RHEUMATOID ARTHRITIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- January 2024

To the CHI Original Clinical Guidance- Issued Rheumatoid Arthritis December 2019

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ALT	Alanine Aminotransferase
APLAR	Asia Pacific League of Associations for Rheumatology
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette-Guerine
bDMARD	Biologic Disease-Modifying Antirheumatic Drug
CADTH	Canadian Agency for Drugs and Technologies in Health
cDMARD	Conventional Disease-Modifying Anti-Rheumatic Drug
CDR	Clinical Decision Rule
CHI	Council of Health Insurance
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
CVD	Cardiovascular Disease
CZP	Certolizumab
DMARD	Disease-Modifying Antirheumatic Drug
ETN	Etanercept
GGT	Gamma Glutamyl Transferase
HAS	Haute Autorite de Sante
HBcAb	Hepatitis B Core Antibodies
HBeAg	Hepatitis B Envelope Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HPV	Human Papilloma Virus
HTA	Health Technology Assessment
IGRA	Interferon Gamma Release Assay
ILD	Interstitial Lung Disease

INR	International Normalized Ratio
JAK	Janus Kinase
JAK-I	Janus Kinase Inhibitor
LFN	Leflunomide
LoA	Level of Agreement
LoE	Level of Evidence
MTX	Methotrexate
NSAID	Nonsteroidal Anti-Inflammatory Drug
PMDA	Pharmaceuticals and Medical Devices Agency
RA	Rheumatoid Arthritis
RMD	Rheumatic and Musculoskeletal Disease
RTX	Rituximab
SARD	Systemic autoimmune rheumatic disease
SFDA	Saudi Food and Drug Authority
SoR	Strength of Recommendation
SR	Systematic Review
SSZ	Sulfasalazine
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitor
tsDMARD	Target Synthetic Disease-Modifying Antirheumatic Drug
TST	Tuberculosis Skin Test
TTT	Treat to Target

Executive Summary

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement. It is a chronic inflammatory disorder caused in many cases by the interaction between genes and environmental factors, including tobacco, that primarily involves synovial joints. It typically starts in small peripheral joints, is usually symmetric, and progresses to involve proximal joints if left untreated. Joint inflammation over time leads to the destruction of the joint with loss of cartilage and bone erosions. RA with a symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is defined as established RA. RA, if untreated, is a progressive disease with morbidity and increased mortality. This activity describes the evaluation and management of rheumatoid arthritis and reviews the role of the interprofessional team in improving care for patients with this condition[1].

The most common and predominant symptoms include joint pain and swelling, usually starting insidiously over a period of weeks to months. Initial joint involvement is typically in the small joints of the hands and feet, followed by larger joints. One of the hallmarks is stiffness, particularly morning stiffness. Usually, the onset of symptoms is slow and insidious; however, in some cases, an episodic pattern of symptoms can be seen and is defined as palindromic rheumatism. Not all patients with palindromic rheumatism develop RA, and they respond to hydroxychloroquine which supports the idea that palindromic rheumatism is a distinct phenotype of RA[1].

The etiology of RA has a significant basis in genetics. It is thought to result from the interaction between patients' genotypes and environmental factors. Cigarette smoking is the strongest environmental risk factor associated with RA. Studies have shown that in anti-citrullinated protein antibody (anti-CCP) positive individuals, there is an interaction between the shared epitope (SE) and smoking that increases the risk of RA. Other environmental triggers may play a role as a trigger for RA, which is more closely associated with seropositive RA. These include silica, asbestos, textile dust, and *P. gingivalis*. This suggests that external exposure to various antigens in parts of the host distant from the joints then triggers an autoimmune inflammatory response in the joints. These distant locations include the lungs, oropharynx, and gastrointestinal tract. Changes in the composition and function of the intestinal microbiome have been related to RA as well. The composition of the gut microbiome becomes altered in patients with RA (dysbiosis), where patients have decreased gut microbiome diversity compared with healthy individuals. There is an increase in these genera: *Actinobacteria, Collinsella, Eggerthalla,* and *Faecalibacterium*. *Collinsella* alters gut mucosal permeability and has been related to increased rheumatoid arthritis disease severity[1].

Complications of RA span multiple organ systems and are known to worsen clinical outcomes in patients. It is imperative to monitor for the development of these complications and quickly alter treatment plans if applicable. Frequent recurrent serious opportunistic infections occur in patients with RA, which warrants withholding disease-modifying antirheumatic drug (DMARD) therapy until they are treated. The increased frequency of infections in patients with RA is thought to be due to underlying immune dysfunction from the disease itself and the use of DMARD therapy[1].

➔ *Complications and Comorbidities Associated with Uncontrolled Systemic Inflammation*:

Chronic joint inflammation results in radiographic damage, progressive deformity, and functional disability. Anemia of chronic disease and Felty syndrome are well-documented complications of seropositive RA. The secondary form of Sjögren syndrome is associated with RA and can have a prevalence of as high as 10% in patients with RA and pulmonary disease. *Pleuritis, bronchiolitis, and interstitial lung disease* are also associated with RA. Although rare, RA treatment with methotrexate and anti-tumor necrosis factor (TNF) agents can also lead to pulmonary injury. *Coronary artery disease* has a strong association with RA. Patients with RA also have a greater risk of developing lymphoma, with a higher incidence of non-Hodgkin lymphoma in these patients. The clinical course of RA in these patients is accelerated, and diffuse B-cell lymphoma is often the most common subtype. Non-Hodgkin's lymphoma is more common in patients with RA, but this occurs mainly in patients with persistently active disease. The use of biologic DMARDs does not appear to increase the risk of lymphoma[1].

➔ *Complications and Comorbidities Associated with RA Disease and Treatment*

Premature death, serious infections, osteopenia, and osteoporosis are complications of the disease itself and can also be associated with drug therapies, mainly glucocorticoids. There is an increased risk of venous thromboembolic disease in patients with RA, as stated above, even after adjusting for other risk factors for thromboembolic disease. Multiple studies have reported a higher risk of thromboembolic disease in patients receiving TNF inhibitor therapy and JAK inhibitors. Depression is a significant complication of RA: it is present in patients with long-term active disease and debilitating physical dysfunction[1].

The epidemiology and prevalence of RA in the Middle East and North Africa (MENA) region is not clearly understood. Only a limited number of studies have investigated the incidence and prevalence rates of RA among the MENA region population. The prevalence of RA in patients visiting the orthropedic clinics of the selected hospitals of the Madinah region of Saudi Arabia was estimated to be 14.46%, which is higher than reported by some other studies conducted in different regions of Saudi Arabia. This variation is because of the differences in study design and due to the regional

differences. Middle and older aged individuals were more prone to be affected by the disease. Further, the prevalence of RA was found to be higher in women as compared to men, which is well supported by the available literature. The most common disease marker of the RA patients was painful joint count, whereas, the most common clinical presentation and comorbidity of RA patients was arthritis and diabetes, respectively[2].

The global RA prevalence estimate was 0.46% (95% confidence interval [CI] 0.39-0.54; I2 = 99.9%) with a 95% prediction interval (0.06-1.27). The global prevalence of RA between 1980 and 2019 was 460 per 100,000 population, with variations due to geographical location and study methodology[3].

Optimal care of patients with RA consists of an integrated approach that includes both pharmacologic and nonpharmacologic therapies. Many nonpharmacologic treatments may be utilized and include 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[4].

Medication-based therapies consist of several classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), 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[4].

A treat-to-target approach is recommended for RA, with the target being low disease activity or remission, as determined by validated instruments for measuring disease activity. In pregnant patients with RA, no special obstetric monitoring is indicated beyond what is performed for usual obstetric care. However, some of the medications used in treating RA can have adverse effects on the fetus and may have to be discontinued several months before conception is planned[4].

Surgical procedures may also be an option for the treatment of RA and include synovectomy, tenosynovectomy, tendon realignment, reconstructive surgery or arthroplasty, arthrodesis[4].

CHI issued Rheumatoid Arthritis guidelines in Dec 2019 updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Rheumatoid Arthritis clinical guidance and seeks to offer guidance for the effective management of **Rheumatoid Arthritis**. It provides an **update on the Rheumatoid Arthritis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI

Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being the **updated guidelines** added to the report such as the National Institute for Health and Care Excellence (**NICE**) Guideline on the Management of Rheumatoid Arthritis in Adults (**2020**)[5], the European Alliance of Associations for Rheumatology (**EULAR**) recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs (**2022**)[6], the American College of Rheumatology (**ACR**) guideline for the treatment of rheumatoid arthritis (**2021**)[7], and the **new guidelines** added to the report such as the **Saudi** Guideline for management of rheumatoid arthritis in adult patients (**2020**)[8], the **Italian Society for Rheumatology** clinical practice guidelines for rheumatoid arthritis (**2019**)[9], the use of biological disease-modifying antirheumatic drugs for inflammatory arthritis in Korea: results of a **Korean Expert Consensus** (**2020**)[10], the **Japan College of Rheumatology** drug treatment algorithm and recommendations from the 2020 update of the clinical practice guidelines for the management of rheumatoid arthritis (secondary publication, **2022**)[11], and the **APLAR** update of the recommendations for treatment of rheumatoid arthritis (**2018**)[12].

After carefully examining clinical guidelines and reviewing the SFDA drug list, there are new SFDA registered drugs to include in the CHI formulary while removing ACEMETACIN, Capsule, hard, 60 mg, ACEMETACIN, Prolonged-release capsule, 90 mg, ASCORBIC ACID, CALCIUM GLYCEROPHOSPHATE, Effervescent tablet, TIAPROFENIC ACID 300 mg as they are no longer registered on the SFDA Drug List of November 2023. There has been a new drug that received FDA approval.

There have been no changes and updates made to the previously listed drugs in terms of drug information and prescribing edits since December 2019.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Rheumatoid Arthritis therapeutic management.

Below is a table summarizing the major changes based on the different Rheumatoid Arthritis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Rheumatoid Arthritis

Management of Rheumatoid Arthritis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Methotrexate (MTX) should be part of the first treatment strategy.	1a, A	EULAR recommendations for the management of rheumatoid arthritis, 2022
Methotrexate administration Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate	Moderate	American College of Rheumatology Guideline, 2021
Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of <15 mg	Moderate/ Very low	American College of Rheumatology Guideline, 2021
In patients with a contraindication to MTX (or early intolerance), leflunomide (LEF) or sulfasalazine (SSZ) should be considered as part of the (first) treatment strategy.	1a, A	EULAR recommendations for the management of rheumatoid arthritis, *2022*
Patients who cannot tolerate MTX may receive other csDMARDs such as LEF and SSZ as 1st-line treatment. Hydroxychloroquine (HCQ), iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability.	Moderate	2018 update of the APLAR recommendations
Short-term glucocorticoids should be considered when initiating or changing conventional synthetic DMARDS, or csDMARDs (MTX, leflunomide, sulfasalazine), in	1a, A	EULAR recommendations for the management of rheumatoid arthritis, *2022*

different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.		
A short-term course of glucocorticoids can be considered to control active RA in combination with csDMARDs. In view of their cumulative side effects, they should be used at the lowest dose necessary and tapered as rapidly as clinically feasible (< 6 months). Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation	Level 1 Strength A	The Italian Society for Rheumatology, 2019
If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a biologic DMARD (bDMARD) should be added; JAK-inhibitors may be considered, but pertinent risk factors must be taken into account.	Efficacy: 1a; Safety: 1b Efficacy: A; Safety: B	EULAR recommendations for the management of rheumatoid arthritis, *2022*
bDMARDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring .	Level of evidence: low Strength of recommendation strong	Korean Expert Consensus 2020's recommendations
bDMARDs ((TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab including biosimilars), abatacept, rituximab, tocilizumab, sarilumab) and targeted synthetic DMARDS (tsDMARDs) (the JAK inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib) should be combined with a csDMARD; in patients who	1a, A	EULAR recommendations for the management of rheumatoid arthritis, *2022*

cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs		
If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD+ should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor.	Efficacy: 1a/+ 5/++3; safety: 1b Efficacy: A/+ D; Safety: B; IL-6R-inhibition: C 9.3±0.8 98	EULAR recommendations for the management of rheumatoid arthritis, *2022*
Hepatitis B infection • Prophylactic antiviral therapy is ***strongly recommended*** over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status). Very low • Prophylactic antiviral therapy is ***strongly recommended*** over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive. Very low • Frequent monitoring alone is *conditionally recommended* over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative. Very low	Very low	American College of Rheumatology Guideline, 2021

All patients should be screened for hepatitis B virus infection before starting bDMARDs, and if hepatitis B virus infection is identified, proper antiviral therapy should be considered	LOE: high for screening/low for antiviral therapy; SOR: strongly recommended	Korean Expert Consensus 2020's recommendations

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Rheumatoid Arthritis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Rheumatoid Arthritis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the December 2019 CHI Rheumatoid Arthritis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 National Institute for Health and Care Excellence (**NICE**) Guideline on the Management of Rheumatoid Arthritis in Adults (**2018**)	1.1.1 National Institute for Health and Care Excellence (**NICE**) Guideline on the Management of Rheumatoid Arthritis in Adults (**2020**)[5]
1.2 European Alliance of Associations for Rheumatology (**EULAR**) Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs (**2019**)	1.1.2 European Alliance of Associations for Rheumatology (**EULAR**) Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs (**2022**)[6]
1.3 American College of Rheumatology (**ACR**) Guideline for the Treatment of Rheumatoid Arthritis (**2015**)	1.1.3 American College of Rheumatology (**ACR**) Guideline for the Treatment of Rheumatoid Arthritis (**2021**)[7]

1.1.1 National Institute for Health and Care Excellence (NICE) Guideline on the Management of Rheumatoid Arthritis in Adults (2020)

*Please refer to **Section 1.1** of CHI Rheumatoid Arthritis original clinical guidance.*

The 2020 revised edition of the NICE guidelines on the management of rheumatoid arthritis in adults introduced a set of amended recommendations without a grading scheme, outlined as follows[5]:

Initial pharmacological management:

- For adults with newly diagnosed active RA:
    - Offer first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.
    - Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.
    - Escalate dose as tolerated. **[2018]**
- Consider short-term bridging treatment with glucocorticoids (oral, intramuscular, or intra-articular) when starting a new cDMARD. **[2018]**
- Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. **[2018]**

Further pharmacological management

<u>Biological and targeted synthetic DMARDs</u>

- On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of RA, except in the context of a controlled, long-term clinical study. **[2009]**
- Patients currently receiving anakinra for RA may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. **[2009]**
- Do not offer the combination of tumor necrosis factor-α (TNF-α) inhibitor therapy and anakinra for RA. **[2009]**

<u>Glucocorticoids</u>

- Offer short-term treatment with glucocorticoids for managing flares in adults with recent-onset or established diseases to rapidly decrease inflammation. **[2009]**
- In adults with established RA, only continue long-term treatment with glucocorticoids when:
    - the long-term complications of glucocorticoid therapy have been fully discussed, ***and***

- all other treatment options (including biological and targeted synthetic DMARDs) have been offered. **[2009, amended 2018]**

Symptom control

- Consider oral non-steroidal anti-inflammatory drugs (NSAIDs, including traditional NSAIDs and cox II selective inhibitors), when control of pain or stiffness is inadequate. Take account of potential gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age and pregnancy. **[2018]**
- When treating symptoms of RA with oral NSAIDs:
  - offer the lowest effective dose for the shortest possible time
  - offer a proton pump inhibitor (PPI), **and**
  - review risk factors for adverse events regularly. **[2018]**
- If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient. **[2009, amended 2018]**

Treat-to-target strategy

- Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). Achieving the target may involve trying multiple conventional and biological DMARDs with different mechanisms of action, one after the other. [2018, amended **2020**]

Monitoring

- Offer all adults with RA, including those who have achieved the treatment target, an annual review to:
  1. Assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
  2. Check for the development of comorbidities, such as hypertension, ischemic heart disease, osteoporosis, and depression.
  3. Assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung, or eyes.
  4. Organize appropriate cross referral within the multidisciplinary team.
  5. Assess the need for referral for surgery.
  6. Assess the effect the disease is having on a person's life. [2018, amended **2020**]

1.1.2 European Alliance of Associations for Rheumatology (EULAR) Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs (2022)

*Please refer to **Section 1.2** of CHI Rheumatoid Arthritis original clinical guidance.*

In 2010, EULAR developed recommendations for the management of RA with DMARDs. Thereafter, updates of these recommendations have been produced every 3 years, as insights have evolved, and new classification criteria,2 new definitions of remission, new treatment strategies and many new drugs have emerged. The last update of the recommendations was in 2019. Two circumstances made it particularly advisable to revisit the current recommendations. First, in 2021, the US Food and Drug Administration (FDA) released a document and warning on cardiovascular and malignancy risks of tofacitinib in comparison with TNF-inhibitors, based on analyses of a randomized trial. Second, in the most recent update of the RA management guidelines of the American College of Rheumatology (ACR), the use of glucocorticoids (GCs) was distinctly discouraged, even though the evidence level for this new guideline was low to moderate, reasoning that the toxicity of GCs outweighs the benefits. Given that EULAR in its recommendations hitherto has strongly advocated the use of short-term GCs as a bridging therapy when starting csDMARD therapy, with subsequent rapid tapering of GCs to discontinuation, revisiting this issue was warranted[6].

Table 3. EULAR Strengths of Recommendations and Levels of Evidence

Strengths of recommendations and levels of evidence			
Level of Agreement (LoA)	Scale of 0–10 (0 indicating no agreement at all and 10 indicating full agreement)		
Grades of recommendation	A	Consistent level 1 studies	
	B	Consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies	
	C	Level 4 studies ***or*** extrapolations from level 2 or 3 studies	
	D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level	
	Level	**Therapy / Prevention, Etiology / Harm**	**Diagnosis**
	1a	Systematic Review (SR) (with homogeneity*) of RCTs	SR (with homogeneity*) of Level 1 diagnostic studies; CDR (clinical decision

			rule)” with 1b studies from different clinical centers.
Levels of Evidence	1b	Individual RCT (with narrow Confidence Interval”¡)	Validating** cohort study with good” ” ” reference standards; or CDR” tested within one clinical center.
	1c	All or none§	Absolute SpPins and SnNouts” “
	2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of Level >2 diagnostic studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Exploratory** cohort study with good” ” ” reference standards; CDR” after derivation, or validated only on split-sample§§§ or databases
	2c	“Outcomes” Research; Ecological studies	
	3a	SR (with homogeneity*) of case-control studies	SR (with homogeneity*) of 3b and better studies
	3b	Individual Case-Control Study	Non-consecutive study; or without consistently applied reference standards
	4	Case-series (and poor-quality cohort and case-control studies§§)	Case-control study, poor or non-independent reference standard
	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs recommendations are assigned the class of recommendations defined in the preceding table:

The task force agreed on 5 overarching principles and 11 recommendations concerning use of conventional synthetic (cs) DMARDs (methotrexate (MTX), leflunomide, sulfasalazine); GCs; biological (b) DMARDs (tumour necrosis factor

inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab including biosimilars), abatacept, rituximab, tocilizumab, sarilumab and targeted synthetic (ts) DMARDs, namely the JAK inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib.

Overarching principles

- 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. **LoE**: n.a., **SoR**: n.a., **LoA**: 10±0, **% LoA ≥ 8**: 100%.
- Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage. n.a., n.a., 9.9±0.4, 100%.
- Rheumatologists are the specialists who should primarily care for patients with RA. n.a., n.a., 9.8±0.9, 96%.
- Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life. n.a., n.a., 9.8±0.6, 100%.
- RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist. n.a., n.a., 9.7±0.6, 100%.

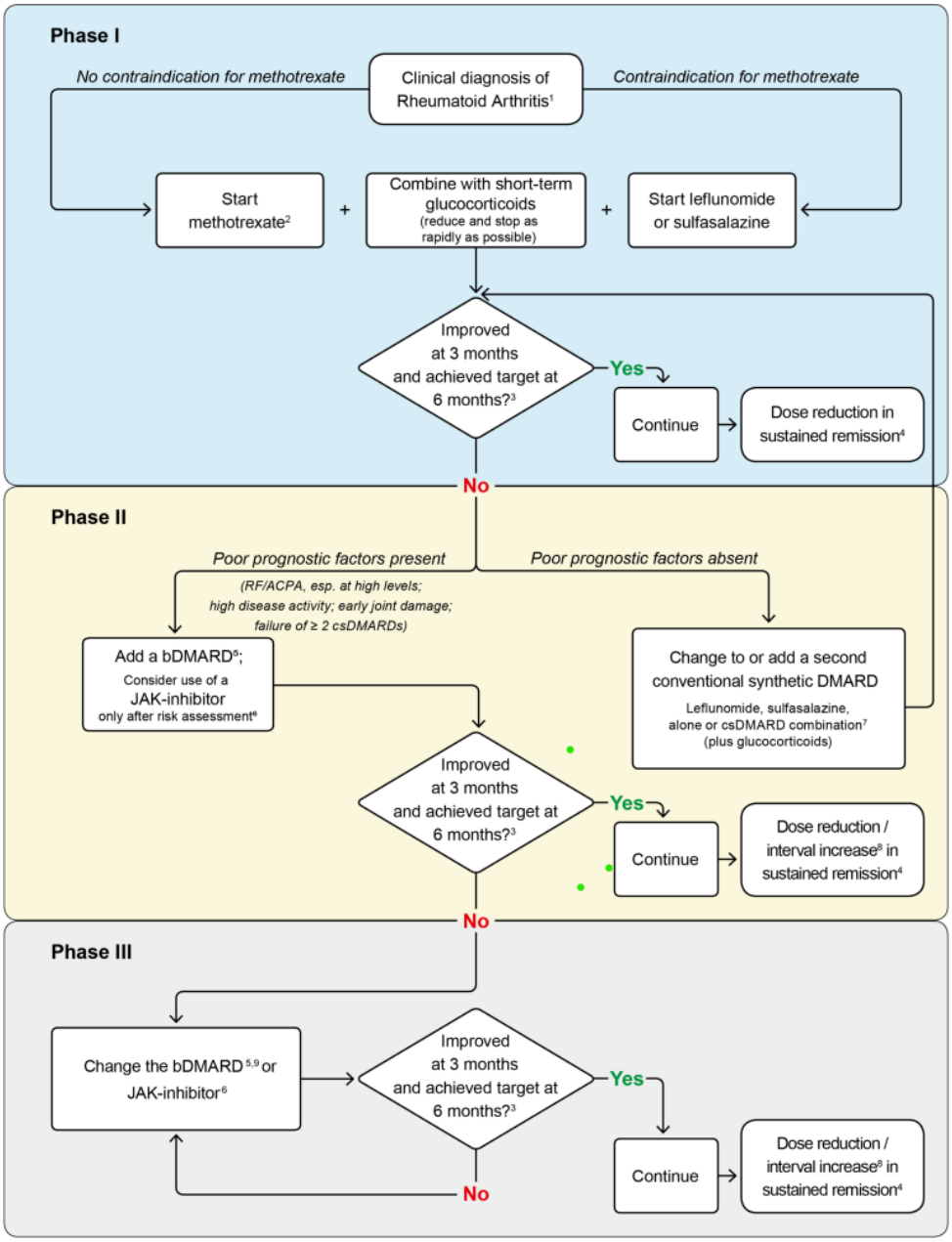
Recommendations

- Therapy with DMARDs should be started as soon as the diagnosis of RA is made. 1a, A, 9.9±0.2, 100%.
- Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. 1a, A, 9.8±0.4, 100%.
- 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. 2b, B, 9.5±0.7, 98%.
- MTX should be part of the first treatment strategy. 1a, A, 9.6±0.8, 96%.
- In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy. 1a, A, 9.1±1.2, 94%.
- Short-term glucocorticoids should be considered when *initiating* or *changing* csDMARDs, in different dose regimens and routes of administration, but

should be tapered and discontinued as rapidly as clinically feasible. 1a, A, 9.3±1.2, 92%.

- If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered. 5, D, 8.6±1.4, 83%.
- If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account. Efficacy: 1a; Safety: 1b Efficacy: A; Safety: B, 9.1±1.1, 92%.
- 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. Efficacy: 1a, Efficacy: A, 9.2±0.9, 96%.
- If a bDMARD or tsDMARD* has failed, treatment with another bDMARD or a tsDMARD*+ should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor++. Efficacy: 1a/+5/++3; safety: 1b, Efficacy: A/+D; Safety: B; IL-6R-inhibition: C, 9.3±0.8, 98%.
- After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered. 1b, A, 9.3±1.1, 89%.

*The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile).



1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.
3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.
5. Consider contraindications and risks. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication IL6-inhibitors and tsDMARDs have some advantages.
6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile)
7. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.
8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued.
9. From a different or the same class.

ACR, American College of Rheumatology; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; FDA, Food and Drug Administration; JAK, Janus kinase; MTX, methotrexate;NMSC, non-melanoma skin caner; tsDMARDs, targeted synthetic DMARDs.

Figure 1. *Flowchart for the Management of Rheumatoid Arthritis (Retrieved from the EULAR 2022 Guidelines)*

1.1.3 American College of Rheumatology (ACR) Guideline for the Treatment of Rheumatoid Arthritis (2021)

*Please refer to **Section 1.3** of CHI Rheumatoid Arthritis original clinical guidance.*

The guideline addresses treatment with DMARDs, including conventional synthetic DMARDs, biologic DMARDs, and targeted synthetic DMARDs, use of glucocorticoids, and use of DMARDs in certain high-risk populations (i.e., those with liver disease, heart failure, lymphoproliferative disorders, previous serious infections, and nontuberculous mycobacterial lung disease). The guideline includes 44 recommendations (7 strong and 37 conditional)[7].

Table 4. ACR Grades of Recommendations and Levels of Evidence

Grades of Recommendations	
Both strong and conditional recommendations required achieving a 70% level of agreement by the voting panel. Each recommendation is qualified as being strong or conditional.	
Strong Recommendation	Those for which the panel is highly confident that the recommended option favorably balances the expected benefits and risks for the majority of patients in clinical practice.
Conditional Recommendation	Those for which the panel is less confident that the potential benefits outweigh the risks. A recommendation can be conditional either because of low or very low certainty in the evidence supporting one option over another, or because of an expectation of substantial variations in patient preferences for the options under consideration.
GRADE approach adopted for the levels of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Disease-modifying antirheumatic drugs (DMARDs) initiation

- Initiation of treatment in DMARD-naive patients with moderate-to-high disease activity:
    - Methotrexate monotherapy is **strongly recommended** over: Hydroxychloroquine or sulfasalazine (Very low/low evidence)

      bDMARD or tsDMARD monotherapy (Very low/moderate evidence)

      Combination of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD (Low/very low evidence)
    - Methotrexate monotherapy is **conditionally** recommended over:

      Leflunomide (Low evidence)

      Dual or triple csDMARD therapy (Moderate evidence)

      Combination of methotrexate plus a TNF inhibitor (Low evidence)
- Initiation of a csDMARD without short-term (< 3 months) glucocorticoids is recommended over initiation of a csDMARD with short-term glucocorticoids (conditional recommendation, very low level of evidence).
- Initiation of a csDMARD without longer-term (≥ 3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids. (strong recommendation, moderate level of evidence).
- Initiation of treatment in DMARD-naive patients with low disease activity
    - Hydroxychloroquine is **conditionally** recommended over other csDMARDs. (conditional recommendation, very low level of evidence).
    - Sulfasalazine is **conditionally** recommended over methotrexate. (conditional recommendation, very low level of evidence).
    - Methotrexate is **conditionally** recommended over leflunomide. (conditional recommendation, very low level of evidence).
- Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to-high disease activity (Other recommendations for this patient population are the same as those for DMARD-naive patients)
    - Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD (** The direction of the beneficial effect is in favor of the nonpreferred option. The certainty of evidence is high for the combination of methotrexate plus a TNF inhibitor and moderate for other bDMARDs), (conditional recommendation, Moderate (combination with bDmarD)/ very low (combination with tsDMARD) level of evidence.

Methotrexate administration

- Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate. conditional recommendation, moderate level of evidence).
- Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is **conditionally** recommended over initiation/titration to a weekly dose of <15 mg. (Conditional recommendation, Moderate (Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks) / very low (initiation/titration to a weekly dose of <15 mg) level of evidence).
- A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folic/folinic acid, is **conditionally** recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate. (conditional recommendation, very low level of evidence).
- Switching to subcutaneous methotrexate is **conditionally** recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target. conditional recommendation, very low level of evidence).

Treatment modification

- A TTT (Treat to target) approach is **strongly** recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs. (strong recommendation, low level of evidence).
- A TTT approach is **conditionally** recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. (conditional recommendation, very low level of evidence)
- A minimal initial treatment goal of low disease activity is **conditionally** recommended over a goal of remission. (Conditional recommendation, low level of evidence)
- Addition of a bDMARD or tsDMARD is **conditionally** recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target. (Conditional recommendation, very low level of evidence)
- Switching to a bDMARD or tsDMARD of a different class is **conditionally** recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target. (Conditional recommendation, very low level of evidence)
- Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target. (Conditional recommendation, very low level of evidence)

- Addition of/switching to DMARDs (with or without IA glucocorticoids) is **conditionally** recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target. (Conditional recommendation, very low level of evidence)

Tapering disease-modifying antirheumatic drugs (DMARDs)*

- Continuation of all DMARDs at their current dose is **conditionally** recommended over a dose reduction of a DMARD. (Conditional recommendation, low level of evidence)
- Dose reduction is **conditionally** recommended over gradual discontinuation of a DMARD. (Conditional recommendation, low level of evidence)
- Gradual discontinuation is **conditionally** recommended over abrupt discontinuation of a DMARD. (Conditional recommendation, low level of evidence)
- Gradual discontinuation of sulfasalazine is **conditionally** recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD. (Conditional recommendation, very low level of evidence)
- Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD. (Conditional recommendation, very low level of evidence)

Specific patient populations

<u>Subcutaneous nodules</u>

- Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity. (Conditional recommendation, very low level of evidence)
- Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules. (Conditional recommendation, very low level of evidence)

<u>Pulmonary disease</u>

- Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity. (Conditional recommendation, very low level of evidence)

Heart failure

- Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs. (Conditional recommendation, very low level of evidence)
- Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure. (Conditional recommendation, very low level of evidence)

Lymphoproliferative disorder

- Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity. (Conditional recommendation, very low level of evidence)

Hepatitis B infection

- Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status). (Strong recommendation, very low level of evidence)
- Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive. (Strong recommendation, very low level of evidence)
- Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative. (Conditional recommendation, very low level of evidence)

Nonalcoholic fatty liver disease

- Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity. (Conditional recommendation, very low level of evidence)

Persistent hypogammaglobulinemia without infection

- In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is **conditionally** recommended over switching to a different bDMARD or tsDMARD. (Conditional recommendation, very low level of evidence)

Previous serious infection

- Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy. (Conditional recommendation, very low level of evidence)
- Addition of/switching to DMARDs is **conditionally** recommended over initiation/ dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity. (Conditional recommendation, very low level of evidence)

Nontuberculous mycobacterial lung disease

- Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is **conditionally** recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease. (Conditional recommendation, very low level of evidence)
- Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients 'with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy. (Conditional recommendation, very low level of evidence)
- Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs. (Conditional recommendation, very low level of evidence)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Rheumatoid Arthritis report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines

1.2.1 **Saudi** Guideline for Management of Rheumatoid Arthritis in Adult Patient (**2020**)[8]
1.2.2 **Italian Society for Rheumatology** (SIR) Clinical Practice Guidelines for Rheumatoid Arthritis (**2019**)[9]
1.2.3 The Use of Biological Disease-Modifying Antirheumatic Drugs for Inflammatory Arthritis in Korea: Results of a **Korean Expert Consensus** (**2020**)[10]
1.2.4 **Japan College of Rheumatology** Drug Treatment Algorithm and Recommendations from the 2020 Update of the Clinical Practice Guidelines for the Management of Rheumatoid Arthritis - Secondary Publication (**2022**)[11]
1.2.5 **Asia Pacific League of Associations for Rheumatology** (APLAR) Recommendations for Treatment of Rheumatoid Arthritis (**2018**)[12]
1.2.6 **American College of Rheumatology** (ACR) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease (**2023**)[13]
1.2.7 **American College of Rheumatology** (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (**2022**)[14]

1.2.1 Saudi Guideline for Management of Rheumatoid Arthritis in Adult Patient (2020)

The Saudi guideline for the management of RA in adult patients was adopted from international guideline including the 2016 European League Against Rheumatism (EULAR), the 2015 American College of Rheumatology (ACR) and BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids), as well as studies in the literature review included systematic reviews, randomized controlled trials (RCTs) and meta-analysis, review the available drugs in the Ministry Of Health (MOH), expert opinion of consultant rheumatologist and consultant rheumatologist clinical pharmacist. **It's worth noting that both EULAR and ACR have since issued updates to their clinical guidelines that have been detailed in section 1.1**[8]**.**

Table 6. Saudi Guidelines Recommendations Based on the GRADE Approach

Grading the strength of the Consensus Based Statements (CBSs)		
	Strong recommendation	**Conditional recommendation**

Patients	Most people in your situation would want the recommended course of action and only a small proportion would not.	The majority of 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 a need for substantial debate and involvement of stakeholders.

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-center trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence

		• One or more studies with very severe limitations

*=majority means > 50% of the people

Assessment

- A definitive diagnosis in a patient with early rheumatoid arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures.
- Early RA is defined as disease duration within 6 months.
- Treatment target should ideally be remission. In patients with established RA or those in whom remission can't be achieved, an alternative target of therapy would be low disease activity.
- Management of early Rheumatoid arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
- Rheumatologists are the specialists who should primarily care for patients with Rheumatoid arthritis.
- The main goal of DMARD treatment is to achieve clinical remission, and regular monitoring of disease activity, adverse events and comorbidities should guide decisions on choice and changes in treatment strategies to reach this target.
- Treatment decisions should be based on the severity of disease activity, as measured by quantitative methods such as the DAS28 or CDAI and the prognostic factors associated with poor outcomes.
- Functional status assessment using a standardized, validated measure should be performed routinely for RA patients, at least once per year, but more frequently if disease is active. Examples of commonly used functional status measures include Health, Assessment Questionnaire, Health Assessment Questionnaire II, Multidimensional Health Assessment Questionnaire, PROMIS)
- Monitoring of disease activity should include tender and swollen joint counts, patient, and physician global assessments, ESR and CRP, usually by applying a composite measure.
- Arthritis activity should be assessed at 1-month to 3-month intervals until the treatment target (Remission or low disease activity) has been reached.
- Radiographic and patient-reported outcome measures, such as functional assessments, can be used to complement disease activity monitoring.

- A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option. However, favoring one medication over the other does not imply that the no favored medication is contraindicated for use in that situation; it may still be a potential option under certain conditions.
- Among the DMARDs, methotrexate is considered to be the anchor drug and, unless contraindicated, should be part of the first treatment strategy. **(LOE low)**
- NSAIDs are effective symptomatic therapies but should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal and cardiovascular risks.
- Systemic glucocorticoids reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (<6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation. **(LOE very low)**
- Consider adding low-dose glucocorticoids (10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure.

Approach to management of RA

Medications for RA typically fall into five categories:

- Conventional Synthetic Disease-modifying anti-rheumatic drugs (csDMARDS).
- Biologic Disease-modifying anti-rheumatic drugs.
- Small molecule DMARDS (sDMARDs) Janus kinase (JAK) inhibitors.
- Glucocorticoids.
- Non-steroidal anti-inflammatory drugs (NSAIDs).

Initial therapy

- In patients with newly diagnosed early Rheumatoid Arthritis (Figure 1), start treatment with a single csDMARD, preferably methotrexate (start with oral 7.5–15 mg/week and increase the dose to 20 mg/week for maximum response

if needed. Use subcutaneous methotrexate if patient had gastric intolerance to oral MTX. (LOE low)

- In patients with contraindication or intolerance to methotrexate, we consider alternatives such as sulphasalazine. (LOE low)
- As we expect DMARDs to take a few weeks to produce a therapeutic effect, we might bridge the patients with a tapering course of corticosteroids and NSAIDs to control the pain and inflammation.
- In patients with moderate to high disease activity, we might consider initiating treatment with combination DMARDs from the beginning.
- A minimal period of 3 months is given before a major change to therapy is made.
- Treatment target should be achieved within 6 months.

Inadequate or no response

- If there's no improvement by 3 months after the initial therapy or the treatment target wasn't reached by 6 months, we alter the therapy.
- In the absence of poor prognostic factors, we add a second csDMARD if we initially started with a single agent.
- In the presence of poor prognostic factors or in those who started initially with a combination csDMARDs, we add a biologic DMARD or JAK inhibitor. (LOE moderate to very low). As we have no preference to any of the biologics, the choice will largely depend on the patient's condition, cost, preference, and comorbidities.

Failure of biologic DMARD

- The general idea for primary failure of the first biologic is to switch to another biologic with a different mechanism of action. (LOE low to very low).
- If a patient has failed a TNFi, we switch to a NON-TNFi or JAK inhibitor. (LOE low to very low).
- If a patient fails a NON-TNFi, we switch to another NON-TNFi with a different mechanism of action or a TNFi or JAK inhibitor. (LOE low to very low).
- If a patient fails multiple biologic DMARDs, switch to JAK inhibitor, like tofacitinib, is considered. (LOE low to very low).

Recommendations

- Patients presenting arthritis should be referred to, and seen by, rheumatologist, within 6 weeks after the onset of symptoms.
- Among the DMARDS, methotrexate is considered to be the anchor drug and, unless contraindicated, should be part of the first treatment strategy.
- Arthritis activity should be assessed at 1-month to 3-months intervals until the treatment target has been reached.

Table 7 shows the recommendations for monitoring CBC, LFT and renal function for patients on csDMARDs therapy.

Table 7. Monitoring Intervals for CBC, LFTs, and Renal Function for Patients on csDMARDs Therapy. Adapted from the 2020 Saudi Guideline.

Agent	< 3 months	3-6 months	> 6 months
Leflunomide	2 – 4 weeks	8 – 12 weeks	12 weeks
Methotrexate	2 – 4 weeks	8 – 12 weeks	12 weeks
Sulfasalazine	2 – 4 weeks	8 – 12 weeks	12 weeks

Recommendations for TB screening in patients receiving biologics or tofacitinib

- Screening for latent tuberculosis (TB) is mandatory for every patient before starting a biologic DMARD. Kindly follow Pathway 1 for screening.
- Biologic therapy can be started immediately if screening was negative, after 1 month of therapy for latent TB or after completion of course of therapy for active TB.

Use of biologics and DMARDs in high-risk populations

- Congestive Heart Failure: Use combination DMARDs or NON-TNFi biologics (Abatacept, Rituximab, Tocilizumab, Tofacitinib) are preferred over TNFi in heart failure. (LOE moderate to very low). -Use of TNFi should be avoided because of the risk of worsening heart failure. -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience.
- Hepatitis B: Patients infected with Hepatitis B Virus can receive immunosuppression after receiving prophylactic antiviral therapy for Hepatitis B. -Same recommendations as in patients without this condition (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience.
- Hepatitis C: Patients receiving treatment for Hepatitis C virus infection can receive the same treatment as in patients without this condition. (LOE very low) -In patients with Hepatitis C infection that are not receiving antiviral

therapy, use of csDMARDs is preferred over TNFi (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience.

- Previously treated or untreated Skin Cancer: csDMARDs are preferred over biologics and tofacitinib. (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience.
- Previously treated Lymphoproliferative Disorder: Rituximab is the preferred biologic in these patients. (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience
- Previously treated solid organ malignancy: Same recommendation as in patients without this condition. (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience

  Previous serious infections -Use combination DMARDs over TNFi Abatacept is the preferred biologic for these patients. (LOE very low) -Choice of therapy according to patients' co-morbidities, contraindications, cost & convenience
- Pregnancy: The safest medication is Hydroxychloroquine, sulfasalazine

  and among biological therapy is certolizumab.
  - Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors.
  - Infliximab may be continued until 16 weeks and etanercept and adalimumab may be continued until the end of the second trimester.
  - To ensure low/no levels of drug in cord blood at delivery, etanercept and adalimumab should be avoided in the third trimester and infliximab stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age.
- Lactation: Certolizumab preferred option since there is minimal transfer into breastmilk. -Women should not be discouraged from breastfeeding on TNFis (Infliximab, etanercept, adalimumab and Certolizumab.

Vaccinations

- Herpes zoster vaccine is recommended for Rheumatoid Arthritis patients that are above 50 years of age before starting biologic therapy. However, once already on a biologic this vaccine is contraindicated because it's a live vaccine.

All killed vaccines are recommended for Rheumatoid Arthritis patients. Preferably they should be given before methotrexate or Rituximab therapy because they can blunt the immune response. These vaccines include pneumococcal vaccine, annual flu vaccine and hepatitis B vaccine.

1.2.2 Italian Society for Rheumatology (SIR) Clinical Practice Guidelines for Rheumatoid Arthritis (2019)

These CPGs aim to offer revised, evidence based, and adapted recommendations for the management and safety of adult patients with RA[9].

Table 8. Guidance to Categories of Evidence and Strength of Recommendations Based on the Oxford Levels

Level	Evidence
1	From meta-analysis of randomized controlled trials or from at least one randomized controlled trial
2	From at least one controlled study without randomization or from at least one cohort study
3	From at least one case-control study
4	From case-series or poor-quality cohort and case-control studies
5	From expert committee reports or opinions and/or clinical experience of respected authorities

Table 9. Glossary and Definitions

Term	Definition
Low-dose glucocorticoid	≤ 7.5 mg/day (prednisone equivalent).
Tapering	Usually reduction of drug dose or increase of application interval (spacing). May include discontinuation (tapering to 0), but then only after slow reduction.
Discontinuation	Stopping of a particular drug.
Cycling (switch) strategy	Change drug with the same mode of action in RA patients failing TNFis.
Swapping (swap) strategy	Change drug with the same mode of action in RA patients failing TNFis.

Synthetic DMARDs	Conventional synthetic DMARDs (csDMARDs): methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
Target synthetic DMARDs (tsDMARDs/JAKi)	Baricitinib, tofacitinib.
Biologic DMARDs (bDMARDs)	Abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab.

➔ The symbols (*, †, §, ‡) relate to the corresponding symbols in the recommendations, showing in the respective grade.

Management of RA

- Treatment with csDMARDs should be started as soon as the diagnosis of RA is made. (Level 1, Strength A)
- MTX should be part of the first treatment strategy. (Level 1, Strength A)
- Short-term courses of glucocorticoids can be considered to control active RA in combination with csDMARDs. In view of their cumulative side effects, they should be used at the lowest dose necessary and tapered as rapidly as clinically feasible (<6 months). Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation. (Level 1, Strength A)
- In patients with a contraindication or intolerance to MTX, LFN or SSZ should be considered as part of the (first) treatment strategy. (Level 1, Strength A)
- If the treatment target is not achieved with a csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered*. 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 (add a TNF-i or a non-TNF-i or JAK-i without any particular order of preference). * *(5, D) † (1, A). (Level 1-5; Strength A-D)
- If a bDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-i therapy has failed, patients may receive another TNF-i or an agent with another mode of action. (Level 5, Strength D)
- Patients who fail to achieve remission or low disease activity with a second bDMARD therapy are recommended to switch to another bDMARD agent or a tsDMARD. If the second bDMARD failure is TNF-i: use another bDMARD (non-TNF-i) or a tsDMARD with or without MTX. (Level 5, Strength D)

- If a patient is in sustained remission, a reduction in treatment should be considered.
    - bDMARDs or tsDMARDs tapering, especially if this treatment is combined with csDMARDs, could be considered. (Level 2, Strength B)
    - csDMARDs tapering could be considered. (Level 4; Strength C)

Safety recommendations

Tuberculosis

Screening for TB is recommended prior to starting bDMARD or tsDMARD therapy. Initial TST or IGRA is recommended. IGRA is preferred if patient has a history of BCG vaccination.* a) Patients with a positive initial or repeat TST or IGRA should have a chest radiograph and, if positive for past TB exposure or active TB, a subsequent sputum examination to check for the presence of active TB.* b) Patients with a negative screening TST or IGRA may not need further workup in the absence of risk factors and/or clinical suspicion for TB.* c) If the RA patient has active or latent TB based on the test results the panel recommends appropriate anti-tubercular treatment and consideration for referral to a specialist.† d) Treatment with tsDMARDs or bDMARDs can be initiated or resumed after 1 month of latent TB treatment with anti-tubercular medications and after completion of the treatment of active TB, if applicable according to reference specialist (pulmonologist or infectious disease specialist).* e) Annual testing is recommended in RA patients who live, travel or work in situations where TB exposure is likely while they continue treatment with biologics.*(2,C) †(2,B) (Level 2; Strength B-C)

HBV infection

a. All RA patients should be screened for HBsAg, antiHBsAb and antiHBcAb especially before starting a bDMARD or a tsDMARD.*
b. AntiHBcAb positive, HBsAg negative patients should undergo further evaluations, including HBV, DNA and liver function tests before starting immunosuppressive therapy. RA treatment should be the same as that for unexposed patients, as long as the patient's viral load is monitored regularly, every 6-12 months.*
c. HBsAg positive patients should undergo further evaluation, including quantitative HBsAg, HBeAg, antiHBe, HBV DNA and anti HDV IgG and liver function tests, before starting immunosuppressive therapy.†
d. Active HBV carriers should be treated with entecavir or tenofovir in accordance with the international guidelines before starting immunosuppressive therapy.†

e. Acute HB occurring in patients with RA, such as asymptomatic infections occurring in patients previously negative for HBV serology, should receive antiviral treatment according to international guidelines.§

f. In inactive HBV carriers, prophylaxis should be started 4 weeks before the immunosuppressive therapy and continued for 12 months after its discontinuation (24 months in the case of rituximab-treated patients).*

g. Patients stopping prophylaxis should be closely monitored.‡*(2, B). † (1, A). § (5, B). ‡ (5, C). (Level 1-5; Strength A-C)

HCV infection

a. All RA patients should be screened for HCV infections, especially before starting a bDMARDs or tsDMARDs.*

b. RA patients with HCV infection should undergo gastroenterological / infectious evaluation for any anti-viral eradicative therapy and should not be treated differently from patients with AR without HCV infection.†*(2, B) † (5, D); (Level 2-5; Strength B-D)

Cardiovascular disease

a. CVD risk assessment is recommended for all patients with RA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy. CVD risk estimation for patients with RA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available.*

b. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model.*

c. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA.*

d. Lifestyle recommendations should emphasize the benefits of a healthy diet, regular exercise and giving up smoking for all patients.†

e. In CVD risk management, antihypertensives and statins may be used as in the general population. *

f. Prescription of NSAIDs in RA should be given with caution, especially for patients with documented CVD or in the presence of CVD risk factors.

g. In case of Congestive Heart Failure: use combination of csDMARDs or non TNF-i or tsDMARDs rather than TNF-i.†

h. Congestive Heart Failure worsening on current TNF-i therapy: use combination of csDMARDs or non-TNF-i or tsDMARDs rather than TNF-i.*

i. A TNF-i should only be used if there are no other reasonable options, and then, perhaps, only in compensated heart failure. * §*(4, D) † (3, C). § (2, A). (Level 2-4; Strength A-D)

Malignancy

If the disease is moderately or highly active in the setting of a low-grade melanoma or non-melanoma skin cancer that had been previously treated, biologics would be an acceptable option with close skin surveillance in conjunction with a dermatologist. *

a. In general - use csDMARDs rather than tsDMARDs or bDMARDs.*
b. Previously treated lymphoproliferative disorders: - use Rituximab rather than TNF-i.† - use combination of csDMARDs or Abatacept or Tocilizumab rather than TNF-i.*
c. Previously treated solid organ malignancy - same recommendations as in patients without this condition (in the absence of active malignancy, according to the reference specialist).**(5, D) † (5, C) (Level 5; Strength C-D)

Vaccination

a. Ideally administration of all vaccines, if indicated, should be undertaken at least 4 weeks before starting a tsDMARD or bDMARD. *
b. Concurrent administration of live, attenuated vaccines is an absolute contraindication for patients being treated with tsDMARDs or bDMARDs. * Killed vaccines (Pneumococcal, Influenza^, Hepatitis B) are recommended, before initiating or during therapy with csDMARDs, tsDMARDs, bDMARDs, in RA patients. (^every year according to epidemiology).†
c. Recombinant Vaccine (Human Papilloma) is recommended before initiating or during therapy with csDMARDs, tsDMARDs, bDMARDs in RA patients (according to National Recommendations).**(4, D) † (1, A). (Level 1-4; Strength A-D)

1.2.3 The Use of Biological Disease-Modifying Antirheumatic Drugs for Inflammatory Arthritis in Korea: Results of a Korean Expert Consensus (2020)

This review provides detailed guidance on bDMARDs use in adults with inflammatory arthritis, including RA as well as ankylosing spondylitis (AS). The quality of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (table 10). The statements covered four topics: (1) who should prescribe, (2) the role of education, (3) indications for use, and (4) required evaluations before and during use for safety. Only recommendations related to RA have been included below[10].

Table 10. Significance of the quality of evidence according to the GRADE system

Quality Level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

General principles of bDMARDs treatment

- bDMARDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring (level of evidence [LOE]: low; strength of recommendation [SOR]: strongly recommended).
- Patients should be provided with education about their treatment with bDMARDs (LOE: moderate; SOR: strongly recommended).
- In RA, if the treatment target is not achieved with the first conventional synthetic DMARDs (csDMARDs) strategy, when poor prognostic factors are present, addition of a bDMARD should be considered (LOE: moderate; SOR: strongly recommended).

Concomitant use of csDMARDs with bDMARDs

- In RA, bDMARDs should be combined with a csDMARDs such as MTX (LOE: high; SOR: strongly recommended)

Treatment options after failure of or intolerance to first bDMARDs

- In RA, if a bDMARD has failed, switching to another bDMARD should be considered (LOE: high; SOR: strongly recommended).

Monitoring strategies before or during use of bMDARDs

- Prior to initiating bDMARDs, disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, vaccination history, and pregnancy status should be assessed in all patients with inflammatory arthritis (LOE: low; SOR: strongly recommended).
- All patients should be screened for active or latent tuberculosis before starting bDMARDs, and if tuberculosis is detected, patients should receive adequate anti-tuberculosis treatment, appropriately (LOE: low; SOR: strongly recommended).
- All patients should be screened for hepatitis B virus infection before starting bDMARDs, and if hepatitis B virus infection is identified, proper antiviral therapy should be considered (LOE: high for screening/low for antiviral therapy; SOR: strongly recommended).
- All patients receiving bDMARDs should be monitored for disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, and drug side effect and toxicity (LOE: low; SOR: strongly recommended.

1.2.4 Japan College of Rheumatology Drug Treatment Algorithm and Recommendations from the 2020 Update of the Clinical Practice Guidelines for the Management of Rheumatoid Arthritis - Secondary Publication (2022)

The aim of this study was to update the Japan College of Rheumatology (JCR) clinical practice guidelines (CPG) for the management of rheumatoid arthritis (RA; JCR CPG for RA) according to recent changes in the medical environment in Japan. This article is a digest version of the guidance[11].

Recommendations were prepared by considering the following four factors: (1) overall quality of evidence, (2) balance of desirable and undesirable consequences, (3) patients' values and preferences, and (4) costs and available resources. The direction of recommendation was either 'recommend' or 'do not recommend' (for/against), and the strength was either 'strong' or 'weak (conditional)'

- We recommend MTX in patients with active RA. strong C (low)
- We recommend folic acid in patients with RA using MTX. strong C (low)
- We suggest combination therapy of MTX and csDMARDs in RA patients who have had an inadequate response to MTX. weak D (very low)
- We suggest csDMARDs other than MTX in RA patients who cannot use MTX or who have had an inadequate response to MTX. weak C (low)
- We suggest tapering of csDMARD in RA patients who are in remission or have low disease activity with a bDMARDs or a JAK inhibitor in combination with csDMARDs. weak D (very low)

- We suggest NSAIDs for pain relief in patients with RA. weak C (low)
- We suggest short-term concomitant use of glucocorticoids with csDMARDs in patients with active early RA. weak D (very low)
- We recommend concomitant use of a TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to csDMARDs. strong A (high)
- We recommend concomitant use of a non-TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to csDMARDs. strong C (low)
- We suggest TNF inhibitor monotherapy in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to csDMARDs including MTX. weak D (very low)
- We suggest non-TNF inhibitor monotherapy in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to csDMARDs including MTX. weak C (low)
- We recommend a non-TNF inhibitor (T-cell selective co-stimulation modulator) and a TNF inhibitor equally when a bDMARD is used in combination with MTX in RA patients with moderate or severe disease activity who have had an inadequate response to MTX. strong A (high)
- We recommend a non-TNF inhibitor (IL-6 inhibitor) when a bDMARD is used without MTX in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to MTX. strong B (moderate)
- We suggest switching to a non-TNF inhibitor vs. to another TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to a TNF inhibitor. weak D (very low)
- We suggest tapering of a TNF inhibitor in RA patients who maintain remission. weak D (very low)
- We suggest tapering of an IL-6 inhibitor in RA patients who maintain remission or low disease activity. weak D (very low)
- We suggest tapering of a T-cell selective co-stimulation modulator in RA patients who maintain remission or low disease activity. weak D (very low)
- We suggest JAK inhibitor monotherapy in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate)

- We suggest concomitant use of a JAK inhibitor with MTX in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate)
- We suggest concomitant use of a JAK inhibitor and a TNF inhibitor with MTX equally in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate)
- We suggest concomitant use of a JAK inhibitor with MTX in RA patients who have had an inadequate response to a TNF inhibitor.
- When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak C (low)
- We suggest tapering of a JAK inhibitor in RA patients who maintain remission or low disease activity. weak C (low)
- We suggest add-on therapy with anti-RANKL antibody to DMARDs to inhibit progression of bone erosion in patients with active RA and bone erosion. Weak A (high)
- We recommend reference bDMARDs and biosimilars equally in RA patients with high or moderate disease activity who have had an inadequate response to csDMARDs. strong A (high)
- We suggest continuing reference bDMARDs and switching to biosimilars from reference bDMARDs equally in patients with RA. weak D (very low)
- We suggest using DMARDs in RA patients with interstitial lung disease with careful monitoring for acute exacerbation of interstitial lung disease. weak D (very low)
- We suggest not initiating TNF inhibitors in RA patients with severe heart failure. weak D (very low)
- We recommend the use of appropriate doses of DMARDs with careful consideration for safety in RA patients with moderate or severe renal dysfunction. strong D (very low)
- Rheumatologists should treat RA patients positive for HBs antigen in collaboration with a hepatologist. Rheumatologists should treat HBVinfected RA patients negative for HBs antigen according to the usual treatment strategy with regular monitoring for HBV infection. strong D (very low)
- Rheumatologists should treat HCV-infected patients with RA according to the usual treatment strategy in collaboration with a hepatologist. strong D (very low)

- We suggest that HTLV-1-positive RA patients are treated with DMARDs under careful monitoring of the disease course. weak D (very low)
- In RA patients with malignancy or past history of malignancy, we suggest that bDMARDs be used with informed consent in collaboration with the attending physician treating the malignancy. weak D (very low)
- We suggest that RA patients treated with glucocorticoids or DMARDs receive influenza and pneumococcal vaccines, but not live vaccines. weak D (very low)
- We suggest use of MTX with full safety consideration in elderly patients diagnosed as having RA with poor prognostic factors. weak D (very low)
- We suggest use of molecular targeted agents with careful consideration of safety in elderly RA patients with inadequate response to sufficient doses of csDMARDs including MTX. When using these drugs, we suggest considering the insufficient long-term safety data. weak D (very low)
- We suggest using short-term glucocorticoids in combination with csDMARDs in elderly patients with active early RA. weak D (very low)

1.2.5 Asia Pacific League of Associations for Rheumatology (APLAR) Recommendations for Treatment of Rheumatoid Arthritis (2018)

This update to the 2015 APLAR treatment recommendations for RA reviewed current evidence focusing on the use of targeted agents, to inform clinicians and support them in their clinical management of RA[12].

Table 11. APLAR's Grade for Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
D	Very Low	We have very little confidence in the effect estimate.

		The true effect is likely to be substantially different from the estimate of effect

- Starting treatment with csDMARD monotherapy, preferably **methotrexate**, is recommended as soon as the diagnosis of RA is made (moderate).
- Patients who cannot tolerate MTX may receive other csDMARDs such as **LEF** and **SSZ** as 1st-line treatment. HCQ, iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability (moderate).
- In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities (low).
- Prior to starting targeted therapy, all patients should be evaluated for the presence of active or inter-current infections, comorbidities including lymphoproliferative disorders and skin cancers, vaccinations, pregnancy, and possible contraindications (not graded).
- All patients should be screened for infections including TB, HBV, HCV, and HIV (high-risk population) infections before initiating targeted therapy. Patients with active or latent infections should receive adequate therapy (low).
    - For RA patients with latent TB, prophylaxis treatment according to country-specific guidelines is recommended to prevent TB reactivation.
    - For RA patients with HBV infection (active or occult), antiviral therapy should be prescribed to prevent HBV reactivation.
- Vaccination should be undertaken prior to initiating targeted therapy. During targeted therapy, live attenuated virus vaccines are contraindicated. Pneumococcal and influenza vaccines are recommended. Vaccines for HBV, HPV and meningococcal infections are conditionally recommended. (moderate)
- Targeted therapies, including TNFi, non-TNFi and JAK inhibitors, can be prescribed to patients who have moderate or high disease activity despite adequate treatment with csDMARD, or in patients with intolerance to csDMARD (moderate).
- Based on currently available evidence, all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs (moderate).
- All patients receiving targeted therapy should be closely monitored for therapy-related toxicities Not graded 10 For RA patients with a history of TB or

latent TB (or in whom the risk remains high despite negative screening), targeted therapies other than monoclonal Ab TNFi are preferred (low).

- In RA patients at increased risk of HBV reactivation, targeted therapies other than RTX are preferred (low).
- Modification of targeted therapy should be performed for failure to achieve remission or low disease activity after 6 months (not graded).
- In patients with established RA, consideration of tapering or discontinuation of targeted therapy should only be made when the disease is in remission for over 12 months, especially if the patient is receiving concomitant csDMARD (moderate).
- For patients with a past history of treated solid cancer, targeted therapies may be used with caution (very low).
- For patients undergoing major surgery, we recommend temporary discontinuation of targeted therapy and resumption when wound healing is satisfactory (low).
- For patients with established RA in whom disease cannot otherwise be controlled, TNFi (preferably etanercept or certolizumab) may be continued
- pregnancy (low).

1.2.6 American College of Rheumatology (ACR) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease (2023)

The American College of Rheumatology (ACR) is developing new clinical practice guidelines for clinicians who care for people with systemic autoimmune rheumatic disease (SARD), which include RA, who are at risk or have been diagnosed with interstitial lung disease (ILD). ACR **conditionally** recommended against Methotrexate. some of those recommendations including the following

- For people with Systemic autoimmune rheumatic disease (SARD) -ILD other than SSc(systemic sclerosis)-ILD, we **conditionally** recommend glucocorticoids as a first-line ILD treatment.
- For people with SARD-ILD, we **conditionally** recommend mycophenolate, azathioprine, rituximab, and cyclophosphamide as first-line ILD treatment options.
- For people with SARD-ILD, we **conditionally** recommend against leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.

- For people with RA-ILD, the Panel **was not able to come to consensus on whether to recommend nintedanib as a first-line ILD treatment option**.
- For people with RA-ILD progression despite first ILD treatment, we **conditionally** recommend adding pirfenidone as a treatment option.

1.2.7 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (2022)

This guideline includes expanded indications for some vaccines in patients with RMDs, as well as guidance on whether to hold immunosuppressive medications or delay vaccination to maximize vaccine immunogenicity and efficacy. Safe approaches to the use of live attenuated vaccines in patients taking immunosuppressive medications are also addressed. Most recommendations are conditional and had low quality supporting evidence.

Expanded indications for specific vaccines in patients with RMDs receiving immunosuppression.

- Influenza vaccination—For patients with RMD age ≥65 years and patients with RMD age >18 years and <65 years who are taking immunosuppressive medication, giving high dose or adjuvanted influenza vaccination is conditionally recommended over giving regular dose influenza vaccination.
- Pneumococcal vaccination—For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is strongly recommended.
- Recombinant varicella-zoster virus (VZV) vaccination—For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is strongly recommended.
- Human papillomavirus (HPV) vaccination—For patients with RMD age >26 years and <45 years who are taking immunosuppressive medication and not previously vaccinated, vaccination against HPV is conditionally recommended.
- Methotrexate—For patients with RMD, holding methotrexate for 2 weeks after influenza vaccination is conditionally recommended, assuming disease activity allows.
- Rituximab—For patients with RMD receiving rituximab, administering influenza vaccination on schedule is conditionally recommended rather than deferring vaccination until the next rituximab administration is due. For patients with RMD receiving rituximab, deferring non–live attenuated vaccinations, other than influenza vaccination, until the next rituximab administration is due, and delaying rituximab for 2 weeks after vaccination, is conditionally recommended.

- Glucocorticoids—Whether to administer non–live attenuated vaccinations to patients taking glucocorticoids or defer vaccination to a later time point to maximize vaccine immunogenicity.

➔ For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live vaccinations is strongly recommended.

➔ For patients with RMD who are taking the equivalent of prednisone >10 mg daily but y but <20 mg daily, administering any non–live attenuated vaccinations is conditionally recommended.

➔ For patients with RMD taking the equivalent of prednisone ≥20 mg daily, administering influenza vaccination is conditionally recommended.

➔ For patients with RMD who are taking the equivalent of prednisone ≥20 mg daily, deferring non–live attenuated vaccinations, other than influenza vaccination, until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily is conditionally recommended.

➔ Given the importance of timely influenza vaccination, a conditional recommendation was made to administer influenza vaccination to patients receiving the equivalent of prednisone ≥20 mg daily. For vaccines other than for influenza, a conditional recommendation was made to delay vaccination until the dose is lower to maximize vaccine efficacy. It is understood, however, that some patients may not be able to delay, e.g., children who require vaccination for school entry.

- Disease activity—Whether to defer vaccination in patients with high disease activity to maximize vaccine immunogenicity and/or avoid worsening disease activity.

➔ For patients with RMD, giving non–live attenuated vaccinations are conditionally recommended regardless of patients' disease activity.

➔ Managing immunosuppressive therapy at the time of live attenuated vaccination to avoid vaccine-associated illness as shown in the figure below:

Table 12. Immunosuppressive Medication Management at the Time of Live Attenuated Virus Vaccine Administration (Retrieved from the ACR 2022 Guidelines)

	Hold before live attenuated virus vaccine administration	Hold after live attenuated virus vaccine administration
Glucocorticoids†	4 weeks	4 weeks
Methotrexate, azathioprine‡	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL-17, IL-12/23, IL-23, BAFF/BLyS inhibitors	1 dosing interval§	4 weeks
IL-6 pathway inhibitors	1 dosing interval¶	4 weeks
IL-1 inhibitors		
Anakinra	1 dosing interval¶	4 weeks
Rilonacept	1 dosing interval¶	4 weeks
Canakinumab	1 dosing interval¶	4 weeks
Abatacept	1 dosing interval§	4 weeks
Anifrolumab	1 dosing interval§	4 weeks
Cyclophosphamide, intravenous	1 dosing interval§	4 weeks
Rituximab	6 months	4 weeks
IVIG#		
300–400 mg/kg	8 months	4 weeks
1 gm/kg	10 months	4 weeks
2 gm/kg	11 months	4 weeks

* TNF = tumor necrosis factor; IL = interleukin; BLyS = B lymphocyte stimulator; IVIG = intravenous immunoglobulin.

† For patients taking the equivalent of prednisone 1 dosing interval approved by the Food and Drug Administration, the longest interval should be chosen (e.g., hold subcutaneous adalimumab for 2 weeks, although it can be dosed every 1 or every 2 weeks).

¶ In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic disease modifying antirheumatic drugs are held is very high, shorter hold times can be considered if live attenuated vaccination is critical.

The recommendation to hold IVIG prior to vaccination is designed to enhance vaccine efficacy, not safety. In some situations, such as during a measles outbreak, earlier vaccination would be preferred over delay.

- ➔ For patients with RMD who are taking immunosuppressive medication, deferring live attenuated vaccines is conditionally recommended.
- ➔ For patients with RMD, holding immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination is conditionally recommended.
- ➔ For neonates/infants with second- and/or third-trimester antenatal exposure to TNFi, giving live attenuated rotavirus vaccine within the first 6 months of life is conditionally recommended.

- ➔ For neonates/infants with second- and/or third-trimester antenatal exposure to rituximab, delaying live attenuated rotavirus vaccine until >6 months of age is conditionally recommended.
- ➔ For patients with RMD, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is conditionally recommended.

Section 2.0 Drug Therapy in Rheumatoid Arthritis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA for the management of RA but are currently not registered by the SFDA.

2.1 Additions

Since December 2019, no new drugs have been registered by the SFDA for the management of rheumatoid arthritis.

2.2 Modifications

Modifications made since December 2019:

Addition of "MD" (to be prescribed by a rheumatologist) as a prescribing edit to bDMARDs; adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, sarilumab) and to upadacitinib, tofacitinib and baricitinib.

2.3 Delisting

The medications below are no longer SFDA registered[15], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Rheumatoid Arthritis original clinical guidance*

- ACEMETACIN, Capsule, hard, 60 mg
- ACEMETACIN, Prolonged-release capsule, 90 mg
- ASCORBIC ACID, CALCIUM GLYCEROPHOSPHATE, Effervescent tablet
- TIAPROFENIC ACID 300 mg

Section 3.0 Key Recommendations Synthesis

Key Recommendation Synthesis

Treat-to-target strategy

- Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). Achieving the target may involve trying multiple conventional disease-modifying anti-rheumatic drugs (cDMARDs) and biological DMARDs with different mechanisms of action, one after the other. [2018, amended **2020**][5]

Treatment

- Therapy with DMARDs should be started as soon as the diagnosis of RA is made. 1a A 9.9±0.2 100[6]
- MTX should be part of the first treatment strategy. 1a A 9.6±0.8 96 5.[6]
- In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy. 1a A 9.1±1.2 94 6.[6]
- Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible. 1a, A, 9.3±1.2 92 7[6]
- If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account. Efficacy: 1a; Safety: 1b Efficacy: A; Safety: B 9.1±1.1 92[6]
- The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile).
- bDMARDs and tsDMARDs* should be combined with a csDMARD; in patients who cannot use csDMARDs (methotrexate, sulfasalazine, and hydroxychloroquine) as comedication, IL-6 pathway inhibitors and tsDMARDs*

may have some advantages compared with other bDMARDs. Efficacy: 1a Efficacy: A 9.2±0.9 96[6]

- If a bDMARD or tsDMARD* has failed, treatment with another bDMARD or a tsDMARD*+ should be considered; if one TNF (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs, abatacept, or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor++. Efficacy: 1a/+ 5/++3; safety: 1b Efficacy: A/+ D; Safety: B; IL-6R-inhibition: C 9.3±0.8 98

Methotrexate administration

- Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate. Moderate[7]
- Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of <15 mg. Moderate/ very low[7]
- Patients who cannot tolerate MTX may receive other csDMARDs such as LEF and SSZ as 1st-line treatment. Moderate.[12]
- A TTT (Treat to target) approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs. Low[7]

Specific patient populations[7]

Subcutaneous nodules

- Methotrexate is conditionally recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity. Very low
- Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules. Very low

Pulmonary disease

- Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity. Very low
- For people with Systemic autoimmune rheumatic disease (SARD) -ILD other than SSc (systemic sclerosis)-ILD, we **conditionally** recommend glucocorticoids as a first-line ILD treatment.

- For people with SARD-ILD, we **conditionally** recommend mycophenolate, azathioprine, rituximab, and cyclophosphamide as first-line ILD treatment options.
- For people with SARD-ILD, we **conditionally** recommend against leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options.
- For people with RA-ILD, the Panel **was not able to come to consensus on whether to recommend nintedanib as a first-line ILD treatment option**.

For people with RA-ILD progression despite first ILD treatment, we **conditionally** recommend adding pirfenidone as a treatment option. Heart failure

- Addition of a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs. Very low
- Switching to a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure. Very low

Lymphoproliferative disorder

- Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity. Very low

Hepatitis B infection

- Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status). Very low[7]
- Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive. Very low[7]
- Frequent monitoring alone is conditionally recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative. Very low[7]

Nonalcoholic fatty liver disease

- Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity. Very low

Persistent hypogammaglobulinemia without infection

- In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD. Very low

Previous serious infection

- Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy. Very low
- Addition of/switching to DMARDs is conditionally recommended over initiation/ dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity. Very low

Nontuberculous mycobacterial lung disease

- Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is conditionally recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease. Very low
- Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients 'with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy. Very low
- Abatacept is conditionally recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs. Very low

<u>General principle of bDMARDs treatment</u>

- bDMARDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring (level of evidence [LOE]: low; strength of recommendation [SOR]: strongly recommended).

<u>Recommendations on treatment strategy in RA (Safety)</u>

- **TUBERCULOSIS**

  Screening for TB is recommended prior to starting bDMARD or tsDMARD therapy. Initial TST or IGRA is recommended. IGRA is preferred if patient has a history of BCG vaccination.* a) Patients with a positive initial or repeat TST or IGRA should have a chest radiograph and, if positive for past TB exposure or

active TB, a subsequent sputum examination to check for the presence of active TB.* b) Patients with a negative screening TST or IGRA may not need further workup in the absence of risk factors and/or clinical suspicion for TB.* c) If the RA patient has active or latent TB based on the test results the panel recommends appropriate anti-tubercular treatment and consideration for referral to a specialist.† d) Treatment with tsDMARDs or bDMARDs can be initiated or resumed after 1 month of latent TB treatment with anti-tubercular medications and after completion of the treatment of active TB, if applicable according to reference specialist (pulmonologist or infectious disease specialist).* e) Annual testing is recommended in RA patients who live, travel or work in situations where TB exposure is likely while they continue treatment with biologics.*(2,C) †(2,B) (Level 2; Strength B-C)[9]

- **HBV INFECTION**

  a) All RA patients should be screened for HBsAg, antiHBsAb e antiHBcAb especially before starting a bDMARD or a tsDMARD.*

  b) AntiHBcAb positive, HBsAg negative patients should undergo further evaluations, including HBV, DNA and liver function tests before starting immunosuppressive therapy. RA treatment should be the same as that for unexposed patients, as long as the patient's viral load is monitored regularly, every 6-12 months.*

  c) HBsAg positive patients should undergo further evaluation, including quantitative HBsAg, HBeAg, antiHBe, HBV DNA and anti HDV IgG and liver function tests, before starting immunosuppressive therapy.†

  d) Active HBV carriers should be treated with entecavir or tenofovir in accordance with the international guidelines before starting immunosuppressive therapy.†

  e) Acute HB occurring in patients with RA, such as asymptomatic infections occurring in patients previously negative for HBV serology, should receive antiviral treatment according to international guidelines.§

  f) In inactive HBV carriers, prophylaxis should be started 4 weeks before the immunosuppressive therapy and continued for 12 months after its discontinuation (24 months in the case of rituximab-treated patients).*

  g) Patients stopping prophylaxis should be closely monitored.‡*(2, B). † (1, A). § (5, B). ‡ (5, C). (Level 1-5; Strength A-C)[9]

- **HCV INFECTION**

  a) All RA patients should be screened for HCV infections, especially before starting a bDMARDs or tsDMARDs.*

b) RA patients with HCV infection should undergo gastroenterological / infectious evaluation for any anti-viral eradicative therapy and should not be treated differently from patients with AR without HCV infection.†*(2, B) † (5, D); (Level 2-5; Strength B-D)[9]

- **CARDIOVASCULAR DISEASE**

  a) CVD risk assessment is recommended for all patients with RA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy. CVD risk estimation for patients with RA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available. *

  b) CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model.*

  c) Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA.*

  d) Lifestyle recommendations should emphasize the benefits of a healthy diet, regular exercise and giving up smoking for all patients.†

  e) In CVD risk management, antihypertensives and statins may be used as in the general population. *

  f) Prescription of NSAIDs in RA should be given with caution, especially for patients with documented CVD or in the presence of CVD risk factors.

  g) In case of Congestive Heart Failure: use combination of csDMARDs or non TNF-i or tsDMARDs rather than TNF-i.†

  h) Congestive Heart Failure worsening on current TNF-i therapy: use combination of csDMARDs or non-TNF-i or tsDMARDs rather than TNF-i.*

  i) A TNF-i should only be used if there are no other reasonable options, and then, perhaps, only in compensated heart failure. * §*(4, D) † (3, C). § (2, A). (Level 2-4; Strength A-D)[9]

- **MALIGNANCY**

  If the disease is moderately or highly active in the setting of a low-grade melanoma or non-melanoma skin cancer that had been previously treated, biologics would be an acceptable option with close skin surveillance in conjunction with a dermatologist. *

  a) In general - use csDMARDs rather than tsDMARDs or bDMARDs.*

b) Previously treated lymphoproliferative disorders: - use Rituximab rather than TNF-i.† - use combination of csDMARDs or Abatacept or Tocilizumab rather than TNF-i.*

c) Previously treated solid organ malignancy - same recommendations as in patients without this condition (in the absence of active malignancy, according to the reference specialist).**(5, D) † (5, C) (Level 5; Strength C-D)[9]

- **VACCINATION**

  a) Ideally administration of all vaccines, if indicated, should be undertaken at least 4 weeks before starting a tsDMARD or bDMARD. *

  b) Concurrent administration of live, attenuated vaccines is an absolute contraindication for patients being treated with tsDMARDs or bDMARDs. * Killed vaccines (Pneumococcal, Influenza^, Hepatitis B) are recommended, before initiating or during therapy with csDMARDs, tsDMARDs, bDMARDs, in RA patients. (^every year according to epidemiology).†

  c) Recombinant Vaccine (Human Papilloma) is recommended before initiating or during therapy with csDMARDs, tsDMARDs, bDMARDs in RA patients (according to National Recommendations).**(4, D) † (1, A). (Level 1-4; Strength A-D)[9]

  Pneumococcal vaccination—For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is strongly recommended.[14]

  Recombinant varicella-zoster virus (VZV) vaccination—For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is strongly recommended.[14]

  For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live vaccinations are strongly recommended.[14]

<u>Monitoring</u>

- Offer all adults with RA, including those who have achieved the treatment target, an annual review to:
  - Assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
  - Check for the development of comorbidities, such as hypertension, ischemic heart disease, osteoporosis, and depression.
  - Assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung, or eyes.
  - Organize appropriate cross referral within the multidisciplinary team.

- Assess the need for referral for surgery.
- Assess the effect the disease is having on a person's life. [2018, amended **2020**][5]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Rheumatoid Arthritis report** and aims to provide recommendations to aid in the management of Rheumatoid Arthritis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Rheumatoid Arthritis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Rheumatoid Arthritis Scope

Section	Rationale/updates
1.1 NICE guidelines for management of Rheumatoid arthritis in adults 2018	**1.1.1**. Rheumatoid arthritis in adults: management, published: 11 July 2018 Last updated: 12 October **2020**[5] Amended recommendation 1.2.1 to clarify that multiple disease-modifying anti-rheumatic drugs can be offered one after the other to achieve treatment targets. We also added a cross-reference to the recommendation from section 1.5 and recommendation 1.9.3.
1.2 EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update	**1.1.2**. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: **2022** update[6] • Therapy with DMARDs should be started as soon as the diagnosis of RA is made. 1a A 9.9±0.2 100 • Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. 1a A 9.8±0.4 100 • **MTX** should be part of the first treatment strategy. 1a A 9.6±0.8 96 5. • In patients with a contraindication to MTX (or early intolerance), **leflunomide or sulfasalazine** should be considered as part of the (first) treatment strategy. 1a A 9.1±1.2 94 6. • ***Short-term glucocorticoids*** should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible. 1a A 9.3±1.2 92 7. • 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. Efficacy: 1a Efficacy: A 9.2±0.9 96

1.3 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis	**1.1.3**. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis[7] • Disease-modifying antirheumatic drugs (DMARDs) initiation • Methotrexate administration • Treatment modification • Tapering disease-modifying antirheumatic drugs (DMARDs) • Specific patient populations • Key clinical questions requiring further research
N/A	**1.2.1.** The Italian Society for Rheumatology clinical practice guidelines for rheumatoid arthritis **2019**[9] <u>Recommendations on treatment strategy in RA (Management)</u> - Treatment with csDMARDs should be started as soon as the diagnosis of RA is made. (Level 1, Strength A) - MTX should be part of the first treatment strategy. (Level 1, Strength A) - Short-term courses of glucocorticoids can be considered to control active RA in combination with csDMARDs. In view of their cumulative side effects, they should be used at the lowest dose necessary and tapered as rapidly as clinically feasible (<6 months). Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation. (Level 1, Strength A) - In patients with a contraindication or intolerance to MTX, LFN or SSZ should be considered as part of the (first) treatment strategy. (Level 1, Strength A <u>Recommendations on treatment strategy in RA (Safety)</u> - TUBERCULOSIS - HBV INFECTION - HCV INFECTION - CARDIOVASCULAR DISEASE - MALIGNANCY - VACCINATION

N/A	1.2.2. The use of biological disease-modifying antirheumatic drugs for inflammatory arthritis in Korea: results of a Korean Expert Consensus 2020[10] <u>General principle of bDMARDs treatment</u> • bDMARDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring (level of evidence [LOE]: low; strength of recommendation [SOR]: strongly recommended). • In RA, if the treatment target is not achieved with the first conventional synthetic DMARDs (csDMARDs) strategy, when poor prognostic factors are present, addition of a bDMARD should be considered (LOE: moderate; SOR: strongly recommended). <u>Concomitant use of csDMARDs with bDMARDs in RA or AS patients</u> • In RA, bDMARDs should be combined with a csDMARDs such as MTX (LOE: high; SOR: strongly recommended) • In AS, bDMARD monotherapy without csDMARDs is recommended patients with purely axial disease (LOE: high; SOR: strongly recommended) <u>Treatment options after failure of or intolerance to first bDMARDs in RA or AS patients</u> • In RA, if a bDMARD has failed, switching to another bDMARD should be considered (LOE: high; SOR: strongly recommended). <u>Monitoring strategies before or during use of bMDARDs in patients with RA or AS</u> • All patients should be screened for hepatitis B virus infection before starting bDMARDs, and if hepatitis B virus infection is identified, proper antiviral therapy should be considered (LOE: high for screening/low for antiviral therapy; SOR: strongly recommended)
N/A	**1.2.3**. Drug treatment algorithm and recommendations from the **2020** update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis-secondary publication[10] • We recommend MTX in patients with active RA. strong C (low) • We recommend folic acid in patients with RA using MTX. strong C (low)

	• We suggest combination therapy of MTX and csDMARDs in RA patients who have had an inadequate response to MTX. weak D (very low) • We suggest csDMARDs other than MTX in RA patients who cannot use MTX or who have had an inadequate response to MTX. weak C (low) • We suggest tapering of csDMARD in RA patients who are in remission or have low disease activity with a bDMARDs or a JAK inhibitor in combination with csDMARDs. weak D (very low) • We suggest NSAIDs for pain relief in patients with RA. weak C (low) • We suggest short-term concomitant use of glucocorticoids with csDMARDs in patients with active early RA. weak D (very low) • We recommend concomitant use of a TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to csDMARDs. strong A (high) • We recommend concomitant use of a non-TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to csDMARDs. strong C (low) • We suggest TNF inhibitor monotherapy in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to csDMARDs including MTX. weak D (very low) • We suggest non-TNF inhibitor monotherapy in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to csDMARDs including MTX. weak C (low) • We recommend a non-TNF inhibitor (T-cell selective co-stimulation modulator) and a TNF inhibitor equally when a bDMARD is used in combination with MTX in RA patients with moderate or severe disease activity who have had an inadequate response to MTX. strong A (high) • We recommend a non-TNF inhibitor (IL-6 inhibitor) when a bDMARD is used without MTX in RA patients with moderate or severe disease activity who are intolerant to MTX or who have had an inadequate response to MTX. strong B (moderate)

	• We suggest switching to a non-TNF inhibitor vs. to another TNF inhibitor in RA patients with moderate or severe disease activity who have had an inadequate response to a TNF inhibitor. weak D (very low) • We suggest tapering of a TNF inhibitor in RA patients who maintain remission. weak D (very low) • We suggest tapering of an IL-6 inhibitor in RA patients who maintain remission or low disease activity. weak D (very low) • We suggest tapering of a T-cell selective co-stimulation modulator in RA patients who maintain remission or low disease activity. weak D (very low) • We suggest JAK inhibitor monotherapy in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate) • We suggest concomitant use of a JAK inhibitor with MTX in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate) • We suggest concomitant use of a JAK inhibitor and a TNF inhibitor with MTX equally in RA patients who have had an inadequate response to MTX. When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak B (moderate) • We suggest concomitant use of a JAK inhibitor with MTX in RA patients who have had an inadequate response to a TNF inhibitor. • When using a JAK inhibitor, we should consider that long-term safety has not been sufficiently established. weak C (low) • We suggest tapering of a JAK inhibitor in RA patients who maintain remission or low disease activity. weak C (low) • We suggest add-on therapy with anti-RANKL antibody to DMARDs to inhibit progression of bone erosion in patients with active RA and bone erosion. Weak A (high) • We recommend reference bDMARDs and biosimilars equally in RA patients with high or moderate disease activity who have had an inadequate response to csDMARDs.

	strong A (high) • We suggest continuing reference bDMARDs and switching to biosimilars from reference bDMARDs equally in patients with RA. weak D (very low) • We suggest using DMARDs in RA patients with interstitial lung disease with careful monitoring for acute exacerbation of interstitial lung disease. weak D (very low) • We suggest not initiating TNF inhibitors in RA patients with severe heart failure. weak D (very low) • We recommend the use of appropriate doses of DMARDs with careful consideration for safety in RA patients with moderate or severe renal dysfunction. strong D (very low) • Rheumatologists should treat RA patients positive for HBs antigen in collaboration with a hepatologist. Rheumatologists should treat HBVinfected RA patients negative for HBs antigen according to the usual treatment strategy with regular monitoring for HBV infection. strong D (very low) • Rheumatologists should treat HCV-infected patients with RA according to the usual treatment strategy in collaboration with a hepatologist. strong D (very low) • We suggest that HTLV-1-positive RA patients are treated with DMARDs under careful monitoring of the disease course. weak D (very low) • In RA patients with malignancy or past history of malignancy, we suggest that bDMARDs be used with informed consent in collaboration with the attending physician treating the malignancy. weak D (very low) • We suggest that RA patients treated with glucocorticoids or DMARDs receive influenza and pneumococcal vaccines, but not live vaccines. weak D (very low) • We suggest use of MTX with full safety consideration in elderly patients diagnosed as having RA with poor prognostic factors. weak D (very low) • We suggest use of molecular targeted agents with careful consideration of safety in elderly RA patients with inadequate response to sufficient doses of csDMARDs including MTX. When using these drugs, we suggest considering the insufficient long-term safety data. weak D (very low) • We suggest using short-term glucocorticoids in combination with csDMARDs in elderly

	patients with active early RA. weak D (very low)
N/A	**1.2.4.** Saudi Guideline for Management of Rheumatoid Arthritis in Adult Patient[8] ➔ Assessment 1- A definitive diagnosis in a patient with early rheumatoid arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures. 2- Early RA is defined as disease duration within 6 months. 3- Treatment target should ideally be remission. In patients with established RA or those in whom remission can't be achieved, an alternative target of therapy would be low disease activity. 4- Management of early Rheumatoid arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist. 5- Rheumatologists are the specialists who should primarily care for patients with Rheumatoid arthritis. ➔ Approach to management of RA ➔ Recommendations for TB screening in patients receiving biologics or tofacitinib. ➔ Use of biologics and DMARDs in high-risk populations ➔ Vaccinations
N/A	**1.2.5** Update of the APLAR recommendations for treatment of rheumatoid arthritis **2018**[12] • Starting treatment with csDMARD monotherapy, preferably methotrexate, is recommended as soon as the diagnosis of RA is made Moderate. • Patients who cannot tolerate MTX may receive other csDMARDs such as LEF and SSZ as 1st-line treatment. **HCQ**, **iguratimod**, **bucillamine**, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability Moderate. • In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities Low. • Prior to starting targeted therapy, all patients should be evaluated for the presence of active or inter-current infections, comorbidities including lymphoproliferative disorders

	and skin cancers, vaccinations, pregnancy, and possible contraindications Not graded. • All patients should be screened for infections including TB, HBV, HCV and HIV (high-risk population) infections before initiating targeted therapy. Patients with active or latent infections should receive adequate therapy. B For RA patients with latent TB, prophylaxis treatment according to country-specific guidelines is recommended to prevent TB reactivation. C For RA patients with HBV infection (active or occult), antiviral therapy should be prescribed to prevent HBV reactivation. Low • A Vaccination should be undertaken prior to initiating targeted therapy. B During targeted therapy, live attenuated virus vaccines are contraindicated. Pneumococcal and influenza vaccines are recommended. Vaccines for HBV, HPV and meningococcal infections are conditionally recommended. Moderate • Targeted therapies, including TNFi, non-TNFi and JAK inhibitors, can be prescribed to patients who have moderate or high disease activity despite adequate treatment with csDMARD, or in patients with intolerance to csDMARD Moderate 8 Based on currently available evidence, all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs Moderate. • All patients receiving targeted therapy should be closely monitored for therapy-related toxicities Not graded 10 For RA patients with a history of TB or latent TB (or in whom the risk remains high despite negative screening), targeted therapies other than monoclonal Ab TNFi are preferred Low. • In RA patients at increased risk of HBV reactivation, targeted therapies other than RTX are preferred Low. • Modification of targeted therapy should be performed for failure to achieve remission or low disease activity after 6 mo Not graded. • In patients with established RA, consideration of tapering or discontinuation of targeted therapy should only be made when the disease is in remission for over 12 mo, especially if the patient is receiving concomitant csDMARD. • For patients with a past history of treated solid cancer, targeted therapies may be used

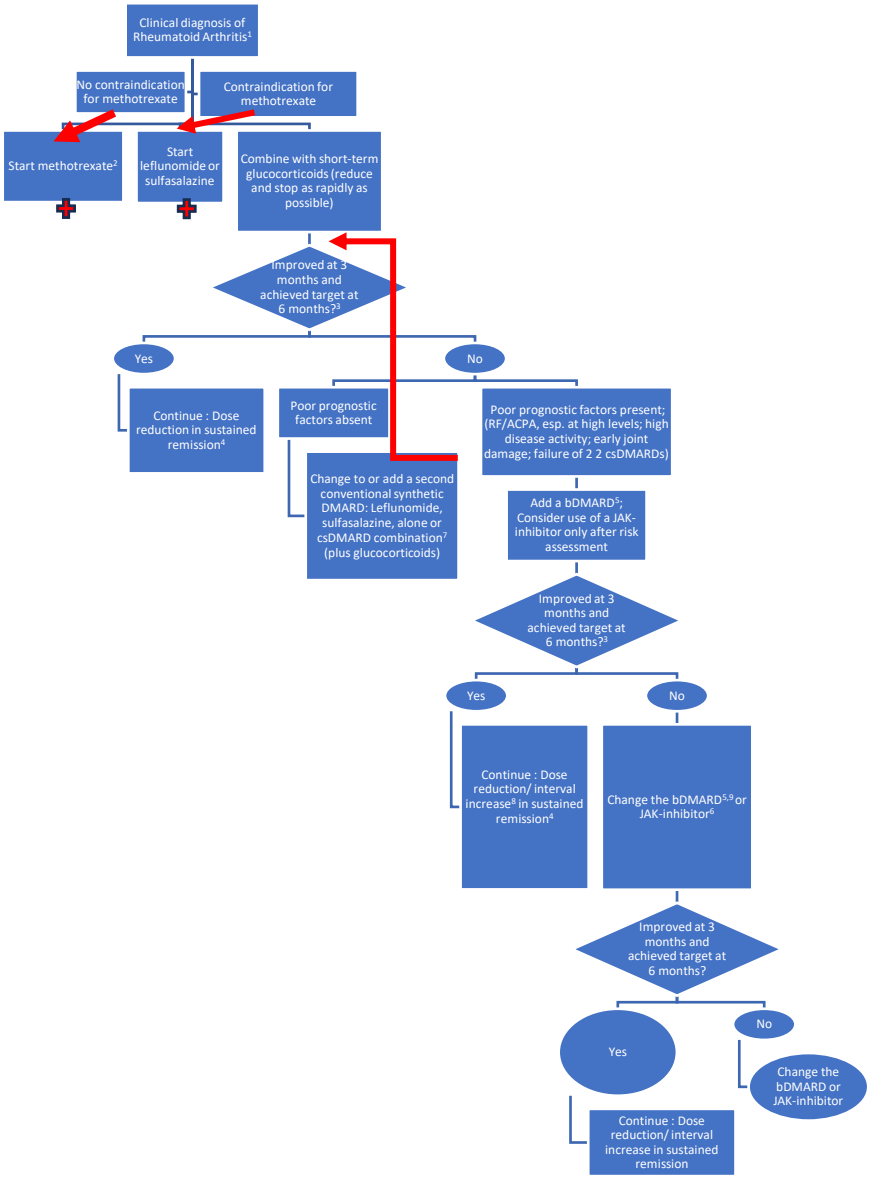
	with caution Very low. • For patients undergoing major surgery, we recommend temporary discontinuation of targeted therapy and resumption when wound healing is satisfactory Low. • For patients with established RA in whom disease cannot otherwise be controlled, TNFi (preferably ETN or CZP) may be continued throughout pregnancy

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Rheumatoid Arthritis:

Query	Filters	Search Details	Results
((Rheumatoid Arthritis [MeSH Terms]) AND (Rheumatoid Arthritis[Title/Abstract])) OR (Rheumatoid Arthritis[Title/Abstract])	Guideline, in the last 5 years	(("arthritis, rheumatoid"[MeSH Terms] AND "rheumatoid arthritis"[Title/Abstract]) OR "rheumatoid arthritis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	21

Appendix D. Treatment Algorithm



1. 2010 ACR-EULAR classification criteria can support early diagnosis.

2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.

3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.

4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

5. Consider contraindications and risks. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication IL6-inhibitors and tsDMARDs have some advantages.

6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile)

7. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.

8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon 9. From a different or the same class. re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinue