CLINICAL PRACTICE GUIDELINES

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Management of Rheumatoid Arthritis

Ministry of Health Malaysia

MSR MALAYSIAN SOCIETY OF RHEUMATOLOGY

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2019 and will be reviewed in a minimum period of four years (2023) or sooner if there is a need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

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KEY RECOMMENDATIONS

The following recommendations were highlighted by the CPG Development Group as the key clinical recommendations that should be prioritised for implementation.

Diagnosis and Investigation

- Consider rheumatoid arthritis if inflammation involving multiple joints is present for at least six weeks.
- Inflammatory markers and rheumatoid factor ± anti-citrullinated peptide antibody should be tested when there is clinical suspicion of rheumatoid arthritis.

Referral

- All patients suspected of having rheumatoid arthritis (RA) should be referred to the rheumatologist.
- All RA patients should be primarily managed by rheumatologists.
  - Co-management plan with primary healthcare providers may be offered subsequently.

Treatment

- Aim to achieve a state of clinical remission or at least low disease activity within six months using a treat-to-target strategy in rheumatoid arthritis.
- Patient education should be included in the management of rheumatoid arthritis.
- Short term low-dose corticosteroids may be used in active rheumatoid arthritis.
- Methotrexate should be used as the first-line Disease Modifying Anti-Rheumatic Drug in all patients with rheumatoid arthritis unless contraindicated.

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these CPG were from the Ministry of Health (MoH), Ministry of Education (MoE) and private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (G-I-N). Refer to **Appendix 1** for **Example of Search Strategy**. The inclusion criteria were all patients with rheumatoid arthritis regardless of study design. The search was limited to literature published in the last 15 years and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 29 May 2017 to 2 June 2017. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 January 2019 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other guidelines as listed below:

- Rheumatoid Arthritis in Adults: Management [National Institute for Health and Clinical Excellence (NICE), July 2018]
- Management of Early Rheumatoid Arthritis [Scottish Intercollegiate Guidelines Network (SIGN), February 2011]

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as reference.

A total of seven main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 19 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf)

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations in rheumatoid arthritis (RA) based on the following aspects:

- diagnosis
- investigations
- treatment (non-pharmacological and pharmacological)
- special considerations
- referral and follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- All patients with RA (16 years and above)

Exclusion criteria

- Juvenile-onset Idiopathic Arthritis

TARGET GROUP/USER

This CPG is intended to guide those in primary, secondary or tertiary care who are involved in management of RA:

- doctors
- allied health professionals
- trainees and medical students
- policy makers
- patients and their advocates
- professional societies

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The draft CPG was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the CPG.

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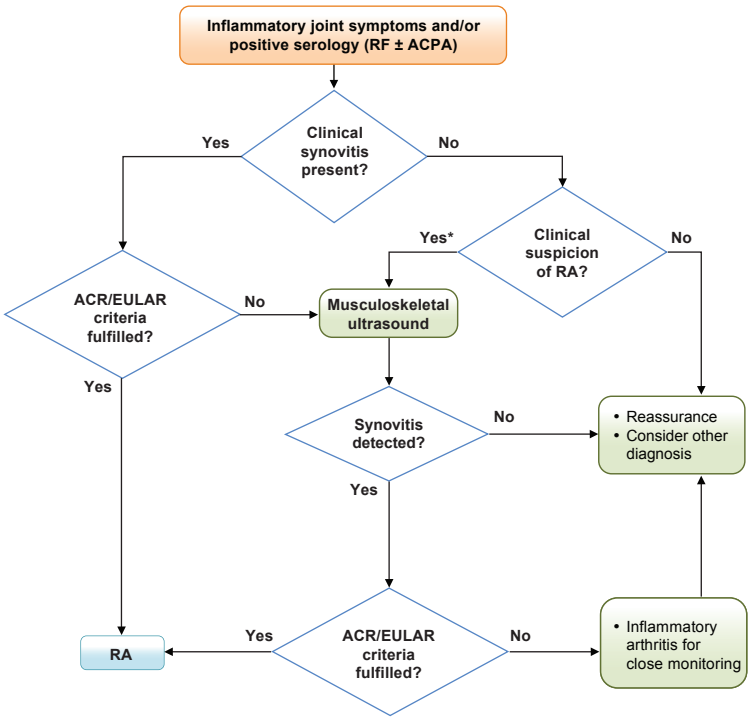
ALGORITHM 1. DIAGNOSIS OF RHEUMATOID ARTHRITIS



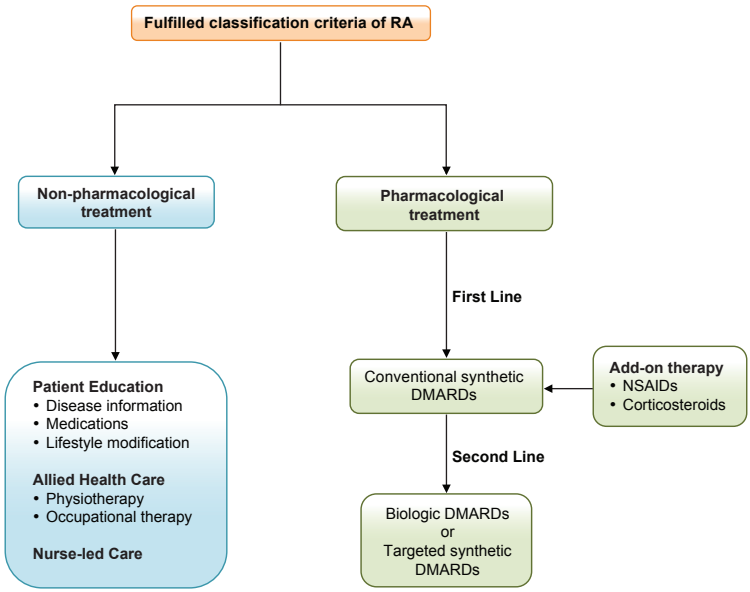
*presence of a first-degree relative with RA, raised inflammatory markers and extra-articular features

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

Modified:

1. D'Agostino MA, Terslev L, Wakefield R, et al. Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. Ann Rheum Dis. 2016 Nov;75(11):1902-1908.
2. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76(3):491-496.

ALGORITHM 2. TREATMENT OF RHEUMATOID ARTHRITIS



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

1. INTRODUCTION

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. The disease has an insidious onset with unpredictable and variable courses. Typically, RA manifests as symmetrical polyarthritis but may also present with non-specific symptoms e.g. fatigue, malaise and mild fever. Bone erosion, destruction of cartilage and complete loss of joint integrity can occur over time if treatment is delayed or inadequate.

Numerous multicentre international studies have shown that disease progression can be minimised with early and appropriate treatment. Treatment paradigm of RA has evolved over the last two decades with the advent of biologics and implementation of treat-to-target (T2T) strategy.

The Malaysian National Inflammatory Arthritis Registry (NIAR) reported that there is often a delay in RA diagnosis as only about 50% of cases are diagnosed within a year of the symptom onset. This may be due to a lack of awareness and understanding of the disease among public and healthcare providers. Furthermore, limited human, financial and infrastructure resources may also contribute to the difficulty of accessing rheumatology care.[4]

This is the first national CPG on the management of RA aimed to increase awareness among healthcare providers on the importance of recognizing early RA, timely referral to rheumatologist and initiation of treatment. We hope that this CPG will foster close collaboration between various stakeholders in providing evidence-based management of RA to improve outcomes and ultimately patients' quality of life (QoL).

2. CLINICAL FEATURES

Clinical features of RA can be divided into articular and extra-articular manifestations. Extra-articular features may involve multiple organs including the skin, eyes, lungs and blood vessels. Non-specific systemic features such as fever, malaise and weight loss may precede overt joint symptoms.

RA may be associated with other connective tissue diseases and chronic non inflammatory pain e.g. fibromyalgia. It is also an independent risk factor for cardiovascular (CV) diseases and osteoporosis.

The key presenting symptoms of joint inflammation are:
- joint pain and swelling
- early morning stiffness lasting ≥30 minutes

The typical articular pattern of RA is symmetrical polyarthritis affecting:
- metacarpophalangeal (MCP) joints
- proximal interphalangeal (PIP) joints
- interphalangeal joint of thumbs
- wrists
- elbows
- metatarsophalangeal (MTP) joints

The symptoms of joint inflammation should be present for at least six weeks.

Findings on physical examination include:
- clinical synovitis
  - joint tenderness
  - boggy swelling (may be subtle in early RA)
- restricted range of motion
- joint deformities e.g. radial deviation of the wrist, ulnar deviation at the MCPs, “swan-neck” [flexion of distal interphalangeal (DIP) joint, hyperextension of PIP] and “boutonniere” (hyperextension of DIP, flexion of PIP) deformities

Differential diagnosis of polyarthritis should take into consideration:
- duration of symptoms
- pattern of joint involvement
- presence of systemic features and/or other diseases

Important differentials include:
- psoriatic arthritis
- erosive inflammatory osteoarthritis
- polyarticular gout
- arthritis related to infection
- systemic lupus erythematosus

- Early diagnosis and prompt treatment of RA are mandatory to prevent irreversible joint damage.

Recommendation 1

- Consider rheumatoid arthritis if inflammation involving multiple joints is present for at least six weeks.

3. INVESTIGATIONS

Laboratory and imaging investigations are performed to assist in diagnosis, screen pre-existing abnormalities and co-morbidities, as well as to monitor treatment-related adverse events (AEs).

3.1 Laboratory Test

Relevant laboratory tests in RA are shown in table below.

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)

RF and ACPA have similar diagnostic sensitivity (67% and 79% respectively)[1] although ACPA has a higher specificity compared with RF (95 - 98% and 79 - 85% respectively).[1-2] Presence of both RF and ACPA indicate a more severe disease. ACPA should be considered in clinically suspected RA where RF is negative. Both RF and ACPA are not recommended for disease monitoring.

- Positive RF does not equate to RA as it is present in normal population with a higher incidence in the elderly.
- Negative RF does not exclude RA as 30 - 40% of patients with RA are seronegative.[3-4]

Recommendation 2
- Inflammatory markers and rheumatoid factor ± anti-citrullinated peptide antibody should be tested when there is clinical suspicion of rheumatoid arthritis.

3.2 Imaging

3.2.1 Plain Radiography

a. Chest X-Ray

Chest X-ray is performed at baseline evaluation and repeated on follow-up for assessment of disease complications and co-morbidities. It is also mandatory as part of pre-biologic tuberculosis screening (refer to **Appendix 8**).

b. Hand X-Ray

Plain radiograph is the most common modality used to assess the joints. It may be normal within the first six months of RA onset. The radiograph findings include soft-tissue swelling, juxta-articular demineralisation, joint space narrowing and bone erosions. These changes are symmetrical and spare the distal IP joints. Refer to **Figure 1** and **2**.

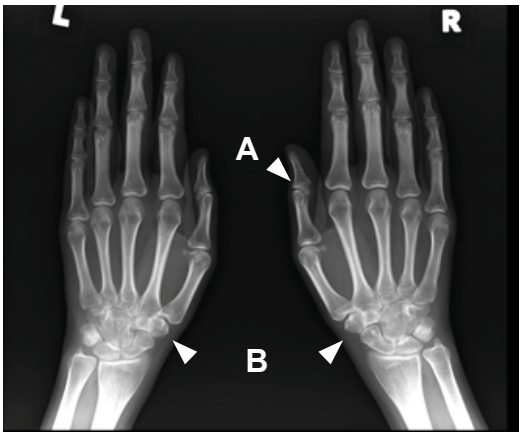


Figure 1. Anteroposterior view (AP) of hands in early RA:
(A) periarticular osteopenia and (B) soft tissue swelling

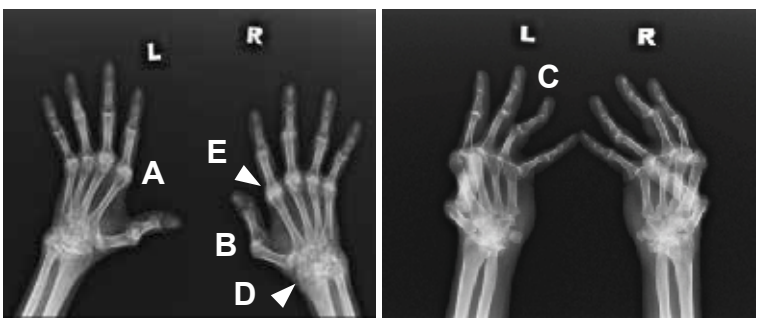


Figure 2. **AP and supinator oblique views of hands in advanced RA:** (A) ulnar deviation of fingers at MCP joints, (B) hitchhiker's thumb deformity, (C) boutonniere deformity, (D) subchondral cyst, (E) sclerosis and joint space narrowing at MCP joints. Similar abnormalities seen in PIP, radiocarpal and intercarpal joints.

3.2.2 Musculoskeletal Ultrasound

Musculoskeletal ultrasound is a useful bedside tool that is increasingly being used by rheumatologists to aid early diagnosis and management of RA. Ultrasound is more accurate than clinical assessment in early RA patients especially those with negative ACPA:

- Clinical synovitis (tender or swollen joint) vs subclinical synovitis (ultrasound detected):[5, level II-2]
  - Gray Scale (GS) ≥1: sensitivity 58.8% vs 78.0%, specificity 79.4% vs 79.4%
  - GS ≥1/Power Doppler (PD) ≥1: sensitivity 58.5% vs 56.2%, specificity 79.4% vs 93.7%

- In patients with negative ACPA, combining ultrasound detected synovitis joint counts with 2010 ACR/EULAR classification criteria increased diagnostic sensitivity from 55.2% to 72.4% and specificity from 78.5% to 87.7%.[6, level II-2]

Presence of ultrasound detected synovitis increases the prevalence of clinical synovitis. This may classify patients with musculoskeletal symptoms more accurately.[5-7, level II-2]

- Ultrasound of the joints is useful in detecting subclinical synovitis for suspected inflammatory arthritis including RA.

3.2.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is another imaging modality to detect synovitis in hands and wrists in early RA which may not be clinically evident:

- In a systematic review, MRI hand and wrist had good accuracy in the diagnosis of RA in patients with <6 months disease duration (AUC=0.81).[8, level I]
- MRI synovitis in PIP joint is a strong predictor of early RA without typical symptoms (OR=3.1, 95% CI 1.2 to 8.1).[9, level II-2]

MRI can detect synovitis, bone erosions and bone marrow oedema better than conventional radiography but its use is limited due to cost and availability.

4. CLASSIFICATION CRITERIA

RA should be suspected in patients who present with inflammatory polyarthritis. Initial evaluation of such patients requires a careful history, physical examination and selected laboratory tests to identify features that are characteristic of RA. Patients are classified as having RA based on the criteria established by American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 (refer to **Table 2**). This classification criteria supersedes the older ACR 1987 revised criteria.

Table 2. 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 2 - 10 large joints 1 - 3 small joints (with or without involvement of large joints) 4 - 10 small joints (with or without involvement of large joints) >10 joints (at least 1 small joint)	 0 1 2 3 5
B. Serology (at least 1 test result is needed for classification) Negative RF and negative ACPA Low-positive RF or low-positive ACPA High-positive RF or high-positive ACPA	 0 2 3
C. Acute-phase reactants (at least 1 test result is needed for classification) Normal CRP and normal ESR Abnormal CRP or abnormal ESR	 0 1
D. Duration of symptoms <6 weeks ≥6 weeks	 0 1

Source: Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81.

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 MCPs, PIPs, second through fifth MTPs, thumb IPs and wrists.
   **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 on the duration of signs or symptoms of synovitis.

5. PROGNOSTIC FACTORS

RA outcome is influenced by many factors and awareness of these factors can guide the healthcare providers on early referral for initiation of treatment.

Poor prognostic factors in RA are:

- older age (OR=1.45, 95% CI 1.08 to 1.94)[10, level II-2]
- female (OR=3.36, 95% CI 1.20 to 9.40)[11, level II-2]
- obesity (OR=5.2, 95% CI 1.8 to 15.2)[12, level I]
- smoking (OR=2.17, 95% CI 1.06 to 4.45)[13, level I]
- presence of ACPA/anti-CCP (OR ranging from 1.01 to 4.22)[11, level II-2; 14, level I; 15-16, level II-2; 17, level III]
- presence of RF (OR ranging from 2.483 to 3.64)[10-11, level II-2; 18, level III]
- high CRP (OR ranging from 1.04 to 1.52)[13, level I; 19, level II-2]
- high ESR (OR ranging from 1.72 to 3.20)1[1, level II-2; 13, level I; 15, level II-2]
- anaemia[20, level II-2]
- high erosion score at baseline (OR ranging from 2.29 to 18.060) [13, level I; 16, level II-2; 19, level II-2]

6. REFERRAL

All RA patients should be primarily managed by rheumatologists. This is due to the complexity of making a definite diagnosis and ensuring adequate treatment of the disease.

Indications for referral are as listed below:[21-22]

a. 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 (refer to **Figure 3**)
   - early morning stiffness of more than 30 minutes

2. Clinical evidence of persistent synovitis of undetermined cause

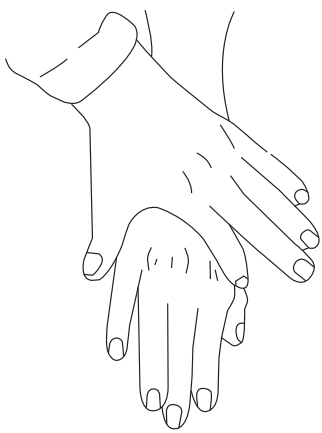


Figure 3. Positive Squeeze Test

b. 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)

c. 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

- Referral of RA cases to rheumatology clinic should provide the following information:
  - Symptoms and signs: duration, joint distribution, severity and impact on activity of daily living
  - Extra-articular involvement
  - Co-morbidities that may require further medical assessment
  - Current medications
  - Relevant investigation results

Recommendation 3

- All patients suspected of having rheumatoid arthritis (RA) should be referred to the rheumatologist.
- All RA patients should be primarily managed by rheumatologists.
  - Co-management plan with primary healthcare providers may be offered subsequently.

7. TREATMENT

Optimal care of patients with RA consists of an integrated approach that includes both non-pharmacological and pharmacological treatments (refer to **Algorithm 2**). Pharmacological treatment should be initiated as soon as RA diagnosis is made to preserve joint function and QoL.

Successful treatment in RA is determined using outcome measures. Although they were originally used in the field of research, the development of effective RA treatment had promoted their use in clinical practice. There are many validated outcome measures reflecting various RA manifestations such as the underlying disease process, level of discomfort and disability, and organ damage (refer to **Appendix 3**). The use of these outcome measures allows standardised objective assessments of RA disease activity, which in turn drives treatment decisions.

- Treatment goals in RA include:
  - pain relief and control of inflammation
  - preservation of joint function and QoL
  - minimising systemic complications and managing co-morbidities
- Treat-to-target (T2T) treatment strategy, formulated in 2010, has resulted in better disease outcomes. It includes:[23]
  - a defined treatment target (clinical remission or at least low disease activity)
  - shared decision making
  - assessment of disease activity
  - regular adjustment of treatment

Recommendation 4
- Aim to achieve a state of clinical remission or at least low disease activity within six months using a treat-to-target treatment strategy* in rheumatoid arthritis.

*Refer to preceding yellow box

7.1 Non-Pharmacological Treatment

7.1.1 Patient Education

Patient education is an important non-pharmacological component in the management of RA. It should include information on the diagnosis, nature of the disease including its complications, benefits and risks of therapeutic options. This may improve patient's understanding and compliance to treatment (refer to **Appendix 4** on **Patient Education Leaflet**).

7.1.2 Occupational Therapy

Patients with RA may benefit from occupational therapy. Joint protection with hand strengthening and mobilisation exercise is adapted to the disease stage, patient and environment.

Joint protection advice with hand strengthening and mobilisation exercises improve Arthritis Impact Measurement Scale (AIMS) of the upper limb function compared with joint protection and hand mobilisation exercises, and joint protection advice alone, in RA at six months (p=0.012).[24, level I]

Most of the advice on joint protection deals with manual activities. They are effective in reducing morning stiffness, pain and functional capacity. These include:

- movement training to facilitate daily activities
- self-exercise programme for hands
- provision of information on assistive devices and handling of orthoses

Refer to **Appendix 5** on **Joint Protection Principles**.

Figure 4 illustrates the various steps for hand strengthening exercise.

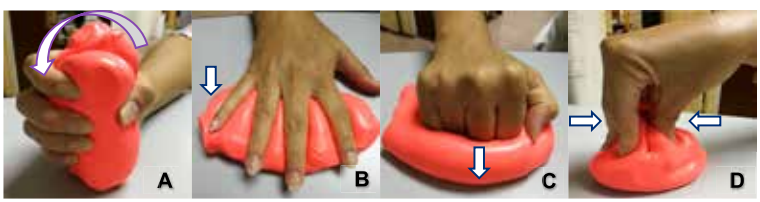


Figure 4. Hand strengthening exercise.

Arrows illustrate the directions of the hand movement. (**A**) The hand is squeezing the putty. (**B**) The putty is moved between the wrist proper and the fingertips. (**C**) The wrist proper is placed in the putty, and then the MCP joints are stretched in the putty. (**D**) The thumb and fingers are shaping the putty. The fingertips are bent during the motion.

7.1.3 Physiotherapy

Physiotherapy may offer beneficial modalities to help RA patients in reducing pain. These include Transcutaneous Electrical Nerve Stimulation (TENS) therapy and aerobic activities.

TENS therapy reduces pain at rest compared with placebo in RA (WMD in VAS 100 mm= -59.50, 95% CI -76.58 to -42.42).[25, level I]

When RA is active, aerobic activities with low impact on the joints or with load alleviation is preferred. Aerobic activity, dynamic muscular

reinforcement and patient education are valuable in the non-pharmacological management of RA.[26]

7.1.4 Podiatry

Every patient with RA should be advised on proper footwear. Customised orthotic insoles are recommended for patients with foot pain from weight-bearing and deformities as they may reduce pain on walking and improve functional capacity. Custom manufactured rigid foot orthoses under podiatry supervision has been shown to be more effective compared with foot orthoses prescribed under normal medical care.[27, level I]

7.1.5 Dietetics

At present, there is no strong evidence that dietary interventions help in reducing disease activity in RA.

Recommendation 5

- Patient education should be included in the management of rheumatoid arthritis (RA).
- Joint protection advice with hand strengthening and mobilisation exercises should be offered in RA.

7.2 Pharmacological Treatment

Pharmacological treatment should be initiated as soon as RA diagnosis is made. It consists of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs. NSAIDs are generally used for symptomatic treatment on a short-term and/or 'as needed basis', to reduce pain, joint stiffness and inflammation, as well as to improve diminished joint function. On the other hand, DMARDs are a group of drugs targeted to the underlying aetiology of RA, used on a longer term to suppress an overactive immune system that causes joint and systemic inflammation. Hence, DMARDs delay disease progression, preserve joint integrity and minimise systemic complications. Corticosteroids serve as a bridging therapy while awaiting the initiation and/or effect of DMARDs. It can also be used as short-term therapy for acute RA flare. Refer **Appendix 6** on **Pharmacological Treatment of RA**.

7.2.1 Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are used to relieve pain and reduce inflammation in RA. There is no evidence to suggest NSAIDs alter the course of the disease. Although there are a variety of preparations, topical and oral forms are the most widely used. This category of medication encompasses traditional NSAIDs (e.g. ibuprofen, ketoprofen, diclofenac and naproxen) and the cyclooxygenase-2 enzyme (COX-2) inhibitors - selective and specific (e.g. meloxicam, etoricoxib and celecoxib). Important side-effects involve the gastrointestinal, renal and CV systems.

A randomised controlled trial (RCT) showed the use of ketoprofen patch for two weeks was more effective than placebo in relieving local pain [mean percentage change in Visual Analogue Scale (VAS) score (%) ± SD: 31.2±30.3, 95% CI 28.0 to 34.4] and as safe (overall incidence and laboratory AEs) as placebo in RA. The most common AE was contact dermatitis.[28, level I]

In another RCT, naproxen 500 mg twice daily was more effective than placebo:[29, level I]

- reduction in tender and swollen joints (MD= -1.39, 95% CI -4.96 to -1.36 and MD= -3.16, 95% CI -2.60 to -0.19 respectively)
- patient global assessment (PGA) of disease activity (MD= -10.0, 95% CI -13.7 to -6.32)
- investigator global assessment (IGA) (MD= -0.51, 95% CI -0.66 to -0.35)
- health assessment questionnaire disability (HAQ disability) (MD= -0.29, 95% CI -0.38 to -0.20)
- PGA of pain (MD= -10.46, 95% CI -14.25 to -6.66)
- American College of Rheumatology 20 (ACR20) responder criteria (MD=16.68, 95% CI 7.80 to 25.57)

The same RCT showed that etoricoxib was more effective than placebo but comparable to naproxen in improving signs and symptoms of RA.[29, level I]

- Etoricoxib 90 mg daily vs placebo
  - tender and swollen joints (MD= -3.42, 95% CI -4.89 to -1.94)
  - PGA of disease activity (VAS 0 - 100 mm) (MD= -9.93, 95% CI -12.96 to -6.90)
  - IGA (0 - 4 Likert scale) (MD= -0.43, 95% CI -0.55 to -0.30)
  - HAQ 0-3 scale (MD= -0.20, 95% CI -0.28 to -0.13)
  - PGA of pain (VAS 0 - 100 mm) (MD= -9.62, 95% CI -12.73 to -6.51)
  - ACR20 responder criteria (MD= 17.83, 95% CI 10.55 to 25.12)
- Etoricoxib 90 mg daily vs naproxen 500 mg twice daily
  - tender and swollen joints (MD= -0.26, 95% CI -2.05 to 1.54)
  - PGA of disease activity (VAS 0-100 mm) (MD=0.09, 95% CI -3.61 to 3.79)
  - investigator global assessment (0-4 Likert scale) (MD=0.08, 95% CI -0.08 to 0.24)
  - HAQ 0-3 scale (MD=0.08, 95% CI -0.08 to 0.24)
  - PGA of pain (VAS 0-100 mm) (MD=0.84, 95% CI -2.96 to 4.63)
  - ACR20 responder criteria (MD=1.15, 95% CI -7.74 to 10.03)

A Cochrane review involving eight RCTs concluded that celecoxib 200 mg daily was more effective than placebo in RA:[30, level I]

- ACR20 improvement (RR=1.53, 95% CI 1.25 to 1.86)
- alleviation of pain (VAS) (NNT= 4, 95% CI 3 to 6)

- improvement in physical function (HAQ) (3.3% absolute improvement, 95% CI 9.6% better to 3.3% worse)

In assessment of ACR20, alleviation of pain (VAS) and HAQ, celecoxib 200 mg daily was as effective as naproxen 1000 mg daily, diclofenac 150 mg daily and meloxicam 15 mg daily.[30, level I]

Etoricoxib 90 mg daily has better gastrointestinal (GI) tolerability than diclofenac 75 mg twice daily for up to 24 months:[31, level I]

- abdominal pain and gastritis (HR=0.70, 95% CI 0.53 to 0.93)
- changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (HR=0.14, 95% CI 0.04 to 0.48)

However, it has significantly more renovascular AEs (oedema and hypertension). There is no difference in cardiac AEs and renal dysfunction.[31-32, level I]

Celecoxib 200 mg daily is as safe as placebo in the incidence of gastroduodenal ulcers ≥3 mm but safer compared with traditional NSAIDs (NNH=9, 95% CI 8 to 10). There is no conclusive evidence that celecoxib has more CV events than traditional NSAIDs.[30, level I]

A Cochrane systematic review concluded that there are no studies to guide clinicians on the best choice of pharmacotherapy for pain management in RA patients with CV and renal co-morbidities.[33, level I]

- NSAIDs are more effective than placebo in reducing pain and improving function of patients with RA. However, concerns of gastrointestinal, renal and CV adverse effects limit their use in the general population.
- NSAIDs do not have disease modifying property in the treatment of RA.
- Use NSAIDs judiciously (at the lowest effective dose and for the shortest duration possible) in RA patients especially those with co-morbidities.

Recommendation 6

- Non-steroidal anti-inflammatory drugs may be used as an adjunct therapy to reduce pain and inflammation in patients with rheumatoid arthritis treated with Disease Modifying Anti-Rheumatic Drugs.

7.2.2 Corticosteroids

Corticosteroids such as cortisone, hydrocortisone and prednisolone are useful in the treatment of inflammatory diseases. Prednisolone is preferred over other long-acting corticosteroids (betamethasone, dexamethasone) in the treatment of RA since it causes less inhibition of

the hypothalamic-pituitary-adrenal axis. Long-term use of corticosteroids predisposes to several complications, in particular osteoporosis and infection (refer to **Appendix 6**). Hence, patients on corticosteroids should be supplemented with calcium and vitamin D, and have regular surveillance for infection.

In a large, multicentre RCT, inclusion of low-dose prednisolone (10 mg daily) in a methotrexate (MTX)-based treatment strategy for tight control in early RA significantly improved erosion score at two years compared with MTX-placebo. It also improved Disease Activity Score 28 (DAS28) at three and six months. The time to first sustained remission was shorter by five months (p=0.001).[34, level I]
In a Cochrane systematic review of moderate quality primary papers, addition of a low-dose prednisolone (≤10 mg) or step-down corticosteroids regime to DMARDs was effective compared with placebo or active control, in early active RA at one year:[35, level I]

- erosion (SMD= -0.39, 95% CI -0.52 to -0.26)
- joint space narrowing (SMD= -0.27, 95% CI -0.50 to -0.04)

In terms of safety profile, there was no significant difference in adverse effects between MTX-prednisolone and MTX-placebo treatment strategies.[34, level I] However, two cohort studies showed corticosteroid therapy was associated with increased risk of myocardial infarction and cerebrovascular accidents in RA.[36 - 37, level II-2]

- Corticosteroids can be used as an add-on therapy to conventional synthetic or biologic DMARDs.

Recommendation 7

- Short-term* low-dose corticosteroids** may be used in active rheumatoid arthritis.

*short-term refers to <3 months
**if oral prednisolone is used, the dose should be ≤10 mg once daily

7.2.3 Disease Modifying Anti-Rheumatic Drugs

Disease Modifying Anti-Rheumatic Drugs (DMARDs) are used as soon as RA is diagnosed to retard disease progression. Treatment options include:

- conventional synthetic DMARDs (csDMARDs)
- targeted synthetic DMARDs (tsDMARDs)
- biologic DMARDs (bDMARDs)
- biosimilar DMARDs (bsDMARDs)

The treatment options are guided by disease severity, presence of co-morbidities, patient's compliance and physician's experience.

a. Conventional Synthetic DMARDs

The four commonly used csDMARDs are MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ) and leflunomide (LEF). They may be used as monotherapy or in combination to achieve treatment target. In general, csDMARDs may take up to eight weeks to exert their effects hence the need for bridging therapy with corticosteroids.

i. Methotrexate

MTX is the mainstay treatment of RA. In a Cochrane systematic review, patients on MTX monotherapy were more likely to achieve ACR50 at one year compared with placebo. The improvement of parameters included number of tender and swollen joints, and inflammatory markers:[38, level I]

- improvement of ACR50 (RR=3.03, 95% CI 1.53 to 5.98)
- reduction of tender joint count (TJC) (RR= -0.64, 95% CI -0.88 to -0.41) and swollen joint count (SJC) (RR= -0.73, 95% CI -0.97 to -0.49)
- reduction of inflammatory markers at 52 weeks; ESR (RR= -12.60, 95% CI -18.97 to -6.23) and CRP (RR= -1.56, 95% CI -2.11 to -1.01)

In another Cochrane systematic review on different groups of populations receiving MTX:[39, level I]

- MTX-naïve patients - MTX monotherapy was as effective as MTX combination therapy with other non-biologic DMARDs
  - improvement in ACR50 (RR=1.76, 95% CI 0.64 to 4.85)
- MTX-inadequate response patients - combination MTX with non-biologic DMARDs was more effective than MTX monotherapy
  - improvement of ACR50 (RR=4.54, 95% CI 2.51 to 8.20)
  - reduction of TJC (SMD= -0.51, 95% CI -0.69 to -0.33) and SJC (SMD= -0.45, 95% CI -0.63 to -0.27)
  - reduction of CRP (SMD= -12.1, 95% CI -19.84 to -4.36)
- Non-MTX DMARDs inadequate response patients - MTX combination therapy was as effective as MTX monotherapy in improvement of ACR50, but was more effective than MTX monotherapy in reduction of TJC and SJC
  - improvement of ACR50 (RR=1.68, 95% CI 0.94 to 2.99)
  - reduction of TJC (WMD= -4, 95% CI -6.82 to -1.18) and SJC (SMD= -0.66, 95% CI -1.15 to -0.17)

Significant AEs experienced by patients on MTX were infection (commonly upper respiratory tract infections, bronchitis and pneumonia), liver enzyme abnormalities, stomatitis, oral ulcers, alopecia and gastrointestinal (GI) AEs.

Patients on MTX were less likely to discontinue medication compared with placebo (RR=0.73, 95% CI 0.62 to 0.88). The main reason for

discontinuation in the MTX group was due to liver enzyme abnormalities (RR=3.75, 95% CI 1.59 to 8.84).[38, level I]

Combination therapy of MTX with other non-biologic DMARDs had significantly more GI AEs [MTX+SSZ (RR=1.75, 95% CI 1.14 to 2.67); MTX+LEF (RR=1.67, 95% CI 1.17 to 2.40)] and abnormal LFT [MTX+LEF (RR=4.30, 95% CI 2.58 to 7.15)].[39, level I]

- Subcutaneous (SC)/intramuscular (IM) MTX can be used in patients intolerant to MTX.
- Folic acid (minimum 5 mg/week) should be given to prevent MTX-related AEs.
- MTX is contraindicated in pregnancy and breastfeeding. It should be stopped for at least three months in women prior to conception.

Recommendation 8
- Methotrexate should be used as the first-line Disease Modifying Anti-Rheumatic Drug in all patients with rheumatoid arthritis unless contraindicated.

ii. Sulfasalazine

In a Cochrane systematic review, SSZ was more effective compared with placebo for the following outcome measures:[40, level I]
- tender joint (SMD= -0.49, 95% CI -0.75 to -0.36)
- swollen joints (SMD= -0.49, 95% CI -0.79 to -0.12)
- pain (SMD= -0.42, 95% CI -0.72 to -0.12)
- ESR (WMD= -17.6 mm, 95% CI -21.93 to -13.23)

Patients on SSZ were significantly less likely to withdraw from treatment due to lack of efficacy (OR=0.23, 95% CI 0.14 to 0.37). However, adverse reactions requiring withdrawal of therapy were three times more frequent in the treatment group, with gastrointestinal and mucocutaneous symptoms being the most frequent.[40, level I]

iii. Hydroxychloroquine

A Cochrane systematic review showed that HCQ was more effective than placebo in improving clinical outcomes i.e:[41, level I]
- tender joints (SMD= -0.33, CI -0.50 to -0.17)
- swollen joints (SMD= -0.52, CI -0.69 to -0.36)
- pain (SMD= -0.45, CI -0.50 to -0.17)

In terms of safety profile, there were no significant withdrawals in HCQ group compared with placebo due to adverse reaction. None of the studies which conducted ophthalmologic evaluations reported withdrawals due to ocular toxicity.

- All patients on HCQ should have a baseline eye examination and ophthalmological review while they are on treatment.

iv. Leflunomide

In a meta-analysis on RA of moderate quality primary papers, LEF monotherapy was:[42, level I]

- more effective than placebo in
  - ACR50 at one year (RR=1.45, 95% CI 1.07 to 1.96)
  - total reduction in TJC (WMD= -5.02, 95% CI -6.41 to -3.64) and SJC (WMD= -3.21, 95% CI -4.32 to -2.09)
  - ESR (WMD= -9.22, 95% CI -12.37 to -6.07)
- as effective as MTX monotherapy at one year in total reduction of TJC, SJC and ESR except for ACR50 where LEF was more effective (RR=1.45, 95% CI 1.07 to 1.96)
- as effective as SSZ monotherapy at one year in improvement of ACR50 and total reduction of TJC, SJC and ESR; however, it was more effective in ACR50 after two years of treatment (RR=2.10, 95% CI 1.25 to 3.53)

LEF was significantly associated with alopecia, elevation of liver enzymes, diarrhoea and allergic reactions compared with placebo. More patients on LEF monotherapy experienced pruritus, hypertension, diarrhoea and alopecia compared with MTX, while less patients on LEF experienced mouth ulceration and liver enzyme elevation (more than three times upper limit normal). When compared with SSZ, more patients on LEF experienced diarrhoea.[42, level I]

b. Targeted Synthetic DMARDs

i. Tofacitinib

In a meta-analysis, tofacitinib 5 mg BD was more effective in ACR50 compared with placebo and adalimumab at 12 weeks in MTX-resistant RA:[43, level I]

- placebo: RR=2.91, 95% CI 2.03 to 4.16
- adalimumab: RR=1.95, 95% CI 1.00 to 3.80

In an RCT, tofacitinib 5 mg BD monotherapy was more effective in ACR50 than MTX in early (<1 year) compared with established RA at 24 months ($p<0.001$ vs $p<0.05$).[44, level I]

No difference in safety profile was observed between patients on tofacitinib and placebo.[43, level I]

ii. Baricitinib

Two RCTs reported that baricitinib 4 mg was effective in treating RA compared to placebo in patients with:

- insufficient response or intolerance to one or more conventional synthetic DMARDs[45, level I]
- inadequate response to or experience unacceptable side effects associated with one or more tumour necrosis factor inhibitors, other biologic DMARDs or both[46, level I]

No difference in safety profile was observed between patients on baricitinib and placebo.[45 - 46, level I]

c. Biologics

bDMARDs are agents designed to specifically target immune cells involved in the pathogenesis of RA. There are a number of bDMARDs that have been shown to be effective and safe. bDMARDs are considered when the treatment target is not achieved with csDMARDs and in the presence of poor prognostic factors. Early introduction of bDMARDs has been shown to retard the development of clinically relevant radiographic progression.[19, level II-2]

bDMARDs currently available and approved in Malaysia for RA are:

- Anti-Tumour Necrosis Factor (anti-TNF): infliximab (IFX), etanercept (ETN), adalimumab (ADA) and golimumab (GOL)
- Interleukin-6 (IL-6) receptor blocker: tocilizumab (TCZ)
- Anti-B cell agent: RTX

The use of bDMARDs for the treatment of RA has increased the risk of tuberculosis (TB) reactivation especially in patients treated with anti-TNF.[47, level I] Thus, screening for latent tuberculosis infection (LTBI) or active TB infection must be done prior to starting bDMARDs (refer to **Table 1** and **Appendix 8**). Mantoux test is the main screening test but where available, IGRA may be considered as an alternative or complementary screening test.

i. Infliximab

A meta-analysis showed that IFX at doses of 3 mg/kg or 5 mg/kg in combination with MTX had better ACR50 in the following comparisons:[48, level I]

- vs MTX monotherapy or combined DMARDs
  - at 20 weeks (RR=2.45, 95% CI 1.73 to 3.48)
  - at 52 weeks (RR=1.47, 95% CI 1.25 to 1.74)
- vs DMARDs in early RA (RR=1.47, 95% CI 1.02 to 2.14)
- vs DMARDs in established or late RA (RR=2.11, 95% CI 1.48 to 3.01)
- vs DMARDs in patients who were MTX-naïve (RR=1.44, 95% CI 1.18 to 1.76)

- vs DMARDs in patients who failed or had insufficient response to MTX (RR=2.13, 95% CI 1.53 to 2.97)

The combination of IFX+MTX favoured clinical remission (RR=1.92, 95% CI 1.35 to 2.74) and showed lower radiographic progression [MD for total Sharp score (TSS)= -2.57, 95% CI -3.64 to -1.49] (in particular those who had insufficient response to MTX or MTX-naïve) compared with DMARDs.[48, level I]

There was no significant difference in AEs of infection, serious infection, serious adverse event, tumour and death between groups. However, infusion reactions occurred more frequently in IFX+MTX group.[48, level I]

ii. Etanercept

Results from a Cochrane systematic review showed that SC etanercept (ETN) 25 mg twice weekly in combination with DMARD (MTX or SSZ) was more effective than DMARD monotherapy (MTX or SSZ) in reducing disease activity and disability as well as delaying joint radiographic progression:[49, level I]

- ETN+DMARD vs DMARD
  - ACR50 at 12 months (RR=1.52, 95% CI 1.36 to 1.70)
  - remission at 12 months (RR=1.95, 95% CI 1.61 to 2.35)
  - improvement in HAQ score at six months (MD in HAQ score= -0.49, 95% CI -0.77 to -0.21)
  - delay in radiographic progression, regardless of response to treatment, at three years (MD for TSS= -6.09, 95% CI -9.22 to -2.96)
- ETN+DMARD vs ETN
  - ACR50 at 12 months (RR=1.43, 95% CI 1.22 to 1.69)
  - remission at 12 months (RR=2.18, 95% CI 1.57 to 3.03)
  - delay in radiographic progression, regardless of response to treatment, at three years (MD for TSS= -1.75, 95% CI -3.27 to -0.23)

These findings are supported by another meta-analysis which analysed ETN as monotherapy or combination but with a longer follow-up:[50, level I]

- ETN ± combination vs MTX
  - ACR50 at one to three years (RR=1.37, 95% CI 1.22 to 1.53)
- ETN vs MTX
  - delay in radiographic progression at three years (MD in TSS= -4.34, 95% CI -7.56 to -1.12)

In terms of safety profile, there was no statistical difference in infection rate between ETN+DMARD vs DMARD monotherapy.[49, level I]

iii. Adalimumab

A systematic review showed that SC ADA 40 mg every two weeks either as monotherapy or in combination with DMARD (mainly MTX) was more effective than DMARD in the treatment of RA:[51, level I]

- ADA vs placebo at 24 weeks
  - ACR50 of RR=3.19, 95% CI 1.81 to 5.62
- ADA+DMARD vs placebo+DMARD at 24 weeks
  - ACR50 of RR=3.23, 95% CI 2.35 to 4.44
  - HAQ reduction: MD= -0.32, 95% CI -0.40 to -0.24
- ADA+MTX vs MTX at 52 and 104 weeks
  - TSS increased by 0.8 vs 2.7 (p≤0.01)

There was no statistical significant difference in safety except for injection site reactions in ADA-treated group up to 52 weeks (RR=1.32, 95% CI 1.02 to 1.71).[51, level I]

iv. Golimumab

A systematic review showed that SC GOL at 50 mg every four weeks combined with MTX was more effective than MTX monotherapy in active RA up to 24 weeks:[52, level I]

- ACR50: RR=2.57, 95% CI 1.34 to 4.94
- DAS remission: RR=5.12, 95% CI 1.67 to 15.66

A multicentre double-blind RCT showed improvements in disease activity and physical function as well as less radiographic progression in SC GOL 50 mg combined with MTX compared with MTX monotherapy at 24 weeks. Extension of the study showed that the improvements were maintained up to five years in the combination group:[53, level I]

- ACR50: 49.4% vs 36.1%
- HAQ-Disability Index (DI) ≥0.25: 67.4% vs 58.6%
- estimated annual rate of radiographic progression (mean±SD): 0.35±1.22 vs 0.63±1.83

An RCT showed that IV GOL 2 mg/kg in combination with MTX given at 0, 4 and subsequently every 8 weeks was more effective than MTX monotherapy in active RA:[54, level I]

- ACR50: 34.9% vs 13.2% at 24 weeks (p<0.001)
- increase in HAQ score 0.50 vs 0.15 at 14 weeks (p<0.001)

The responses were seen as early as two weeks.

There was no significant difference in the number of AEs and serious adverse events (SAEs) in SC GOL+MTX vs placebo+MTX.[52, level I] Safety findings through five years follow-up were generally consistent with studies of other anti-TNF agents.[53, level I] There were similar AEs between IV GOL+MTX vs placebo+MTX but SAE particularly infection was higher in IV GOL+MTX.[54, level I]

v. Tocilizumab

Results from four meta-analyses and two RCTs showed that intravenous (IV) TCZ as monotherapy or in combination with DMARDs was more effective than MTX and combination DMARDs in improving clinical and functional outcomes in RA:

- TCZ monotherapy 8 mg/kg vs MTX
  - ACR50: 44% vs 34% (p=0.002)[55, level I]
  - DAS28-ESR remission at 24 weeks: RR=3.70, 95% CI 2.47 to 5.55[56, level I]
  - sustained remission (DAS28 <2.6, swollen joint count ≤4, persisting for at least 24 weeks): RR=1.86, 95% CI 1.48 to 2.32[57, level I]
  - radiographic progression at 104 weeks: 1.45 vs 1.53 (p=0.0381)[57, level I]
- TCZ combination vs DMARD
  - ACR50:
    - OR=4.67, 95% CI 2.63 to 8.29[58, level I]
    - RR=3.79, 95% CI 2.39 to 6.00[59, level I]
  - DAS28-ESR remission at 24 weeks: RR=4.77, 95% 3.19 to 7.14[56, level I]
  - sustained remission: RR=2.00, 95% CI 1.59 to 2.51[57, level I]
  - reduction in HAQ score: -0.81 vs -0.64 (p=0.0024)[56, level I]
  - radiographic progression at 104 weeks:
    - 1.18 vs 1.53 (p=0.0207)[57, level I]
    - 0.37 vs 1.96 (p<0.0001)[60, level I]

In patients with inadequate response to anti-TNF, TCZ+MTX was shown to be more effective than MTX monotherapy (28.8% vs 3.8%, p<0.0001).[55, level I; 58, level I]

An RCT showed that SC and IV TCZ were comparable in ACR50, DAS28, HAQ DI and safety.[61, level I]

TCZ in combination with MTX as compared with placebo or DMARD is associated with a slight increased risk of AEs [OR=1.53 (95% CI 1.26 to 1.86)] and infection [OR=1.30 (95% CI 1.07 to 1.58)]. No increased incidence of malignancy, TB reactivation or hepatitis has been observed.[62, level I]

vi. Rituximab

A Cochrane systematic review showed that IV RTX (given two weeks apart) in combination with MTX was more effective in improving clinical, functional and radiographic outcomes compared with MTX monotherapy at 24 weeks:[63, level I]

- RTX (1000 mg at D1 and D15)+MTX vs MTX
  - ACR50: RR=3.25, 95% CI 2.31 to 4.58

  - HAQ-DI minimal clinically important difference (MCID) of -0.22: RR=1.61, 95% CI 1.22 to 2.12
  - no radiographic progression: RR=1.18, 95% CI 1.03 to 1.35
- RTX (500 mg at D1 and D15)+MTX vs MTX
  - ACR50: RR=2.69, 95% CI 1.85 to 3.90
  - HAQ-DI MCID of -0.22: RR=1.58, 95% CI 1.18 to 2.11
  - no radiographic progression: RR=1.33, 95% CI 1.07 to 1.64

A greater proportion of patients receiving RTX (1000 mg x 2 doses) in combination with MTX developed infusion reaction after the first infusion compared with those receiving MTX monotherapy and placebo infusions (RR=1.6, 95% CI 1.3 to 1.9). However, no significant differences were noted in the rates of SAEs.[63, level I]

d. Biosimilars

Biosimilars are products which are highly similar to the reference biologics and have no clinically meaningful differences in efficacy and safety. A recent systematic review demonstrated comparable effectiveness and safety outcomes between the pivotal trials of originators (IFX, ADA and ETN) and their respective biosimilars in DMARDs-experienced RA patients.[64, level I]

i. Biosimilar Infliximab

CT-P13 (Remsima) infusion in combination with MTX is effective, well tolerated and highly comparable with reference IFX.[65, level I] Results from a meta-analysis also showed no significant differences between the efficacy of IFX-biosimilar and other biologics.[66, level I]

ii. Biosimilar Adalimumab

Biosimilar adalimumab is also effective, well tolerated and highly comparable with reference ADA in DMARDs-naïve patients.[67, level I]

- bMARDs and tsDMARDs are effective in both early-onset and established RA.

Recommendation 9

- Biologic Disease Modifying Anti-Rheumatic Drug (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) should be considered when the treatment target is not achieved with conventional synthetic DMARDs. Where available, biosimilar DMARDs (bsDMARDs) may be considered as effective alternatives.
- All patients should be screened for tuberculosis, hepatitis B and C, and human immunodeficiency virus prior to treatment with bDMARDs, bsDMARDs or tsDMARDs.

8. TRADITIONAL AND COMPLEMENTARY MEDICINES

Traditional and complementary medicines (TCM) is often part of the cultural practice in Malaysian society in maintaining health. The intake of nutritional supplements as well as Chinese herbal medicine and Ayurvedic therapies are common practices among patients with RA.

- There is insufficient evidence on safety and efficacy of TCM to support its use in the treatment of RA.

9. RHEUMATOLOGY NURSE-LED CARE

The escalating demand for rheumatology care has extended the role of nurses in addressing unmet management needs of patients with RA. In some countries, rheumatology nurse-led care was established to enhance follow-up care for patients with RA, which includes monitoring of laboratory results, assessment of disease activity, patient education and psychosocial support.

The effectiveness of nurse-led care in rheumatology was reported in three systematic reviews. Short-term (12 - 24 months) rheumatology nurse-led care was as effective as medical-care involving rheumatologists, physicians and general practitioners in the management of RA (DAS28, HAQ, pain and fatigue scores).[68, level I] There was no significant difference in RA disease activity at one to two years follow-up between nurse-led care and care by rheumatologists and junior hospital doctors.[69 - 70, level I]

Nurse-led care was safe in the management of patients with RA when compared with medical care involving rheumatologists, physicians and general practitioners. The outcome measures were out of range blood test, monitoring adherence, healthcare contacts, hospitalisations and death.[68, level I]

Recommendation 10

- Rheumatology nurse-led care should be considered in the management of rheumatoid arthritis.

10. SPECIAL CONSIDERATIONS

10.1 Co-morbidity

10.1.1 Infection

All DMARDs should be discontinued in the presence of serious infection but can be recommenced once the infection has resolved.[71]

10.1.2 Elective Surgery

csDMARDs may be continued throughout the perioperative period in patients undergoing elective joint replacement surgery. tsDMARDs and bDMARDs should be withheld close to one dosing cycle prior to elective surgery and restarted after evidence of wound healing, typically 14 days, in the absence of infection (refer to **Table 3**).[72]

Table 3. Guideline for the Perioperative Management of bDMARDs and tsDMARDs in Patients with Rheumatic Diseases Undergoing Elective Surgery

Drugs	Schedule surgery (relative to last dose administered)
Adalimumab	Week 2 or 3
Etanercept	Week 2
SC Golimumab IV Golimumab	Week 5 Week 9
Infliximab	Week 5, 7 or 9 (depending on dosing interval of every 4, 6 or 8 weekly)
Rituximab	Month 7
SC Tocilizumab IV Tocilizumab	Week 2 Week 5
Tofacitinib	7 days after last dose
Baricitinib	1 day after last dose (withhold on day of surgery)

Adapted: Goodman SM, Springer B, Guyatt G, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. J Arthroplasty. 2017;32(9):2628-38

10.2 Pregnancy and Lactation

RA often affects women in their reproductive years. The disease activity may improve, stabilise or become active during pregnancy.[73, level II-3] Although there are medications to control disease activity, several are

contraindicated in pregnancy and lactation due to limited available safety data. Refer to **Appendix 6**.

Pre-conception counselling includes disease course and medication safety during pregnancy and lactation. These must be addressed in women with RA and men who wish to father a child to ensure favourable pregnancy outcomes.

10.3 Vaccination

Vaccinations are important in the management of RA since the patients are at higher risk of infections compared with general population. This is due to the underlying autoimmune disease and immunosuppressive therapies (e.g. corticosteroids and DMARDs). The 2015 ACR recommendations regarding the use of vaccines in patients with RA are outlined in **Table 4**.

Table 4. 2015 ACR recommendations regarding the use of vaccines in RA on DMARDs or biologic agents.

RA treatment	Killed vaccines			Recombinant	Live attenuated
	Pneumococcal	Influenza (IM)	Hepatitis B	Human papillomavirus	Herpes zoster
Before initiating therapy					
DMARDS monotherapy	✔	✔	✔	✔	✔
Combination DMARDS	✔	✔	✔	✔	✔
Anti-TNF biologics	✔	✔	✔	✔	✔
Non-TNF biologics	✔	✔	✔	✔	✔
While already taking therapy					
DMARDS monotherapy	✔	✔	✔	✔	✔
Combination DMARDS	✔	✔	✔	✔	✔
Anti-TNF biologics	✔	✔	✔	✔	Not recommended
Non-TNF biologics	✔	✔	✔	✔	Not recommended

Source: Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26.

- Killed and conjugate vaccines are safe and may be considered in RA patients.

11. MONITORING AND FOLLOW-UP

Many drugs used in the treatment of RA have potential side-effects and may aggravate co-morbidities associated with the underlying disease. Combination of DMARDs are often needed to control disease activity and this may pose a greater risk for AEs. Hence, an integral part in the management of RA include the healthcare provider's understanding of the safety profiles of each therapy and vigilance in monitoring for potential harms to patients. Nurse- and/or pharmacy-led patient counselling on the importance of routine laboratory tests and recognition of adverse symptoms may enable early detection of drug toxicity and appropriate action to be taken to minimise harm.

An overview of laboratory abnormalities of each drug and a summary of current guidelines for laboratory monitoring as well as recommendation on frequency of monitoring is provided in the **Appendix 7**.

12. IMPLEMENTING THE GUIDELINES

Implementation of this CPG is important as it helps in providing quality healthcare services based on the best and most recent available evidence applied to local scenario. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

12.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

1. availability of CPG to healthcare providers (hardcopies and softcopies)
2. conferences and updates on management of RA including those involving professional bodies (e.g. Malaysian Society of Rheumatology)
3. Key Performance Indicator on Rheumatology Services monitored by MoH (i.e. screening for viral hepatitis on RA patients prior to starting MTX)
4. related registries - Malaysian NIAR (myNIAR) and Malaysian Rheumatology Biologics Registry (MARBLE)
5. public awareness during World Arthritis Day

Limiting factors in the CPG implementation include:

1. limited awareness and knowledge in management of RA among healthcare providers
2. insufficient resources in RA care e.g. expertise, diagnostic tests and medications
3. poor access to rheumatology services
4. misconception on the disease and its management by the public

12.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

1. ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
2. reinforce training of healthcare providers via regular seminars and workshops
3. involve multidisciplinary team at all levels of health care
4. improve the diagnostic and therapeutic facilities
5. train more experts and develop rheumatology nurse-led care in the field of RA
6. strengthen related national registries on RA

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

- Percentage of patients with clinical suspicion of RA tested for CRP±ESR and RF±ACPA* = $\frac{\text{Number of patients with clinical suspicion of RA tested for CRP±ESR and RF±ACPA in a period}}{\text{Number patients with clinical suspicion of RA within the same period}}$ X 100%

*Target of 70%

- Percentage of RA patients prescribed with MTX as first-line DMARD** = $\frac{\text{Number of RA patients prescribed with MTX as first-line DMARD in a period}}{\text{Number of RA patients prescribed with DMARD within the same period}}$ X 100%

**Unless contraindicated; Target of 80%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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APPENDIX 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: Is methotrexate effective and safe in the treatment of RA?

1. ARTHRITIS, RHEUMATOID/
2. rheumatoid arthritis.tw.
3. 1 or 2
4. METHOTREXATE/
5. amethopterin.tw.
6. mexate.tw.
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to (English language and humans and last 15 years)

APPENDIX 2

CLINICAL QUESTIONS

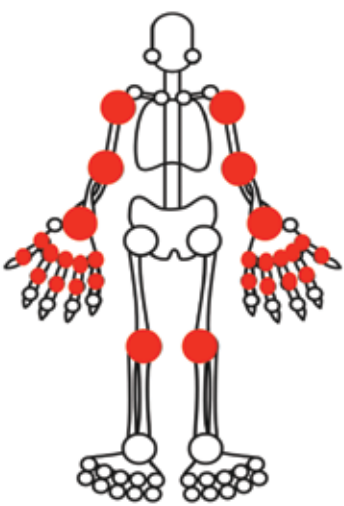
1. Are the following investigations accurate in supporting the diagnosis of RA?
   - musculoskeletal ultrasound
   - MRI
2. What are the poor prognostic factors of RA?
3. What are the effective and safe non-pharmacological treatments of RA?
   - patient education
   - smoking cessation
   - physiotherapy
   - occupational therapy
   - podiatry
   - dietetics
4. Is rheumatology nurse-led care effective and safe in the treatment of RA?
5. What are the effective and safe pharmacological treatments of RA?
   - NSAIDs
   - corticosteroids
   - analgesics (paracetamol, opioids)
   - corticosteroids
   - DMARDs (synthetic, biologic)
6. Is TCM effective and safe in the treatment of RA?
7. What are the indications for referral to secondary/tertiary care?

APPENDIX 3

OUTCOME MEASURES

Measurement of RA disease activity & improvement	
Clinical Disease Activity Index (CDAI)	A composite index based on a summation of four parameters without using acute phase reactant, which are: - TJC - SJC } based on 28 joints assessment* - PGA of disease activity based on VAS 0 - 10 cm - physician global assessment of disease activity based on VAS 0 - 10 cm Definition of RA disease activity (ranges from 0-76): - Remission: ≤2.8 - Low disease activity: >2.8 to ≤10 - Moderate disease activity: >10 to ≤22 - High disease activity: >22
Simplified Disease Activity Index (SDAI)	A composite index based on summation of parameters similar to CDAI but with the addition of CRP in mg/dL Definition of RA disease activity (ranges from 0-86): - Remission: ≤3.3 - Low disease activity: >3.3 to ≤11 - Moderate disease activity: >11 to ≤26 - High disease activity: >26
Disease Activity Score (DAS28)	A composite calculation of four parameters which includes TJC and SJC (based on 28 joints assessment*), ESR (or CRP) and PGA (VAS 0-100mm). 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
American College of Rheumatology 50 (ACR50)	A composite measure defined as improvement of 50% in number of tender (68 joints) and swollen joints (66 joints; hip joints excluded) AND in three of the following five criteria: - PGA - physician global assessment - functional ability measurement - visual analogue pain scale - ESR and CRP

Measurement of functional status and quality of life	
Health Assessment Questionnaire (HAQ)	A self-administered questionnaire to assess functional status in adults with arthritis. It evaluates patient difficulty with activities of daily living over the past week; it covers eight categories including dressing and grooming, arising, eating, walking, hygiene, reaching, gripping and, errands and chores, as well as the use of specific aids or devices and the need for assistance from another person
Short Form 36 Health Survey (SF36)	A 36-item, patient-reported survey of patient health, used to measure health status and QoL
Measure of radiological changes	
Total Sharp Score (TSS)	A scoring system used to quantify the radiological changes in patients with RA; the system describes 16 areas of erosions (evaluated from 0 to 5 points) and 15 areas of narrowing of the joint space (evaluated from 0 to 4 points) of 27 small joints of the hand, including the carpal bones



*28 joints assessed are PIP joints (10 joints), MCP joints (10), wrists (2), elbows (2), shoulders (2) and knees (2)

Source:

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APPENDIX 4

PATIENT EDUCATION LEAFLET

A. Disease Information

I. How does RA affect the joints?

- RA causes inflammation in the joints. This leads to pain and stiffness in the morning, lasting more than 30 minutes. Other symptoms include redness, warmth and swelling at the joint.
- RA affects joints by causing inflammation at the synovium (refer **Figure 5**). If untreated, the inflammation may damage cartilage and bone.
- The commonly affected joints are the small joints of the hands and feet but other joints like shoulders, elbows, knees and ankles may also be affected.
- In some people, RA may also affect other parts of the body including the eyes, lungs and blood vessels. Other associated symptoms include fatigue and mild fever.

II. Causes

- RA is caused by a problem in the immune system, unlike osteoarthritis which is usually caused by 'wear and tear'.
- The exact cause of RA is still unclear but certain factors are thought to increase the risk of developing it:
  - environment - e.g. infection
  - genes - the chance of developing RA is partly genetic
  - hormones - women are more likely to have RA
  - lifestyle - smoking cigarettes can double the risk of developing RA

III. Diagnosis

- There is no single test to diagnose RA. The diagnosis is made based on symptoms, physical examination, x-rays and/or ultrasound and blood tests.

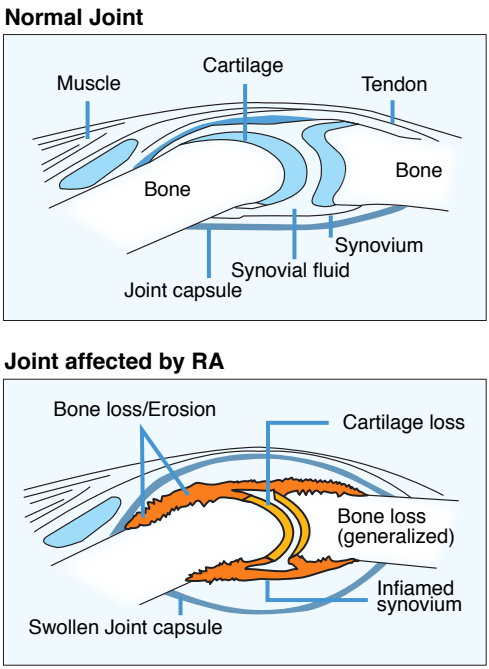

Figure 5. Normal joint and joint affected by RA

B. Medication

There is no cure for RA but treatment is available to control joint pain, minimise joint damage and ultimately, improve physical function and QoL. Types of medications commonly prescribed:

- NSAIDs to relieve joint pain and swelling
- DMARDs to treat joint inflammation and slow the disease process; used long-term
- corticosteroids to treat joint inflammation; used short-term
- biologics and targeted DMARDs when DMARDs are not effective or not tolerated

Treatment is individualised and not all medications work for everyone. Hence, it is important to discuss treatment options and inform your doctor if there are any issues with the prescribed medications. Your doctor will monitor for any possible side effects from medications and adjust treatment as needed. It is important to adhere to your clinic appointments and treatment for optimal management of your RA.

C. Lifestyle Modification

Lifestyle modification is also important to improve RA symptoms and QoL. By staying active, eating well and limiting stress, overall health can be optimised.

I. Physical activity

- It is best to rest the joint when it is acutely inflamed (painful and swollen).
- Regular, gentle exercises can be done once inflammation has resolved. This will improve joint flexibility and general well-being. They include:
  - low impact aerobic exercises e.g. line dancing, water-aerobic
  - strengthening exercises e.g. walking, swimming, stationary cycling
  - stretching and range-of-motion exercises e.g. tai chi, yoga

II. Daily tasks

You may need to make some adaptations to your daily tasks to make it safer and easier to be performed. Some examples include:

- At home
  - change door knobs to lever type
  - replace squatting toilets with sitting toilets
  - place regularly used items on reachable shelves
  - replace heavy appliances with lighter ones
- At work
  - arrange the workspace to make it easier to complete tasks with the least amount of physical strain
  - take breaks from repetitive motion tasks

III. Healthy eating

There is no specific diet that improves or worsens RA. A healthy and well-balanced diet is important to maintain a healthy weight and prevent other diseases e.g. diabetes mellitus and heart disease. In general, a healthy dietary habit includes the following:

- consume more fresh fruits and vegetables
- reduce sugar and salt
- avoid processed food and high saturated fat diet
- if you drink alcohol, do so in moderation; some people on certain RA medications may need to avoid alcohol completely

IV. Emotional health

Living with RA can be a challenge. It is normal to feel angry or frustrated because tasks that used to be done routinely may now be difficult. Emotional stress may make it harder to deal with pain. Some steps that you can take to understand and control your emotional health include:

- avoid things that cause you stress e.g. make changes to your daily routine to reduce physical strain

- make time for things that you enjoy e.g. listening to music
- find positive ways to cope with stress e.g. joining a support group
- learn relaxation techniques e.g. deep breathing technique

V. <u>Smoking</u>

Smoking is one of the poor prognostic factors for RA. Cessation of smoking is advisable in view of its association with high CV risk.

Talk to a health care worker if you are experiencing symptoms of depression, having relationship problems or facing sleep difficulties.

APPENDIX 5

PRINCIPLES OF JOINT PROTECTION

The purpose of joint protection is to allow patients to participate in daily activities with the least amount of damage to the affected joints. These principles can help to reduce pain, inflammation and injury caused by excessive stress on the joint.

The Principles of Joint Protection:

1. **Respect pain**
   There are many activity-related factors influencing the onset and intensity of joint pain.

   Time - the length of time one spends on an activity can influence pain; e.g. pain resulting from five minutes of an activity may be manageable, but an hour of the same task may result in pain that lasts for a few days.

   Weight - weight can influence pain in several ways; e.g. carrying a lighter bag of groceries a few times may not cause any difficulties but a heavier bag can cause or worsen pain in the affected joint.

   Repetition - repetition of an activity can cause or worsen pain; e.g. stapling a few sheets of paper may not cause any pain, but repeating this activity 50 times may cause significant pain that lingers for hours or days.

2. **Distribute the load over stronger joints and/or larger surface areas**
   Small hand joints are vulnerable to pain and inflammation when overused, causing overstretching of ligaments leading to instability (a). When possible, spread the load over several joints or to a larger joint (b).

(a)   (b)

3. **Avoid maintaining the same joint position for prolonged periods**
   Joints kept in one position for prolonged periods of time are inclined to get stiff. Immobilisation of a joint for days or weeks can lead to muscle atrophy and joint contractures. Shifting weight, stretching or changing positions frequently can alleviate the pain and stiffness.

4. **Use good posture and body mechanics**
   Each joint should be used in its most anatomically stable and functional plane. Good body mechanics and posture are important to minimise musculoskeletal strain, thereby preventing or reducing pain. While it takes more energy initially, once it becomes a habit, less energy is needed to maintain a good posture.

5. **Use the minimum amount of force necessary to complete the job**
   Squeezing and pinching activities should be avoided, as they tend to aggravate soft tissue injury and hand deformities. Holding an object with less effort, taking rest breaks and using special aids can reduce stress on the joint.

(a) (b)

(c)   (d)

(e)   (f)

Photos (a), (c) and (e) indicate the improper ways of performing an activity.
Photos (b), (d) and (f) show the recommended ways.

6. **Simplify work by using efficiency principles: plan, organise, balance work with rest**
   Planning, organising and balancing work with rest are useful principles to be employed in reducing stress on joints.

7. **Maintain strength and range of motion**
   Remain active to maintain/increase strength and range of motion. Exercise plays an important role in control of body weight, CV fitness and prevention of coronary heart disease. When individualised for people with arthritis, exercise is expected to improve rather than worsen joint pain and function.

Source: Arthritis Foundation. Pain Management: Joint Protection. (Available at: https://www.arthritis.org/living-with-arthritis/pain-management/joint-protection)

Appendix 6

PHARMACOLOGICAL TREATMENT OF RHEUMATOID ARTHRITIS

Drug	Administration	Recommended Dosage	Possible Adverse Events	Pregnancy and Lactation
Non-steroidal anti-inflammatory drugs				
Ibuprofen	Oral	400 - 800 mg TDS (maximum: 3200 mg daily)	• GI intolerance • Rash • Peripheral oedema • Changes in ALT/AST • Elevated blood pressure	**Pregnancy** • Traditional NSAIDs can be used if needed to control symptoms but use is restricted to first and second trimester • Selective cyclooxygenase-2 (COX-2) inhibitors should be avoided in pregnancy **Lactation** NSAIDs are compatible with lactation Celecoxib is compatible with lactation, other COX-2 inhibitors should be avoided
Diclofenac	Oral	50 mg TDS		
Naproxen	Oral	250 - 500 mg BD (equivalent to 275 - 550 mg naproxen sodium)		
Meloxicam	Oral	7.5 - 15 mg OD		
Etoricoxib	Oral	60 - 90 mg OD		
Celecoxib	Oral	200 mg OD or BD		
Ketoprofen	Patch	Apply for 12 hours	• Contact dermatitis at application site	
Corticosteroids				
Corticosteroids	Oral IM IA	Low dose as suggested in **Recommendation 7** **Example: Triamcinolone 40 - 80 mg or equivalent** **Dose depends on the site of injection**	• Body fluid retention • Elevated blood pressure • Acne • Decreased body growth • Hyperglycaemia • Osteoporosis • Muscle weakness • Headache • Injection site infection	**Pregnancy** • Can be continued at lowest effective dose **Lactation** • Compatible with breastfeeding* *breastfeeding after 4 hours from the last dose if taking prednisolone more than 20 mg daily

Drug	Administration	Recommended Dosage	Possible Adverse Events	Pregnancy and Lactation
Disease Modifying Anti-Rheumatic Drugs (DMARDs)				
		Conventional Synthetic DMARDs		
Methotrexate	Oral SC Intramuscular (IM)	7.5 - 20 mg weekly Dose adjustment for renal impairment: CrCl (ml/min /1.7 m²) / % Standard dose ≥60 / Full dose 30-59 / 50 <30 / Contraindicated	• GI intolerance • Alopecia • Mucositis • Photosensitivity, rash • Abnormal FBC • Elevated ALT/AST • Interstitial pneumonia (acute/chronic)	**Pregnancy** • Contraindicated in pregnancy • Stop at least three months in women prior to conception **Lactation** • Avoid in lactation
Sulfasalazine	Oral	500 - 1000 mg BD	• Pruritus • Rash • GI intolerance • Abnormal FBC • Elevated ALT/AST • Oligospermia	**Pregnancy** • Compatible in pregnancy with folate supplementation **Lactation** • Breastfeeding is safe in a healthy, full-term infant • Caution in premature infant, hyperbilirubinemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency
Hydroxychloroquine	Oral	200 - 400 mg OD (not exceeding 6.5 mg/kg ideal body weight) *BSR 2017	• Retinal disorder	• Compatible in pregnancy and lactation
Leflunomide	Oral	10 - 20 mg OD	• Alopecia • Abnormal FBC • Elevated ALT/AST • Elevated blood pressure	• Avoid in pregnancy and lactation • A washout procedure should be completed pre-conception

Drug	Administration	Recommended Dosage	Possible Adverse Events	Pregnancy and Lactation
Targeted Synthetic DMARDs				
Tofacitinib	Oral	5 mg BD 5 mg OD (CrCl 30 - 60 mL/min)	• Increased low-density lipoprotein and high-density lipoprotein level • Herpes Zoster infection • Elevated ALT/AST • Gut perforation (especially in diverticulitis)	**Pregnancy** • Avoid in pregnancy • Should be stopped 2 months before conception **Lactation** • Insufficient data to support safety
Baricitinib	Oral	4 mg OD 2 mg OD (CrCl 30 - 60 mL/min)	• Elevated ALT/AST • GI intolerance • Herpes Zoster infection • Abnormal FBC • Increased low-density lipoprotein, high-density lipoprotein and triglyceride levels	• Insufficient data to support safety in pregnancy and lactation
Biologic DMARDs				
Infliximab	IV	3 mg/kg every 8 weeks May increase to 5 mg/kg	• Rash • GI intolerance • Infusion related reaction • Infections (including TB)	**Pregnancy** • Can be continued up to gestational week 20; if indicated can be used throughout pregnancy **Lactation** • Compatible with lactation
Etanercept	SC	50 mg every week	• Injection site reaction • Infections (including TB)	**Pregnancy** • Can be continued up to gestational week 30-32; if indicated can be used throughout pregnancy **Lactation** • Compatible with lactation

Drug	Administration	Recommended Dosage	Possible Adverse Events	Pregnancy and Lactation
Biologic DMARDs				
Adalimumab	SC	40 mg every 2 weeks	• Injection site reaction • Rash • GI intolerance • Infections (including TB)	**Pregnancy** • Can be continued up to gestational week 20; if indicated can be used throughout pregnancy **Lactation** • Compatible with lactation
Golimumab	SC	50 mg every month	• Injection site reaction • Rash • Infections (including TB) • Elevated ALT/AST	**Pregnancy** • Limited evidence; consider alternative treatments **Lactation** • Compatible with lactation
	IV	2 mg/kg every 8 weeks		
Tocilizumab	SC	162 mg every week	• Injection site reaction • Rash • GI intolerance • Elevated ALT/AST • Abnormal FBC • Infections (including TB) • Gut perforation (especially in diverticulitis) • Increased low-density lipoprotein level	• Contraindicated in pregnancy and lactation
	IV	4 - 8 mg/kg every 4 weeks		

Drug	Administration	Recommended Dosage	Possible Adverse Events	Pregnancy and Lactation
Rituximab	IV	1000 mg on day 1 and day 15 May be repeated every 6 months	• Peripheral oedema • Pruritus • Rash • GI intolerance • Abnormal FBC • Infections • Infusion related reaction • Low IgG/IgA/IgM	**Pregnancy** • Can be used in exceptional cases in early gestation; if used at later stages of pregnancy, clinician should be aware of risk of B cell depletion and other cytopaenias in the neonate **Lactation** • Avoid in lactation

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

Adapted:

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APPENDIX 7

DRUG MONITORING

csDMARDs					
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	

tsDMARDs					
Drug	**Baseline investigations**	**Subsequent investigations**	**Frequency of monitoring**	**Additional monitoring**	**Action**
Tofacitinib	• FBC • LFT • Serum creatinine • Fasting glucose • Fasting lipid • Serology for HIV, HBsAg, HBcAb and hepatitis C virus • Urine pregnancy test (if indicated) • TB screening (refer to **Appendix 8**)	• FBC • Serum creatinine • ALT and/or AST • ESR/CRP • Fasting lipid • Albumin	• At week 4 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 10^9/L iv. MCV >105 fL v. Platelet <140 x 10^9/L vi. Creatinine increase >30% vii. AST/ALT > 3x ULN
Baricitinib	As above	As above	• 4 - 8 weeks after initiation then 3-monthly		

Biologics					
Drug	**Baseline investigations**	**Subsequent investigations**	**Frequency of monitoring**	**Additional monitoring**	**Action**
Adalimumab Etanercept Infliximab/ Biosimilar Golimumab	• FBC • LFT • Serum creatinine • Fasting glucose • Fasting lipid • Serology for HIV, HBsAg, HBcAb and hepatitis C virus • Urine pregnancy test (if indicated) • TB screening (refer to **Appendix 8**)	• FBC • Serum creatinine • ALT and/or AST • ESR/CRP	• At week 4 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 ii. Unexplained eosinophilia >0.5 x 10^9/L iv. MCV >105 fL v. Platelet <140 x 10^9/L vi. Creatinine increase >30% vii. AST/ALT > 3x ULN Caution in initiating RTX in patients with hypogammaglobulinaemia
Tocilizumab	As above	As above	• 8 weeks after initiation then 3-monthly	• Fasting lipid	
Rituximab	As above	As above	• During and up to 12 months after treatment	• IgG level • Hepatitis B virus reactivation	

Source:

1. Xeljanz® (Tofacitinib) [package insert]. New York, NY. Pfizer Inc; 2018.
2. Cosentyx® (Secukinumab) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corp; 2018
3. Simponi® (Golimumab) [package insert]. Hoddesdon, Herts. Merck Sharp & Dohme Ltd; 2018.

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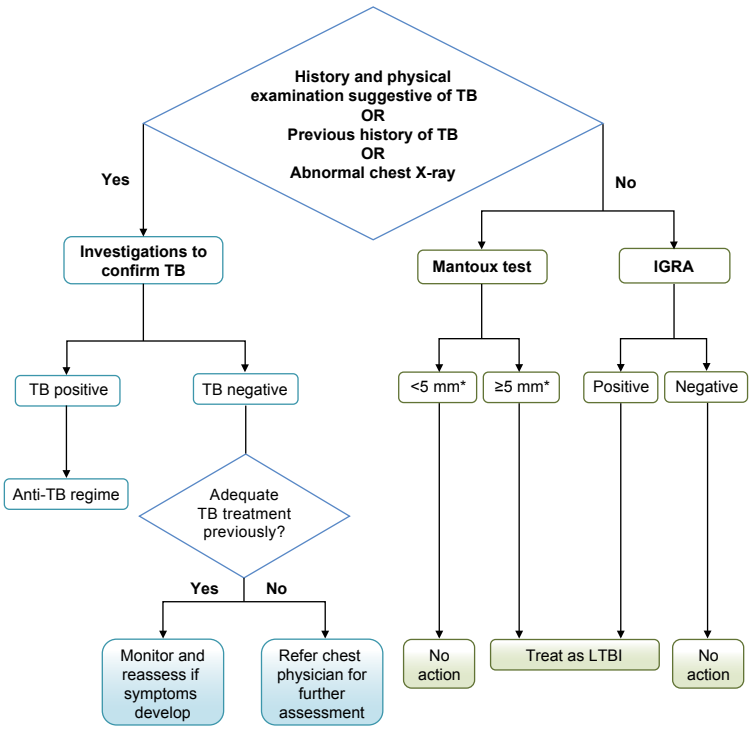
APPENDIX 8

TUBERCULOSIS WORKUP PRIOR TO TARGETED SYNTHETIC DMARDs AND BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS



IGRA: Interferon Gamma Release Assay
LTBI: latent tuberculosis infection
TB: tuberculosis

Adapted: Ministry of Health Malaysia. Management of Tuberculosis (3rd Edition). Putrajaya: MoH; 2012; Centers for Disease Control and Prevention. TB Elimination: Tuberculin Skin Testing. Atlanta: CDC; 2011

LIST OF ABBREVIATIONS

ACPA	anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse events
AGREE	Appraisal of Guidelines for Research and Evaluation
AIIRD	autoimmune inflammatory rheumatic diseases
AIMS	Arthritis Impact Measurement Scale
ALT	alanine aminotransferase
AP	anteroposterior
anti-CCP	anti-cyclic citrullinated peptide
anti-TNF	anti-Tumour Necrosis Factor
AST	aspartate aminotransferase
AUC	area under the curve
BD	twice daily
bDMARDs	biologic Disease Modifying Anti-Rheumatic Drugs
CI	confidence interval
COX-2	cyclooxygenase
CPG	clinical practice guidelines
CRP	C-reactive protein
csDMARDs	conventional synthetic Disease Modifying Anti-Rheumatic Drugs
CV	cardiovascular
D	day
DI	disability index
DAS28	Disease Activity Score 28
DIP	distal interphalangeal
DG	Development Group
DMARDs	Disease Modifying Anti-Rheumatic Drugs
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FBC	full blood count
G6PD	glucose-6-phosphate dehydrogenase
GI	gastrointestinal
GOL	golimumab
GS	Gray Scale
HAQ	health assessment questionnaire
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCQ	hydroxychloroquine
HR	hazard ratio
HIV	human immunodeficiency virus
IFX	infliximab
IG	immunoglobulin
IGA	investigator global assessment
IGRA	Interferon Gamma Release Assay
IL-6	interleukin 6
IM	intramuscular
IV	intravenous
LEF	leflunomide
LFT	liver function test
LTBI	latent tuberculosis infection

MaHTAS	Malaysian Health Technology Assessment Section
MARBLE	Malaysian Rheumatology Biologics Registry
MCP	metacarpophalangeal
MCID	minimal clinically important difference
MD	mean difference
MoH	Ministry of Health
MRI	magnetic resonance imaging
MTP	metatarsophalangeal
MTX	methotrexate
myNIAR	Malaysian National Inflammatory Arthritis Registry
NNT	number needed to treat
NNH	number needed to harm
NSAIDs	non-steroidal anti-inflammatory drugs
NIAR	National Inflammatory Arthritis Registry
NICE	National Institute for Health and Clinical Excellence
OD	daily
OR	odds ratio
PD	Power Doppler
PIP	proximal interphalangeal
PGA	patient global assessment
QoL	quality of life
RA	rheumatoid arthritis
RC	Review Committee
RCT	randomised controlled trial
RF	rheumatoid factor
RP	renal profile
RR	relative risk
RTX	rituximab
SAE	serious adverse events
SC	subcutaneous
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SJC	swollen joint count
SMD	standardised mean difference
SSZ	sulfasalazine
T2T	treat-to-target
TB	tuberculosis
TCM	Traditional and Complementary Medicines
TCZ	tocilizumab
TDS	thrice daily
TENS	Transcutaneous Electrical Nerve Stimulation
TJC	tender joint count
tsDMARDs	targeted synthetic Disease Modifying Anti-Rheumatic Drugs
TSS	total Sharp score
ULN	upper limit normal
URTI	upper respiratory tract infection
VAS	Visual Analogue Scale
vs	versus

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