QUICK REFERENCE
FOR HEALTHCARE PROVIDERS

Management of
Rheumatoid Arthritis

Ministry of Health
Malaysia

MSR MALAYSIAN SOCIETY OF RHEUMATOLOGY

Academy of
Medicine Malaysia

KEY MESSAGES

1. Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease which primarily affects the joints. It is characterised by uncontrolled proliferation of synovial tissue and a wide array of multisystem co-morbidities.
2. Consider RA if inflammation involving multiple joints is present for at least 6 weeks as early diagnosis and prompt treatment are mandatory to prevent irreversible joint damage.
3. Inflammatory markers and rheumatoid factor (RF) ± anti-citrullinated peptide antibody (ACPA) should be tested when there is clinical suspicion of RA. Positive RF does not equate to RA while negative RF or ACPA does not exclude RA.
4. All patients suspected of having RA should be referred to the rheumatologist and a co-management plan may be offered subsequently.
5. Treat-to-target (T2T) treatment strategy aims to achieve a state of clinical remission or at least low disease activity within 6 months, utilising standardised objective assessments of RA disease activity e.g. Disease Activity Score 28 (DAS28).
6. Optimal care of patients with RA which consists of an integrated approach that includes both non-pharmacological and pharmacological treatments should be initiated as soon as the diagnosis is made, to preserve joint function and quality of life.
7. Patient education should be included in the management of RA.
8. Short-term (<3 months) low-dose corticosteroids (if oral prednisolone is used, the dose should be ≤10 mg OD) may be used as bridging therapy during initial diagnosis and acute flare of RA.
9. Methotrexate should be used as the first-line Disease Modifying Anti-Rheumatic Drug (DMARD) in all patients with RA unless contraindicated.
10. Biologic DMARDs and targeted synthetic DMARDs should be considered when the treatment target is not achieved with conventional synthetic DMARDs. Where available, biosimilar DMARDs may be considered as effective alternatives.

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Rheumatoid Arthritis.

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
Ministry of Health Malaysia: www.moh.gov.my
Academy of Medicine Malaysia: www.acadmed.org.my
Malaysian Society of Rheumatology: www.msr.my

CLINICAL PRACTICE GUIDELINES SECRETARIAT
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Presint 1,
Federal Government Administrative Centre 62590
Putrajaya, Malaysia
Tel: 603-88831229
E-mail: htamalaysia@moh.gov.my

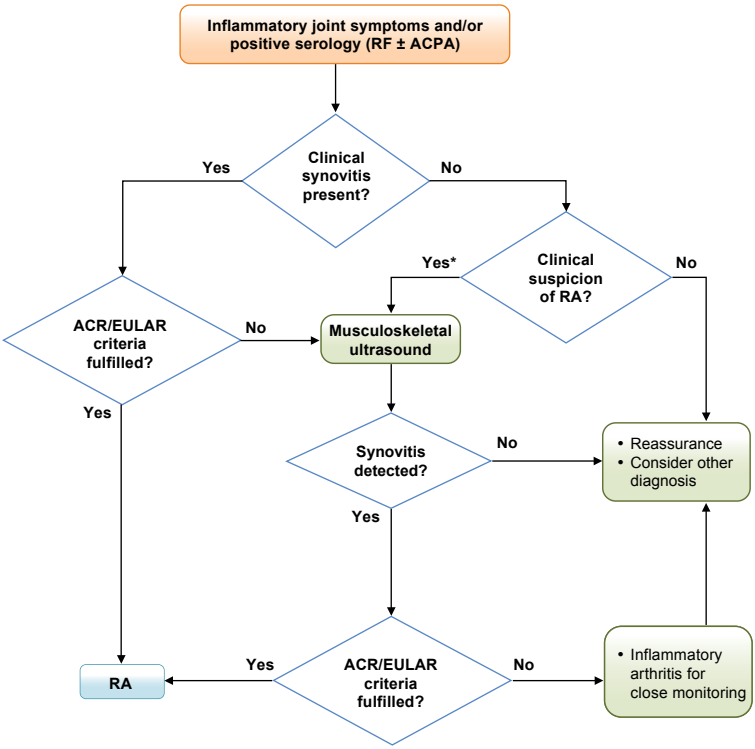
THE 2010 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

	Scores
Target population (Who should be tested?): Patients who 1) have at least 1 joint with definite clinical synovitis (swelling)* 2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	**0**
2 - 10 large joints	**1**
1 - 3 small joints (with or without involvement of large joints)	**2**
4 - 10 small joints (with or without involvement of large joints)	**3**
>10 joints (at least 1 small joint)	**5**
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	**0**
Low-positive RF *or* low-positive ACPA	**2**
High-positive RF *or* high-positive ACPA	**3**
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	**0**
Abnormal CRP *or* abnormal ESR	**1**
D. Duration of symptoms	
<6 weeks	**0**
≥6 weeks	**1**

A score of ≥6 is classified as having definite RA
A score of <6 may fulfil the criteria over time
There are four domains in the classification criteria:

A. Joint involvement (swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis)
   Large joints refer to shoulders, elbows, hips, knees and ankles.
   Small joints refer to metacarpophalangeal (MCPs), proximal interphalangeal (PIPs), second through fifth metatarsophalangeal (MTPs), thumb IPs and wrists.
   **Distal interphalangeal (DIP) joints, first carpometacarpal joints and first MTP joints are excluded from assessment*
B. Serology
   High positive refers to International Unit values >3 times upper limit normal.
C. Acute-phase reactants
   Normal or abnormal is determined by local laboratory standards.
D. Duration
   Patient self-report of the duration of signs or symptoms of synovitis.

DIAGNOSIS OF RHEUMATOID ARTHRITIS



*presence of a first-degree relative with RA, raised inflammatory markers and extra-articular features

ACPA: anti-citrullinated peptide antibody
ACR/EULAR: American College of Rheumatology/European League Against Rheumatism
RA: rheumatoid arthritis
RF: rheumatoid factor

LABORATORY INVESTIGATIONS

Phase of management	Investigations

Diagnosis	• Inflammatory markers
	  ○ erythrocyte sedimentation rate (ESR) and/or
	  ○ C-reactive protein (CRP)
	• Rheumatoid factor (RF) and/or
	• anti-citrullinated peptide antibody (ACPA)*

Pre-treatment and co-morbidities screening	• Full blood count (FBC) • Renal profile (RP) • Fasting blood sugar • Fasting lipid profile • Liver function test (LFT) • Viral hepatitis screening [hepatitis B surface antigen (HBsAg), hepatitis C antibody] • Human immunodeficiency virus (HIV) if risk factor present
Treatment: Disease activity monitoring and treatment AEs	• FBC • RP • LFT • ESR and CRP
Pre-biologic therapy	• Hepatitis B core antibody, if HBsAg negative • Mantoux ± Interferon Gamma Release Assay (IGRA) • HIV screening • Immunoglobulin (Ig) G, A and M [prior to rituximab (RTX)]

*ACPA is interchangeable with anti-cyclic citrullinated peptide (anti-CCP)

REFERRAL

Referral for diagnosis

1. Clinical suspicion of RA supported by the presence of any of the following:
   - more than three swollen joints
   - MCP/MTP joint involvement with positive squeeze test
   - early morning stiffness of more than 30 minutes
2. Clinical evidence of persistent synovitis of undetermined cause

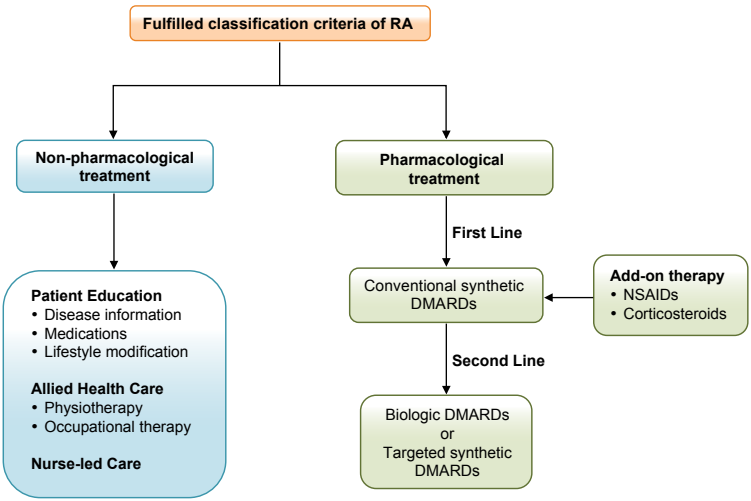
Referral following diagnosis

1. Development of a co-management plan
2. Optimisation of therapy in active disease
3. Disease-related complications (e.g. acute flare or interstitial lung disease) or treatment-related complications (e.g. infection or transaminitis)

Referral of patients with special considerations

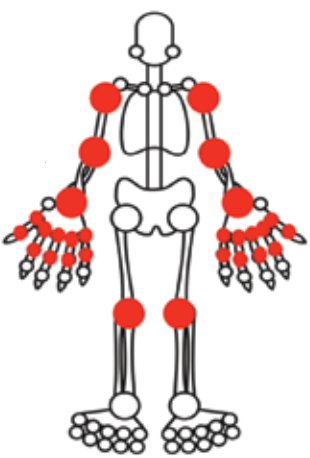
1. Pre-pregnancy care, pregnancy and lactation
2. History of hepatitis B and/or hepatitis C
3. History of malignancy

TREATMENT OF RHEUMATOID ARTHRITIS



DMARDs: Disease Modifying Anti-Rheumatic Drugs
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
RA: Rheumatoid Arthritis

DAS28 (OUTCOME MEASURE)



A composite calculation* of 4 parameters which includes tender joint count and swollen joint count (based on 28 joints assessment as shown in red), ESR (or CRP) and patient global assessment (VAS 0 - 100 mm).

Definition of RA disease activity based on DAS28-ESR:

- Remission: ≤2.6
- Low disease activity: >2.6 to ≤3.2
- Moderate disease activity: >3.2 to ≤5.1
- High disease activity: >5.1

*DAS28 calculator is available online.

DMARDS IN RHEUMATOID ARTHRITIS

DRUG	DOSING	COMMON ADVERSE EFFECTS
Conventional Synthetic DMARDs		
Methotrexate	7.5 - 20 mg weekly Dose adjustment for renal impairment: CrCl (ml/min/1.7 m^2) → % Standard dose ≥60 → Full dose 30 - 59 → 50 <30 → Contraindicated	• Gastrointestinal (GI) intolerance • Alopecia • Mucositis • Photosensitivity, rash • Abnormal FBC • Elevated alanine aminotransferase (ALT) / aspartate aminotransferase (AST) • Interstitial pneumonia (acute/chronic)
Sulfasalazine	500 - 1000 mg BD	• Pruritus • Rash • GI intolerance
Hydroxychloroquine	200 - 400 mg OD (not exceeding 6.5 mg/kg ideal body weight)	• Retinal disorder
Leflunomide	10 - 20 mg OD	• Alopecia • Abnormal FBC • Elevated ALT/AST • Elevated blood pressure
Targeted Synthetic DMARDs		
Tofacitinib	5 mg BD 5 mg OD (CrCl 30 – 60 mL/min)	• Increased low-density lipoprotein (LDL) and high-density lipoprotein (HDL) level • Herpes Zoster infection • Elevated ALT/AST • Gut perforation (especially in diverticulitis)
Baricitinib	4 mg OD 2mg OD (CrCl 30 – 60 mL/min)	• Elevated ALT/AST • GI intolerance • Herpes Zoster infection • Abnormal FBC • Increased LDL, HDL and triglyceride level
Biologic DMARDs		
Infliximab	3 mg/kg every 8 weeks May increase to 5 mg/kg	• Rash • GI intolerance • Infusion related reaction • Infections [including tuberculosis (TB)]
Etanercept	50 mg every week	• Injection site reaction • Infections (including TB)
Adalimumab	40 mg every 2 weeks	• Injection site reaction • Rash • GI intolerance • Infections (including TB)
Golimumab	SC: 50 mg every month IV: 2 mg/kg every 8 weeks	• Injection site reaction • Rash • Infections (including TB) • Elevated ALT/AST
Tocilizumab	SC: 162 mg every week IV: 4 - 8 mg/kg every 4 weeks	• Injection site reaction • Rash • GI intolerance • Elevated ALT/AST • Abnormal FBC • Infections (including TB) • Gut perforation (especially in diverticulitis) • Increased LDL level
Rituximab	SC: 162 mg every week IV: 4 - 8 mg/kg every 4 weeks	• Peripheral oedema • Pruritus • Rash • GI intolerance • Abnormal FBC • Infections • Infusion related • Low IgG/IgA/IgM

OD=once a day; BD=two times a day; TDS=three times a day

DRUG MONITORING

Conventional Synthetic DMARDs					
Drug	**Baseline investigations**	**Subsequent investigations**	**Frequency of monitoring**	**Additional monitoring**	**Action**
Methotrexate Sulfasalazine	• FBC • Serum creatinine • ALT and/ or AST • Albumin • HBsAg • Anti-hepatitis C virus • Chest X-ray	• FBC • Serum creatinine • ALT and/ or AST • Albumin	2 - 4 weekly for the first 3 months or at every dose increase, then 3-monthly	-	Early consultation with rheumatology team or consider interruption in treatment if any of the following occurs: i. WBC <3.5 x 10^9/L ii. Neutrophils <1.6 x 10^3/L iii. Unexplained eosinophilia >0.5 x 10^3/L iv. MCV >105 fL v. Platelet <140 x 10^9/L vi. Creatinine increase >30% vii. AST/ALT > 3x ULN (upper limit normal) viii. Unexplained reduction in albumin <30 g/L
Leflunomide	As above	As above	As above	• BP and weight at each visit	
Hydroxy-chloroquine	As above	-	-	• Baseline ophthalmic examination within 1 year of commencing treatment and annually after 5 years	