RHEUMATOID ARTHRITIS [RA]

DEFINITION

Rheumatoid arthritis (RA) is a common systemic inflammatory autoimmune disease characterized by painful, swollen joints that can severely impair physical function and quality of life.

EVALUATION

SIGNS AND SYMPTOMS

- Joint stiffness, pain, or swelling that persists for few weeks.

Joint pain in RA is typically **symmetrical and polyarticular**, but may also be asymmetrical, oligoarticular (involving 2 to 4 joints), or monoarticular at onset. New-onset symmetrical joint swelling with morning stiffness lasting longer than an hour that improves with use throughout the day is characteristic.

DIAGNOSIS

Diagnosis is based on a detailed history as well as joint swelling found on physical examination that is unexplained by another diagnosis, taking into account duration of symptoms as well as presence of rheumatoid factor/Anti CCP antibodies and presence of acute phase reactants. The 2010 EULAR/ACR criteria classifies RA based on clinical and lab criteria.

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted	2
4-10 small joimts (large not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive	3
SYMPTOM DURATION (0-1)	
< 6 weeks	0
≥ 6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥ 6 = definite RA

INVESTIGATIONS

CBC, ESR, CRP, RA factor, Anti CCP antibody, BUN, creatinine, LFTs, HBsAg, Anti HCV antibody.	Radiographs of hands, Radiographs of cervical spine. MSK ultrasound, MRI of involved joints (early onset RA).
IGRA assay (prior to initiation of treatment) Chest X-ray, HRCT chest and pulmonary function tests if extra-articular lung involvement.	Fasting, random blood glucose, lipid profile, ECG, echocardiogram for comorbidities.

MANAGEMENT

Please refer to table of recommendations for detailed management.

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Key to understanding level of evidence and strength of recommendation

(*2021- American College of Rheumatology guidelines)	
LOE	Level of Evidence

(*2018- The APLAR Recommendations)		
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.

Table of Recommendations

Treatment Principles	
RA requires **early** evaluation, diagnosis, and management.	☐
Treatment decisions should follow a **shared decision-making process.**	☐
Treatment decisions should be **re-evaluated** within a minimum of **3 months** based on efficacy and tolerability of the DMARD(s) chosen.	☐
Disease activity levels refer to those calculated using RA disease activity measures endorsed by the ACR.	☐
Recommendations are intended for the **general RA patient population** and assume that patients do not have contraindications to the options under consideration.	☐
Recommendations are limited to DMARDs approved by the US FDA for treatment of RA. **csDMARDs:** hydroxychloroquine, sulfasalazine, methotrexate, leflunomide.	☐

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bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab,golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab),anti-CD20 antibody (rituximab), tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib).	☐
Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide.	☐
Serious infection refers to an infection requiring intravenous antibiotics or hospitalization.	☐
Biosimilars are considered equivalent to FDA-approved originator bDMARDs.	☐
Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy.	☐
Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission).	☐
Target refers to low disease activity or remission.	☐
Recommendations specify that patients be at target (low disease activity or remission) for at least 6 months prior to tapering.	☐
Dose reduction refers to lowering the dose or increasing the dosing interval of a DMARD.	☐
Gradual discontinuation of a DMARD is defined as gradually lowering the dose of a DMARD and subsequently stopping it.	☐
Disease-Modifying Antirheumatic Drugs (DMARD) Initiation	
Initiation of treatment in DMARD-naïve patients with moderate-to- high disease activity	
Methotrexate monotherapy is strongly recommended over: Hydroxychloroquine or sulfasalazine. *[LOE: Very low/low]* bDMARD or tsDMARD monotherapy *[LOE: Very low/moderate]* Combination of methotrexate plus a non–TNFinhibitor bDMARD or tsDMARD *[LOE: Low/very low]*	☐

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Methotrexate monotherapy is conditionally recommended over: Leflunomide. *[LOE: Low]* Dual or triple csDMARD therapy. *[LOE: Moderate]* Combination of methotrexate plus a TNF inhibitor. *[LOE: Low]*	☐
Initiation of a csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids. *[LOE: Very low]*	☐
Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids. *[LOE: Moderate]*	☐
Initiation of treatment in DMARD-naïve patients with low disease activity Hydroxychloroquine is conditionally recommended over other csDMARDs. *[LOE: Very low]* Sulfasalazine is conditionally recommended over methotrexate. *[LOE: Very low]* Methotrexate is conditionally recommended over leflunomide. *[LOE: Very low]*	☐
Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to- high disease activity.	
Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD. *[LOE: Moderate/very low]*	☐
Methotrexate Administration	
Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate. *[LOE: Moderate]*	☐
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. *[LOE: Moderate/ very low]*	☐

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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. *[LOE: very low]*	☐
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 *[LOE: Very low]*	☐
Treatment Modification	
TTT approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs. *[LOE: Low]* A TTT approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. *[LOE: Very low]*	☐
A **minimal initial treatment goal** of low disease activity is conditionally recommended over a goal of remission. *[LOE: Low]*	☐
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. *[LOE: Very low]*	☐
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. *[LOE: Very low]*	☐
Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target. *[LOE: Very low]*	☐

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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. *[LOE: Very low]*	☐
Tapering disease-modifying antirheumatic drugs (DMARDs)	
Continuation of all DMARDs at their current dose is **conditionally recommended** over a dose reduction of a DMARD. *[LOE: Low]*	☐
Dose reduction is **conditionally recommended** over gradual discontinuation of a DMARD. *[LOE: Low]*	☐
Gradual discontinuation is **conditionally recommended** over abrupt discontinuation of a DMARD. *[LOE: Low]*	☐
Gradual discontinuation of **sulfasalazine** is **conditionally recommended** over gradual discontinuation of hydroxychloroquinefor patients taking triple therapy who wish to discontinue a DMARD. *[LOE: Very low]*	☐
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. *[LOE: Very low]*	☐
Specific patient populations	
Subcutaneous nodules	
Methotrexate is **conditionally recommended** over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity. *[LOE: Very low]*	☐
Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules. *[LOE: Very low]*	☐

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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. *[LOE: Very low]*	☐
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. *[LOE: 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. *[LOE: 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. *[LOE: 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). *[LOE: 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. *[LOE: Very low]*	☐

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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.
[LOE: Very low]

☐

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.
[LOE: 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.
[LOE: 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.
[LOE: 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.
[LOE: 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.
[LOE: Very low]

☐

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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. *[LOE: 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. *[LOE: Very low]*	☐
APLAR rheumatoid arthritis treatment recommendations: focus on targeted therapy	
Starting treatment with **csDMARD monotherapy, preferably methotrexate**, is **recommended** as soon as the diagnosis of RA is made. *[Grade: 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. *[Grade: Moderate]*	☐
In patients with **high disease activity, combination csDMARD** therapy should be considered, with close monitoring of therapy-related toxicities. *[Grade: 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. 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. *[Grade: Low]*	☐

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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. *[Grade: 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. *[Grade/LOE: Moderate]*	☐
Based on currently available evidence, all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs. *[Grade: Moderate]*	☐
All patients receiving targeted therapy should be closely monitored for therapy-related toxicities. *[Not graded]*	☐
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 *[Grade: Low]*	☐
In RA patients at increased risk of HBV reactivation, **targeted therapies other than RTX** are preferred. *[Grade: Low]*	☐

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ACRONYMS AND ABBREVIATIONS

ACR	American College of Rheumatology	**IL-6**	Interleukin-6
APLA	Asia-Pacific League of Associations for Rheumatology	**JAK Inhibitor**	Janus Kinase Inhibitors
bDMARDs	Biologic DMARDs	**LEF**	Leflunomide
CsDMARDs	Conventional Synthetic DMARDs	**MTX**	Methotrexate
CZP	Certolizumab Pegol	**NSAID**	Nonsteroidal Anti-Inflammatory Drugs
DMARDs	Disease-Modifying Antirheumatic Drugs	**RA**	Rheumatoid Arthritis
ETN	Etanercept	**RTX**	Rituximab
FDA	Food and Drug Administration	**SSZ**	Sulfasalazine
HBV	Hepatitis B Virus	**TB**	Tuberculosis
HCQ	Hydroxychloroquine	**TNFi**	Tumor Necrosis Factor Inhibitor
HCV	Hepatitis C Virus	**tsDMARDs**	Targeted Synthetic DMARDs
HPV	Human Papilloma Virus	**TTT**	Target To Treat

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