# Rheumatoid Arthritis
## Clinical Presentation, Diagnosis and Pharmacological Treatment (DMARD's)

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune condition with periods of exacerbation and remission, characterized by synovitis and joint destruction mediated by cytokines, chemokines, and metalloproteases. RA can affect any body part but most commonly the peripheral joints, interphalangeal, metacarpophalangeal and wrist, as well as the ankles and metatarsophalangeal joints, leading to progressive destruction of articular structures and accompanied by systemic symptoms. Triggers and aetiology of RA are unclear but hormones, genetics, stress, smoking and environmental factors are thought to be contributing factors. An autoimmune etiology is currently the most widely accepted.

### Clinical features and presentation of rheumatoid arthritis

Approximately 10% of patients with rheumatoid arthritis have an abrupt onset, but in most cases onset is insidious and initial presenting symptoms can be vague, including fatigue, malaise, morning stiffness, weight loss and low-grade fever. Progression of the illness leads to joint inflammation and swelling which causes difficulty performing activities of daily living, such as dressing, standing, walking, or use of the hands.

Clinical features of RA are persistent symmetric polyarthritis (synovitis) which affects the hands and/or feet, although any joint lined by a synovial membrane may be involved. Severity fluctuates over time, but chronic RA results in the progressive development of various degrees of joint destruction, deformity, and a significant decline in functional status. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can also be significant.

Patients with RA are at an increased risk of co-morbidities such as CVD, severe infections, and over-lapping autoimmune disease, e.g. mixed connective tissue diseases, autoimmune thyroiditis and lymphoma.

### Criteria for diagnosis of rheumatoid arthritis

A diagnosis of RA is based on specific clinical, laboratory and imaging features and the ACR/EULAR Classification Criteria. The ACR 'RA Disease Activity Measures', define the ranges and level of disease activity. All patients with suspected RA should be referred urgently to a rheumatologist.

**Medical history** refers to current presenting symptoms, past medical history, family medical history, medications including any OTC medications, allergies and lifestyle factors such as smoking and alcohol intake. Presenting symptom history includes questions about the type, duration, location and pattern of pain experienced, how it affects mobility and lifestyle, and whether it is affecting sleep and causing fatigue. Past medical history and other medical illnesses will be discussed as some medical problems tend to occur along with RA and may be suggestive of the disease. A family medical history is important due to the hereditary

component to RA, and information about any close relative with the condition or any other autoimmune disease will provide more information on the individual's risk. Smoking is a high risk factor, and alcohol which effects the liver, can promote inflammation and interact with some NSAID and methotrexate medication. Therefore, a knowledge of lifestyle factors is also important in the diagnosis and treatment of RA.

**Physical examination** is a key part of the assessment process. In addition to checking general vital signs, including temperature, blood pressure, pulse rate, heart and lung function, the doctor will evaluate the patient's joints in detail, paying particular attention to function, swelling, and pain. The physical exam will help determine the severity of the illness and help guide treatment decisions.

**Laboratory blood tests** required to determine a diagnosis suggestive of RA or inflammatory disease include:

- Rheumatoid factor (RF)
- Anti-citrullinated protein antibodies (ACPA) (including anti-CCP and anti-MCV antibody tests)
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Antinuclear antibody (ANA)
- Full blood count (FBC)

**Imaging tests** include x-rays taken of symptomatic joints which can reveal signs of joint involvement (inflammation) and damage (bone erosion) indicative of RA. Other imaging tests useful in diagnosis of RA include magnetic resonance imaging (MRI) and ultrasound.

The **ACR/EULAR Classification Criteria**, is associated with a point value. **Diagnosis of RA** can be made when a total of **6 points or more** is reached across the separate criteria.

Target population: Patients who (i) have at least 1 joint with clinical synovitis and (ii) with the synovitis not better explained by another disease.

| | Score |
|---|---|
| **A. Joint involvement (tender/swollen)** | |
| 1 large joint | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (± involvement of large joints) | 2 |
| 4-10 small joints (± involvement of large joints) | 3 |
| > 10 joints (at least 1 small joint) | 5 |
| **B. Serology** | |
| Negative RF & ACPA | 0 |
| Low-positive RF/low-positive ACPA | 2 |
| High-positive RF/high-positive ACPA | 3 |

| | Score |
|---|---|
| **C. Acute-phase reactants** | |
| Normal CRP & ESR | 0 |
| Abnormal CRP & ESR | 1 |
| **D. Duration of symptoms** | |
| < 6 weeks | 0 |
| ≥ 6 weeks | 1 |

Add score of categories A-D:

**≥ 6/10 = definite RA**

## ACR recommendations for the measurement of RA disease activity.

| Instruments | Threshold of Disease Activity Level |
|---|---|
| Disease activity score in 28 joints (DAS 28) (Range 0 – 9.4) | • Remission <2.6<br>• Low activity ≥ 2.6 to < 3.2<br>• Moderate activity ≥ 3.2 to ≤ 5.1<br>• High activity > 5.1 |
| Clinical disease activity index (CDAI) (Range 0- 76.0) | • Remission ≤ 2.8<br>• Low activity > 2.8 to 10<br>• Moderate activity > 10 to 22<br>• High activity > 22 |
| Simplified disease activity index (SDAI) (Range 0 – 86.0) | • Remission ≤ 3.3<br>• Low activity > 3.3 to ≤ 11<br>• Moderate activity > 11 to ≤ 26<br>• High activity > 26 |

**DMARD's and the pharmacological treatment of rheumatoid arthritis**

Current pharmacological management of RA includes the initiation of DMARDs by a rheumatologist and medication for symptom control such as a corticosteroid. The lowest dose possible for the shortest period of time is recommended when using corticosteroids. NSAIDs are typically prescribed to control pain and inflammation in the RA patient. The ACR and EULAR guidelines recommend that if used NSAIDs be prescribed in the lowest dose that provides symptom relief, and the dose reduced when a good response to DMARDs is achieved.

DMARDs, (Disease-modifying anti-rheumatic drugs) are also called immune-suppressive or slow-acting anti-rheumatic drugs (SAARDs). They are classed in two major groups; synthetic (sDMARDs) and biological (bDMARDs). These groups are then further subdivided and classed as conventional synthetic (csDMARDs) or targeted synthetic (tsDMARDs). Conventional synthetic (csDMARDs) include methotrexate, leflunomide and sulfasalazine.

Targeted synthetic DMARDs (tsDMARDs) example Tofacitinib and Baricitinib are a new therapeutic class that inhibit JAK **(**Janus kinase inhibitors)**.** They can be used in combination with methotrexate or as monotherapy if patients have contraindications or are intolerant of methotrexate. Concurrent use of tsDMARDS with bDMARDs is however contraindicated and tsDMARDs cannot be used with live vaccines.

Combination therapy which allows for lower dosage of an individual drug, may reduce the risk of adverse effects that can occur with higher doses. Methotrexate, leflunomide and sulfasalazine have similar efficacy, however methotrexate is considered the 'anchor drug' for the treatment of RA. It is prescribed in up to 70% of patients as a monotherapy or as combination therapy with other DMARDs.

**Methotrexate as the DMARD of choice in the treatment of rheumatoid arthritis**

Methotrexate (MTX), a disease-modifying anti-rheumatic drug (DMARD), interferes with the production and maintenance of DNA, the genetic material in the cells of the body. It is not known exactly how methotrexate works in rheumatoid arthritis, but it can reduce inflammation and slow progression of the illness.

Methotrexate is the most common DMARD used to treat rheumatoid arthritis. It may be used in the early stages to prevent progression of the illness and in combination with other DMARDs. It is effective in relieving joint inflammation and pain, slowing RA progression, and preventing disability by delaying joint destruction.

Methotrexate produces a beneficial effect in 2-6 weeks and is given once weekly. The initial weekly dose is *7.5-15* mg but can be increased up to 25mg per week if required, based on assessment of response and side effects. It can be administered by oral, intramuscular or subcutaneous routes.

Rheumatoid arthritis patients taking methotrexate must be monitored closely for signs of infection and require regular FBC, LFT and renal function blood tests. Intensive monitoring is required when initiating therapy, changing doses and in patients with co-morbidities. FBC, LFTs and U&Es are required every two weeks when initiating therapy until blood tests are stable for 6 weeks. This is followed by monthly blood tests until the dosage and illness is stable for 1 year. Thereafter, blood test monitoring may be reduced in frequency to every 2-3 months based on clinical judgement and discussion with the specialist team. Patients must be closely monitored when taking methotrexate as it is associated with many adverse side effects including infections, gastro-intestinal problems, leukopenia, headache, dizziness; fatigue, raised LFTs, rash and alopecia. Some side effects may be reduced by taking folic acid at a dose of at least 5mg/week, taken on a different day from the methotrexate.

Patient education about their weekly methotrexate regimen, folic acid requirement and the risk of drug interactions is important as a number of medications such as salicylates, hypoglycaemics, sulphonamides, phenytoin, and trimethoprim have the potential to interact with methotrexate. Drug interactions can enhance the action of methotrexate resulting in an increased risk of methotrexate toxicity. Live vaccines should be avoided, however, flu and pneumococcal vaccination is recommended. Screening for TB and infections such as hepatitis B and C should be performed prior to initiating treatment and screening for varicella zoster is also recommended by some experts. It is advisable that if a person with RA develops an infection, requires antibiotic treatment or develops shingles or chicken pox, that they stop taking their anti-rheumatic medication until the infection has cleared. Advice on smoking cessation, contraception when applicable, and the risks associated with alcohol consumption while taking methotrexate should be provided for the patient.

Assessment, monitoring, audit and evaluation for disease activity, progression, and effects of the therapeutic regime on a patient with rheumatoid arthritis is a continuous process. Implementing person-centred care, monitoring and evaluating symptoms, outcomes and responses to therapy plays a pivotal role in managing the illness and improving the patient's quality of life.

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