344576	CTZ + MTX	126	-0.32***
	MTX + PBO	121	-0.09
19015207	MTX + PBO	127	11%
	CTZ + MTX	246	53%***
19909548	CTZ + MTX	390	-0.6
	MTX + PBO	199	-2***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
Etanercept			
24618266	MTX + PBO	55	-0.31
	ETN + MTX	55	-0.4***
20937671	MTX + PBO	249	-0.62
	RTX + MTX	250	-0.91***
18794178	ETN	103	1***
	ETN + SSZ	101	1.2
	SSZ	50	1.5
Golimumab			
23861303	MTX + PBO	160	0.58***
	GOL + MTX	318	0.7
22661646	MTX + PBO	197	45.20%
	GOL + MTX	395	67.30%***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
19066176	MTX + PBO	133	-0.13
	GOL + PBO	133	-0.13
	GOL + MTX	178	-0.44***
20131276	MTX + PBO	129	-9.7***
	GOL	257	14.4
	GOL + MTX	257	34.3
19644849	MTX + PBO	160	36.90%
	GOL + PBO	159	31%
	GOL + MTX	318	45%***
25005327	MTX + PBO	160	73.60%
	GOL + MTX	159	82.60%***
Infliximab			

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
15641102	MTX + PBO	10	-10***
	IFX + MTX	10	-80
15529377	MTX + PBO	298	65.20%
	IFX + MTX	373	75.50%***
11096166	MTX + PBO	88	10%
	IFX + MTX	86	30%***
10622295	MTX + PBO	88	-3
	IFX + MTX	81	-24***
Rituximab			
22012969	MTX + PBO	249	-0.62
	RTX + MTX	250	-0.91***
20488885	MTX + PBO	172	47.70%

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
	RTX + MTX	170	58.20%***
16649186	MTX + PBO	149	-0.16
	RTX + MTX	192	-0.49***
16947627	MTX + PBO	209	-0.1
	RTX + PBO	311	-0.4***
17062648	MTX + PBO	40	-0.3
	RTX	40	-0.5
	RTX + MTX	40	-0.6***
16947627	MTX + PBO	209	-0.1
	RTX + MTX	301	-0.4***
Tocilizumab			
18625622	MTX + PBO	158	-0.05

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
	TCZ + MTX	170	-0.39***
22562983	TCZ + MTX	277	-0.55***
	TCZ + PBO	276	-0.51
21360490	MTX + PBO	393	-0.6***
	TCZ + MTX	398	-0.4
19297346	MTX + PBO	259	-0.5
	TCZ + PBO	265	-0.7***
18358926	MTX + PBO	204	-0.34
	TCZ + MTX	205	-0.52***
Abatacept			
19124524	MTX + PBO	253	62.10%
	ABA + MTX	256	72.90%***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
16052582	MTX + PBO	119	7.60%
	ABA + MTX	115	15.70%***
25367713	ABA + MTX	119	26***
	ABA	116	19
	MTX	116	12
Tofacitinib			
27002108	MTX + PBO	37	7.3
	TOFA	36	7.5
	TOFA + MTX	36	7.6***
23348607	MTX + PBO	79	-0.55
	TOFA + MTX	316	-0.66***
22006202	MTX + PBO	69	-0.16
	TOFA + MTX	71	-0.53***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
25186034	MTX + PBO	66	-0.18
	TOFA + MTX	134	-0.46***
27734232	MTX + PBO	40	-0.28
	TOFA + MTX	94	-0.68***
DOI: 10.1056/NEJMoa1310476	MTX	186	-0.7
	TOFA	373	-0.9***
Conventional synthetic + biologics			
23755969	MTX + SSZ + HCQ	178	-0.46
	ETN + MTX	175	-0.64***
22508468	ETN + MTX	244	-0.1***
	MTX + SSZ + HCQ	132	0

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
	MTX + SSZ + LEF	104	-0.45***
	Anti-TNF	101	-0.3
Head to head biologics			
18055472	MTX + PBO	110	-1.48
	IFX + MTX	165	-2.25
	ABA + MTX	156	-2.53***
21360491	Anti-TNF + MTX + PBO	18	0.70%
	Anti-TNF + RTX + MTX	33	-22%***
16935912	ABA + ETN	85	-0.3***

Study PubMed ID	Arms	Participants/Arm	HAQ-DI/ (% achieving M-HAQ score of 0 or reduction of 0.3)
	ETN + PBO	36	-0.2
27654603	NON-TNFI	146	-0.43***
	Alternate Anti-TNF	146	-0.38
24442884	RTX	604	-0.6***
	Alternate Anti-TNF	507	-0.5
	RTX	144	-0.49***
	Anti-TNF	151	-0.38

Appendix 7 Table 8. Quality of life score change reported in trials

Study PubMed ID	Arms	Participants/Arm	Quality of Life Mean change SF36
Leflunomide			
10573044	MTX + PBO	182	7.6***

	LEF + PBO	182	4.6
Adalimumab			
22739990	MTX + PBO	85	2.7
	ADA + MTX	87	3.3***
15146409	MTX + PBO	200	6
	ADA + MTX	207	16***
12528101	MTX + PBO	62	
	ADA + MTX	73	Better***
18821658	MTX + PBO	75	-4.7
	ADA + MTX	73	-7.6***
Certolizumab			
26533965	MTX + PBO	213	12.7***
	CTZ + MTX	655	12.4
22344576	CTZ + MTX	126	5.12***
	MTX + PBO	121	-0.38
19015207	MTX + PBO	127	0.9
	CTZ + MTX	246	5.5***
19909548	CTZ + MTX	390	8.1***
	MTX + PBO	199	2
Etanercept			
24618266	MTX + PBO	55	6.93
	ETN + MTX	55	8.1***
18794178	ETN	103	25%

	ETN + SSZ	101	30%***
	SSZ	50	0%
Golimumab			
20131276	MTX + PBO	129	9.3***
	GOL	257	6
	GOL + MTX	257	9.1
Infliximab			
15641102	MTX + PBO	10	-12
	IFX + MTX	10	-85***
15529377	MTX + PBO	298	10.1
	IFX + MTX	373	13.2***
11096166	MTX + PBO	88	18%
	IFX + MTX	86	40%***
Rituximab			
20488885	MTX + PBO	172	2.49***
	RTX + MTX	170	5.7
Tocilizumab			
22562983	TCZ + MTX	277	-5.97***
	TCZ + PBO	276	-5.19
18358926	MTX + PBO	204	5
	TCZ + MTX	205	9.7***
Abatacept			
19124524	MTX + PBO	253	9.18

	ABA + MTX	256	11.68***
18383390	ABA + MTX	378	9.7***
	MTX + PBO	161	6.4
Tofacitinib			
25186034	MTX + PBO	66	49.1
	TOFA + MTX	134	66.4***
Conventional synthetic + biologics			
	MTX + SSZ + LEF	104	
	Anti-TNF	101	Better***
Head to head biologics			
18055472	MTX + PBO	110	4
	IFX + MTX	165	6
	ABA + MTX	156	7***
16935912	ABA + ETN	85	7.5***
	ETN + PBO	36	3.4
23148339	ADA + MTX	60	0.7
	ETN + MTX	60	0.7
	RTX	144	0.2***
	Anti-TNF	151	0.3

Appendix 7 Table 9. Baseline trial details from selected abstracts

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
Strand, 2013	USA	52	MTX	462	100	100	NR	NR	NR	NR
			TOFA							
Strand, 2017	USA	52	TOFA	1146	NR	NR	20	NR	NR	NR
			TOFA + MTX							
			ADA + MTX							
Weinblatt, 2013	USA	52	ABA + MTX	646	100	100	NR	1.8	5.5	NR
			ADA +							

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
			MTX							
Fleischmann, 2013	International	104	ABA + MTX	646	100	100	NR	NR	NR	NR
			ADA + MTX							
Koehm, 2017	International	24	TCZ	325	100	100	NR	NR	NR	NR
			ADA							
Alten, 2014	Germany	104	TOFA	392	NR	NR	NR	NR	NR	NR
			MTX							
Burmester, 2015	Germany	24	MTX	579	0	0	NR	NR	6.6	1.52
			TCZ							

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS28	HAQ-DI
Emery, 2013a	UK	52	MTX	319	0	0	NR	NR	NR	NR
			MTX + GOL							
Emery, 2013b	International	26	ADA + MTX	1032	0	0	NR	NR	NR	NR
			MTX + PBO							
Kremer, 2017	USA	52	TCZ + MTX	296	100	100	15	6.8	6.3	NR
			TCZ							
Kavanaugh, 2012	International	52	ADA +	1032	0	0	NR	1.5	NR	NR

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
			MTX							
			MTX + PBO							
O'dell, 2012	International	48	MTX + SSZ + HCQ	353	100	100	19.6	5.2	5.8	NR
			MTX + ETN							
Fleischmann, 2012	International	78	ADA + MTX	926	0	0	NR	<1	NR	NR
			MTX + PBO							

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
Detert, 2012	Germany	48	ADA + MTX	172	0	0	15	0.2	6.2	1.4
			MTX + PBO							
Weinblatt, 2014	USA	52	GOL + MTX	393	100	100	20	NR	NR	NR
			MTX+ PBO							
Harrold, 2016	USA	26	TCZ	431	100	100	10	NR	NR	NR
			TNF + MTX							
Kremer, 2013	USA	260	TCZ +	1190	NR	NR	NR	8.96	NR	NR

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
			MTX							
			MTX + PBO							
Detert, 2013	Germany	48	ADA + MTX	172	NR	NR	15	1.7	6.3	NR
			MTX + PBO							
De Filippis, 2014	Italy	52	ENT	54	100	NR	NR	NR	NR	NR
			INF							
Weinblatt, 2014	USA	104	ABA + MTX	646	NR	NR	NR	NR	NR	NR

Study	Country	Duration (week)	Arms	N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/week)	Disease duration (year)	DAS 28	HAQ-DI
			ADA + MTX							
Kremer, 2017	USA	NR	TCZ ICZ +MTX	294	NR	NR	NR	NR	NR	NR

Appendix 7 Table 10. Outcomes reported in the selected conference abstracts

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
Strand, 2013	MTX	328	NR	NR	NR	NR	-0.98	12.34
	TOFA	134	NR	NR	NR	NR	-0.68	7.42
Strand, 2017	TOFA	384	NR	NR	NR	NR	-0.6	22.2
	TOFA + MTX	376	NR	NR	NR	NR	-0.6	24.9
	ADA + MTX	386	NR	NR	NR	NR	-0.6	24.2
Weinblatt, 2013	ABA + MTX	318	46.20%	NR	0.58	3.50%	NR	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	ADA + MTX	328	46%	NR	0.38	6.10%	NR	NR
Fleischmann, 2013	ABA + MTX	318	NR	NR	NR	NR	54.10%	9.3
	ADA + MTX	328	NR	NR	NR	NR	48.80%	8.6
Koehm, 2017	ABA + MTX	NR	NR	90.10%	NR	NR	NR	NR
	ADA +	NR	NR	59.10%	NR	NR	NR	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	MTX							
Alten, 2014	ABA + MTX	286	NR	NR	NR	NR	-1	12.5
	ADA + MTX	106	NR	NR	NR	NR	-0.7	7.6
Burmester, 2015	ABA + MTX	287	43.20%	15%	NR	NR	-0.61	NR
	ADA + MTX	292	47.60%	38.70%	NR	NR	-0.65	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
Emery, 2013a	ABA + MTX	160	35.60%	26.30%	NR	NR	62.5	NR
	ADA + MTX	159	48.40%	39.60%	NR	NR	70.4	NR
Emery, 2013b	ABA + MTX	515	NR	29.70%	NR	NR	NR	NR
	ADA + MTX	517	NR	16.10%	NR	NR	NR	NR
Kremer, 2017	ABA +	148	NR	NR	NR	0.01	NR	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	MTX							
	ADA + MTX	148	NR	NR	NR	0.02	NR	NR
Kavanaugh, 2012	ABA + MTX	515	NR	-0.80	NR	NR	NR	NR
	ADA + MTX	515	NR	-0.90	NR	NR	NR	NR
O'dell, 2012	ABA + MTX	NR	NR	-2.10	0.87	NR	NR	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	ADA + MTX	NR	NR	-2.30	0.23	NR	NR	NR
Fleischmann, 2012	ABA + MTX	456	NR	39.00	86%	NR	48%	NR
	ADA + MTX	460	NR	31	72%	NR	45%	NR
Detert, 2012	ABA + MTX	87	54%	43.80%	6.3	NR	0.6	NR
	ADA +	85	48.20%	36.80%	11.4	NR	0.65	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	MTX							
Weinblatt, 2014	ABA + MTX	204	37.00%	NR	NR	NR	-0.43	NR
	ADA + MTX	189	37.80%	NR	NR	NR	-0.37	NR
Harrold, 2016	ABA + MTX	112	19.50%	NR	NR	NR	-0.1	NR
	ADA + MTX	119	15.20%	NR	NR	NR	-0.1	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
Kremer, 2013	ABA + MTX	NR	NR	NR	47%	65%	NR	NR
	ADA + MTX	NR	NR	NR	65%	16%	NR	NR
Detert, 2013	ABA + MTX	87	52.60%	42.40%	Better	NR	0.61	41.4
	ADA + MTX	85	51.40%	36.80%		NR	0.66	42
	ABA +	18	54.40%	NR	NR	NR		NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
De Filippis, 2014	MTX							
	ADA + MTX	36	74.40%	NR	NR	NR	Better	NR
Weinblatt, 2014	ABA + MTX	318	44.70%	-2.35	84.80%	NR	54.10%	NR
	ADA + MTX	328	46.60%	-2.33	83.80%	NR	48.80%	NR
Kremer, 2017	ABA + MTX	147	51.70%	50.30%	NR	8	NR	NR

	Arms	Participants/ Arm	Events ACR 50 responses	Remission (DAS28)	Radiological progression mean change	Adverse events	HAQ-DI/% (achieving M-HAQ score of 0 or reduction of 0.3)	Quality of life mean change SF36
	ADA + MTX	147	63.90%	59.20%	NR	14	NR	NR