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Ministry of Health

Guideline for Management of Rheumatoid Arthritis in Adult Patient

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Introduction:

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may result in significant disability. It is the most common autoimmune inflammatory arthritis in adults [1]. RA has a significant negative impact on the ability to perform daily activities, including work and household tasks, and health related quality of life, and it increases mortality [2.3].The management of RA has seen significant advances during the past 2 decades. Although some patients with RA experience mild illness with minimal joint destruction, disease progression can lead to significant deformity of the affected joints.

RA is characterized by inflammation and swelling of the synovium of the joint, with subsequent destruction of articular structures.[4] Patients with active RA also experience systemic inflammation that is associated with a variety of comorbidities, most importantly cardiovascular disease, which contribute to the increased morbidity and mortality noted in this group compared with the general population.[5.6]

The pain, fatigue, and disability associated with RA result in a significant reduction in health-related quality of life.[7] Additionally, RA imposes a substantial economic burden upon patients, due to both increased cost of medical care and loss or reduction of employment, frequently during peak working years.[8.9]

Reason to develop this guideline:

The reason to develop this guideline due to:

- Some of the RA medications are known or suspected to cause adverse drug reactions or have black box warning.
- High budget impact of Biologic Disease-modifying anti-rheumatic drugs and Small molecule DMARDS Janus kinase inhibitors.
- Availability in Saudi Arabia of some RA medications, especially for biologics.
- Presence of bio-similar medications.

Methodology:

It was adopted from international guideline like: (2016 European League Against Rheumatism (EULAR) , 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), 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.

Table 1: Implications of strong and conditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology recommendations.
***=majority means >50% of the people.**

	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*

Table 2: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

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

Population:

Adult 18 years and elderly male and female with RA.

Epidemiology:

Incidence:

Rheumatoid arthritis is a relatively common disorder that affects men and women at the prime of their lives. Only 30% of the causes of rheumatoid arthritis can be attributed to genetic factors; the rest remain unexplained. Descriptive and analytic epidemiologic methods may lead to a better understanding of the causative, precipitating, and modulatory factors in rheumatoid arthritis.[10]

Prognosis:

Depending on how bad the progression of the disease is, there are some possible complications patients may experience outside of the regular joint-related symptoms. These complications and side effects include:

- Heart disease, Hypertension
- Eye inflammation
- Osteoporosis
- Anemia
- Depression and anxiety
- Increased risk of illness and infection
- Cancer – especially lymphoma
- Respiratory conditions caused by nodules.

Factors that Determine Rheumatoid Arthritis Prognosis:

Some of the factors that can affect the rheumatoid arthritis prognosis in patients include:

- Seropositive (positive for rheumatoid factor or anti-CCP)
- Patient's age at diagnosis
- How soon treatment began after symptoms appeared
- Patient's overall health including diet, exercise, and smoking habits
- Whether or not complications have developed through the course of the disease
- Patient's personalized treatment plan
- Response to treatment
- How active the condition has been including the frequency of flare-ups and remission periods.[11]

Mortality:

Rheumatoid arthritis life expectancy is difficult to determine. As a chronic disease, rheumatoid arthritis tends to be progressive. This means that it's a long-term disease in which symptoms tend to get worse over time. As of now, doctors do not know what triggers the disease although it is likely brought on by a combination of factors including genetics and environmental influences.

Because there isn't one specific cause of the disease, there is also no known cure for rheumatoid arthritis. Today's medical technology and research, however, provides a variety of treatment options, which can improve the prognosis.

All of these factors make it difficult to predict an exact rheumatoid arthritis life expectancy for patients. What research has found is that it isn't the disease itself that reduces the life expectancy of patients. Life expectancy is shortened by the varying complications that develop as a result of the disease.

Rheumatoid arthritis complications like respiratory and cardiovascular conditions, can compound over time and lead to a shortened lifespan and possibly eventual fatality.[12]

Disease impact and Comorbidities:

Comorbidities and extra-articular manifestations of RA

Blood vessels:
Major cutaneous vasculitis, atherogenesis, vasculitis, Raynaud's syndrome

Bone
Osteoporosis, low bone mineral density, fractures.

Brain and nerves
Reduced cognitive function, depression, neuropathy, myelopathy, low stress tolerance

Cardiovascular system
Pericarditis, ischemic heart disease, congestive heart failure.

Nervous system
Stroke

Liver
Acute phase response, iron redistribution, altered lipid metabolism

Mouth
Secondary Sjögren's syndrome, periodontitis

Muscle
Insulin resistance, sarcopenia

Joints
Septic arthritis

Eyes
Scleritis, retinal vasculitis, secondary Sjögren's syndrome, kerato-conjunctivitis sicca

Lungs
Pleuritis, pulmonary fibrosis, bronchiolitis, pneumonia

Spleen
Felty's syndrome.[13]

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.
6- 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.
7- Treatment decisions should be based on the severity of disease activity, as measured by quantitative method such as the DAS28 or CDAI and the prognostic factors associated with poor outcomes.
8- 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)
9- 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.
10- Arthritis activity should be assessed at 1-month to 3-month intervals until the treatment target (Remission or low disease activity) has been reached.
11- Radiographic and patient-reported outcome measures, such as functional assessments, can be used to complement disease activity monitoring.
12- 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.
13- Among the DMARDs, methotrexate is considered to be the anchor drug and, unless contraindicated, should be part of the first treatment strategy. **(LOE low)**
14- 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.
15- 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)**
16- 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).

Mechanism of Action and adverse effects:

- **Disease-Modifying Anti-Rheumatic Drugs (DMARDs):**

Various drugs of different categories are used as DMARDs such as methotrexate, sulfasalazine, hydroxychloroquine and Leflunomide. Most of the DMARDs are immunosuppressant drugs which are reported to retard joint degeneration in about two third of patients[14] . The use of MTX should be considered as anchor therapy in patients with rheumatoid arthritis, and should be started within the first three months of diagnosis. Each DMARDs acts by different mechanism. Methotrexate is the core therapy for management of RA. Sulfasalazine acts by scavenging toxic oxygen metabolites produced by neutrophils as well as by inhibiting translocation of NF-kB resulting into inhibition of transcription of various chemokines[15]. Leflunomide has a relatively specific inhibitory effect on activated T cells. Leflunomide retards proliferation of activated T cells in addition to inhibiting adhesion and migration of inflammatory cells. Leflunomide give rise to a metabolite that inhibits de novopyrimidine synthesis by inhibiting dihydroorotic acid dehydrogenase. Leflunomide has been reported to have clinical improvement in arthritic patients[16] .

Drug	Regular Dose [17]	Adverse drug reaction [18,19]
Methotrexate	7.5–15 mg every week at doses exceeding 20 mg/wk the incidence and severity of toxic reactions are increased	• Nausea; vomiting and diarrhea • Hepatotoxicity • Alopecia • New-onset cough or shortness of breath • Photosensitivity • Myelosuppression.
Hydroxychloroquine	5mg/kg/day max. 400 mg/day	• Nausea; diarrhea • Headache • Vision changes (retinal damage) • Skin pigmentation
Sulfasalazine	500–1000 mg twice daily	• Nausea; diarrhea • Headache • Rash, yellow-orange discoloration • Photosensitivity • Myelosuppression
Leflunomide	10–20 mg/day Maximum : 20 mg/day	• Nausea; diarrhea and abdominal pain • Hepatotoxicity • hypertension, headache • Alopecia and rash

Biological Agents:

1. Tumor necrosis factor inhibitors (TNF-Inhibitors)

Drug	Regular Dose[18]	Adverse drug reaction [19.20]
Etanercept	50 mg subQ once weekly	• Central nervous system: Headache • Dermatologic: Skin rash • Gastrointestinal: Abdominal pain , diarrhea and vomiting • Infection: Infection • Local: Injection site reaction: bleeding, bruising, erythema, itching, pain, or swelling. • Respiratory: Upper respiratory tract infection ,rhinitis • Miscellaneous: Antibody development, positive ANA titer
Adalimumab	40 mg subQ every other week; May increase to 40 mg subQ every week in patients not receiving concomitant methotrexate	• Central nervous system: Headache • Dermatologic: Skin rash • Immunologic: Antibody development • Local: Injection site reaction • Neuromuscular & skeletal: Increased creatine phosphokinase • Respiratory: Upper respiratory tract infection and sinusitis
Infliximab	3 mg/kg IV at 0, 2, and 6 wk; then every 8 wk thereafter	• Central nervous system: Headache • Gastrointestinal: Abdominal pain and nausea • Hepatic: Increased serum ALT • Immunologic: Increased ANA titer, antibody development (anti-infliximab) • Infection • Respiratory: Upper respiratory tract infection, sinusitis, cough, pharyngitis • Miscellaneous: Infusion related reaction

Certolizumab	400 mg subQ at 0, 2, and 4 wk; then 200 mg every other week or 400 mg every 4 weeks	• Gastrointestinal: Nausea • Immunologic: Antibody development • Infection • Respiratory: Upper respiratory tract infection

2. Interleukin-6 inhibitors:

Drug	Regular Dose[17]	Adverse drug reaction [18,19]
Tocilizumab	**IV infusion** 4 mg/kg over 1 hour every 4 weeks; increase to 8 mg/kg every 4 weeks based on clinical response; doses exceeding 800 mg per infusion are not recommended **SubQ dosing** **(Weight less than 100 kg)**: 162 mg subQ every other week; increase to 162 mg SUBQ every week based on clinical response **(Weight 100 kg or greater)** 162 mg subQ every week Switching from IV to subQ, give the first subQ dose instead of the next scheduled IV dose	• *Endocrine & metabolic: Increased serum cholesterol (>240 mg/dL; >1.5-2 x ULN; combination therapy)* • *Hepatic: Increased serum ALT and increased serum AST* • *Miscellaneous: Infusion-related reaction.*

3. Selective T-Cell Costimulation Blocker

Drug	Regular Dose [17]	Adverse drug reaction [18,19]
Abatacept	**IV infusion:** Weight based dose every 2 wk for two doses and then monthly (i.e., 750 mg for those weighing 60–100 kg) **SubQ dosing with IV loading dose**: Give weight-based IV loading dose, then 125 mg subQ within 1 day of loading dose, followed by 125 mg subQ once weekly **SubQ dosing without IV loading dose:** 125 mg subQ weekly **Transitioning from IV to subQ therapy:** 125 mg subQ in place of next scheduled IV dose, followed by 125 mg subQ once weekly	• Central nervous system: Headache • Gastrointestinal: Nausea • Respiratory: Nasopharyngitis, upper respiratory tract infection • Miscellaneous: Infection, antibody development.

4. Anti-CD20 Monoclonal Antibody

Drug	Regular Dose [17]	Adverse drug reaction [18,19]
Rituximab	1000 mg IV followed by a second 1000-mg IV dose 2 weeks later in combination with methotrexate every 24 weeks or based on clinical evaluation;	• Cardiovascular: Peripheral edema, hypertension • Central nervous system: Fever, fatigue, chills, headache, insomnia, pain • Dermatologic: Rash, pruritus, angioedema

		• Gastrointestinal: Nausea, diarrhea, abdominal pain, weight gain. • Hematologic: Cytopenias ,lymphopenia, anemia , leukopenia, neutropenia ,neutropenic fever , thrombocytopenia • Hepatic: ALT increased • Neuromuscular & skeletal: Neuropathy, weakness, muscle spasm, arthralgia • Respiratory: Cough , rhinitis, epistaxis • Miscellaneous: Infusion-related reactions, human antichimeric antibody (HACA) positive , night sweats

- **Small molecule DMARDS (sDMARDs) Janus kinase (JAK) inhibitors.**

Drug	Regular Dose [17]	Adverse drug reaction [18,19]
Tofacitinib	5 mg orally twice daily	• Cardiovascular: Hypertension, peripheral edema • Central nervous system: Headache, fatigue, insomnia, paresthesia • Dermatologic: Erythema, pruritus, skin rash • Endocrine & metabolic: Dehydration • Gastrointestinal: Diarrhea, abdominal pain, diverticulitis, dyspepsia, gastritis, nausea, vomiting. • Genitourinary: Urinary tract infection • Hematologic & oncologic: Anemia, skin carcinoma • Hepatic: Increased serum ALT , liver steatosis • Infection • Neuromuscular & skeletal: Arthralgia, joint swelling, musculoskeletal pain, tendonitis

		• Renal: Increased serum creatinine • Respiratory: Upper respiratory tract infection, nasopharyngitis, cough, dyspnea, sinus congestion • Miscellaneous: Fever

- **Glucocorticoids:**

Steroids have been widely used for suppressing pain and inflammation in arthritis since many years. Corticosteroids acts by inhibiting induction of COX enzyme. Moreover, corticosteroids also inhibits release of collagenase and lysosomal enzyme by reducing macrophage phagocytosis and IL-1 secretion. [20]
Glucocorticoids are generally better avoided on the long-run because of adverse effects which include :
- CNS: Headache and steroid psychosis.
- Cardiovascular: hypertension.
- Skin: easy bruising, poor wound healing, skin atrophy and acne.
- Endocrine: Cushing's syndrome, osteoporosis, diabetes, hirsutism, hypokalemia and weight gain.
- Musculoskeletal: steroid myopathy and avascular necrosis.
- Eye: cataract and glaucoma.[21]

- **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):**

NSAIDs are pain relieving agents. They offer little protection against tissue degeneration. NSAIDs like Ibuprofen, Diclofenac or others act non-selectively by inhibiting both Cyclooxygenase enzymes (COX 1 and COX 2) which are responsible for synthesis of protanoids from its precursor Arachidonic acid. COX 1 enzyme is constitutively present in cells whereas COX 2 is inducible form and is generated at sites of inflammation. It is reported that NSAIDs provides pain relief by reducing prostaglandin, bradykinins and oxygen radicals.[22]

Initial Therapy

1-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)**
2-In patients with contraindication or intolerance to methotrexate, we consider alternatives such as sulphasalazine. **(LOE low)**
3-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.

4-In patients with moderate to high disease activity, we might consider initiating treatment with combination DMARDs from the beginning.
5-A minimal period of 3 months is given before a major change to therapy is made.
6-Treatment target should be achieved within 6 months.

Inadequate or no response:

1-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 **(Figure1)**
2-In the absence of poor prognostic factors, we add a second csDMARD if we initially started with a single agent.
3-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:

1-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).**
2-If a patient has failed a TNFi, we switch to a NON-TNFi or JAK inhibitor. **(LOE low to very low).**
3- 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).**

4-If a patient fails multiple biologic DMARDs, switch to JAK inhibitor, like tofacitinib, is considered. **(LOE low to very low).**

Recommendations:

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

b DMARDs → Privileges of consultant Rheumatologist
Jak-I → Privileges of consultant Rheumatologist

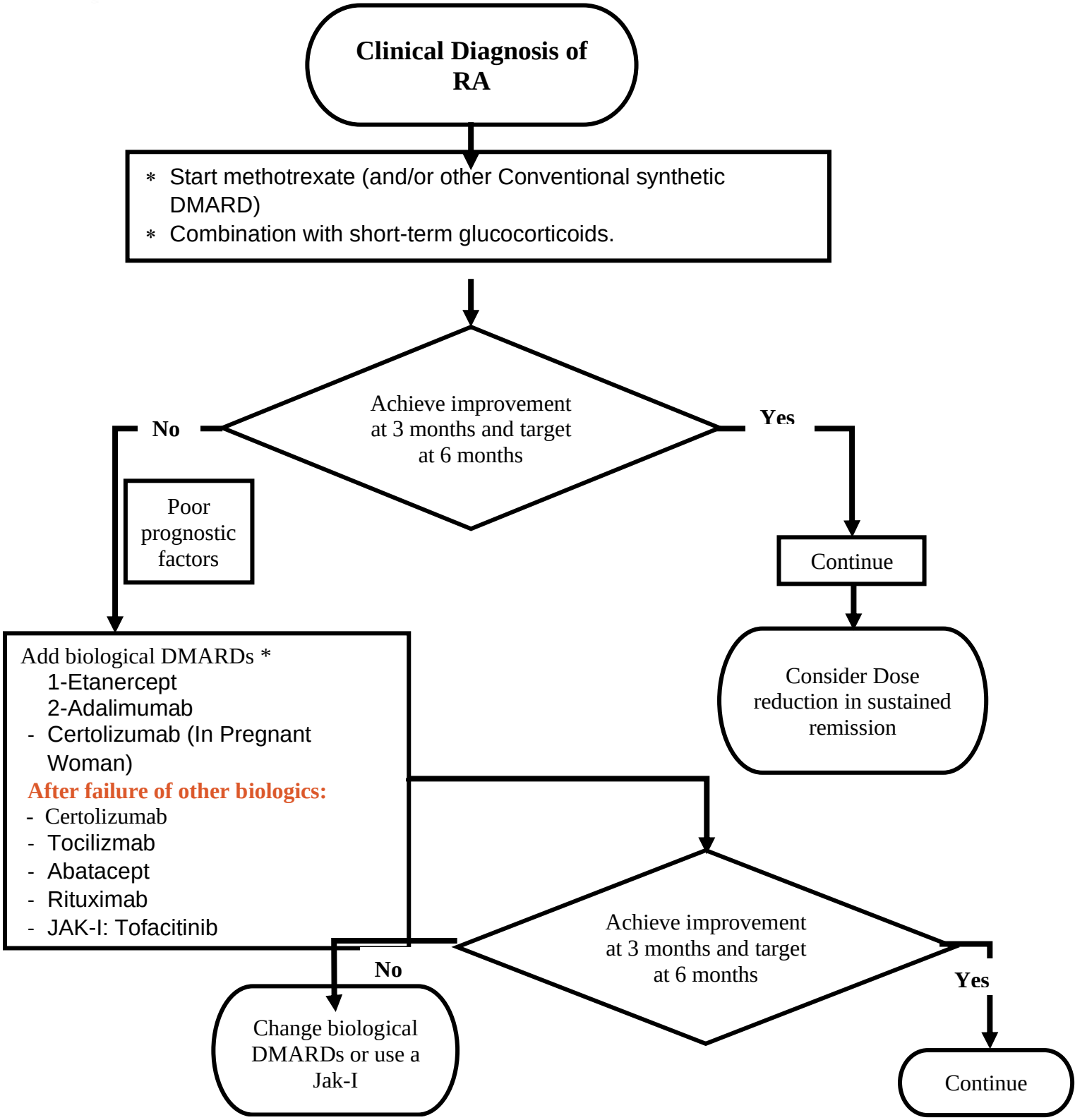


Figure 1:

➔ Conventional synthetic DMARDs (cs DMARDs) e.g. methotrexate, leflunomida, SSZ, HCQ

➔ Targeted synthetic DMARDs (ts DMARDs) e.g. Tofacitinib

*Based on logistic issues (MOH)

* We have no preference to any of the biologics; the choice will be largely dependent on the patient's condition, preference and comorbidities.

The following table shows the recommendations for monitoring CBC, LFT and renal function for patients on csDMARDs therapy.

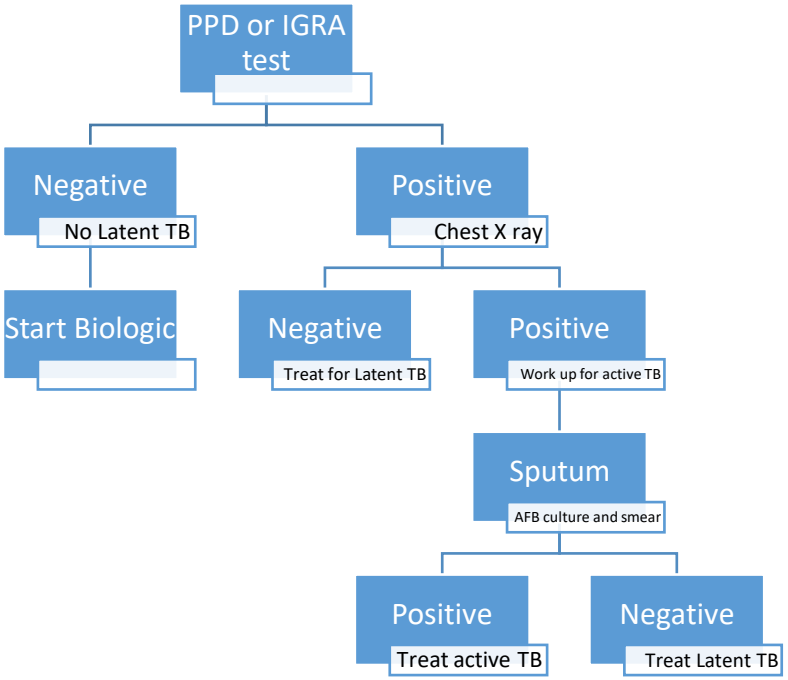
Agent	< 3 months	3 – 6 months	> 6 months
Leflunomide	2 – 4 weeks	8 – 12 weeks	12 weeks
Methotrexate	2 – 4 weeks	8 – 12 weeks	12 weeks
Sulfasalazine	2 – 4 weeks	8 – 12 weeks	12 weeks

Recommendations for TB screening in patients receiving biologics or tofacitinib[23]

Screening for latent tuberculosis:

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:[23.24.25,26]

Risk factor	Recommendations
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 are:** 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:[23]

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.

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Guideline for management of Rheumatoid Arthritis in Adult patients at Prince Sultan Military Medical City (PSMMC).

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