RHEUMATOID ARTHRITIS

1. **AIMS**

On completion of this chapter you will be able to recognise the clinical presentation of rheumatoid arthritis and effectively manage the medical, surgical and physical treatments.

2. **LEARNING OBJECTIVES**

- Understanding the pathophysiology of rheumatoid arthritis.
- Diagnosing rheumatoid arthritis on clinical, radiological and laboratory grounds.
- To develop a management plan for treating rheumatoid arthritis.

3. **INTRODUCTION**

Rheumatoid arthritis is the commonest form of inflammatory arthritis and affects about 1% of all populations. It is a systemic disease, but the locomotor involvement dominates the clinical picture. The clinical presentation has a wide variation in age at onset, degree of joint involvement and severity. It is difficult to predict early in the course of the disease which patients will develop severe disease. Life expectancy in the more severe forms of the disease is reduced by about 7 years in men and 3 years in women. The disease occurs three times more frequently in women than men.

At present we have no test to predict which patients will develop severe disease.
4. **ETIOLOGY**

There is abundant evidence that rheumatoid arthritis is immune mediated, but it is uncertain if the initiating agent is an infectious antigen, a self antigen, or both. Epidemiological data support the case for both environmental and genetic factors causing rheumatoid arthritis, but the genetic component is at most 30%. The current view is that chronic inflammation is initiated by antigen induced activation of T cells, but whether the perpetuation of the disease depends on T cells is unknown.

Rheumatoid arthritis is characterised by infiltration of the synovium with lymphoid cells, formation of new blood vessels, synovium proliferation and joint destruction.

Both genetic and environmental factors are involved in the etiology of rheumatoid arthritis.

5. **THE JOINT IN RHEUMATOID ARTHRITIS**

Synovial cell proliferation is central to the disease process. The synovial lining of the normal joint is usually just one cell layer thick. It completely lines the inside of the joint, except for the surfaces covered by cartilage. It is these synovial cells that undergo proliferation in rheumatoid arthritis, ultimately forming long strings of cells called villi. This proliferation can be so exuberant that the entire joint is filled with a mass of synovial tissue. The expanding synovial mass is clinically seen as swollen joints and has a soft, doughy consistency on palpation. The capsule and other soft tissues around the joint become stretched with resulting joint instability and ultimately deformity. Normally synovium never comes into contact with the cartilage, but in rheumatoid arthritis this mass of expanding synovium is pushed over the cartilage and adheres to the cartilage surface. Large numbers of cytokines and proteolytic enzymes are released from the inflamed synovium. They cause cartilage and bone loss. The bone loss is seen radiographically as peri-articular osteopaenia in the subchondral bone, and as small marginal erosions around the edges of the joint. These erosions gradually expand and ultimately destroy the joint.
6. **CLINICAL PICTURE**

**AMERICAN RHEUMATISM ASSOCIATION REVISED CRITERIA FOR RHEUMATOID ARTHRITIS CLASSIFICATION**  
*(Can also used for diagnostic purposes in established disease)*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
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<tr>
<td>2. Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas (out of 14 possible areas: right or left PIP, MCP, wrist, elbow, knee, ankle, MTP joints) simultaneously have had soft-tissue swelling or fluid (not bony overgrowth alone) as observed by a physician.</td>
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<td>3. Arthritis of hand joints</td>
<td>At least one area swollen (as defined above) in a wrist, MCP or PIP joint</td>
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<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs or MTPs, without absolute symmetry is acceptable)</td>
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<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician</td>
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<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 6% of normal control subjects</td>
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<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify)</td>
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Note: For classification purposes, a patient has RA if at least 4 of these criteria are satisfied (criteria 1-4 must have been present for at least 6 weeks)
Onset

The best described onset of the disease (60% of cases) is an insidious onset of pain, stiffness, and symmetrical swelling of the small joints. It usually occurs in a middle-aged woman over a period of weeks to a few months.

In up to 20% of patients the onset is acute or subacute.

In 10% vague arthralgias occur for months or even years before the onset of chronic disease.

In some patients fatigue, malaise, loss of weight, low grade fever, myalgia, morning stiffness, and depression, but no objective joint abnormalities, make diagnosis difficult. This prodromal phase may last for weeks or months.

Asymmetrical onset is common but later almost always becomes symmetrical.

Onset:
- 60% insidious
- 20% acute or subacute
- 10% vague pains for years
- 5% fatigue, malaise for weeks

Articular involvement

The single most characteristic feature of rheumatoid arthritis is synovitis of:

- the proximal interphalangeal joints of the hands
- metacarpophalangeal joints of the hands
- metatarsophalangeal joints of the feet

♦ Sparing of the distal interphalangeal joints
♦ The initial involvement may be confined to a few joints only.
♦ Spread occurs within months to years but the total number of affected joints tends to reach a plateau after the first years of illness.
♦ The number of joints involved in the early stages of rheumatoid arthritis is related to disease severity and functional outcome.
♦ The other main sites are the wrists, the ankles, knees, shoulders, hips and the elbows, although virtually any joint may be affected.

The hand

The soft swelling of the proximal interphalangeal and metacarpophalangeal joints is at first subtle with the patient noticing she cannot get her rings on or off. Later the swelling of the joints becomes obvious.

As the disease progresses, signs of irreversible damage appear:

- Stretching of the capsule of the PIP joint as a result of the synovitis can lead to hyperextension of the joint, resulting in the so called swan neck deformity because the finger looks rather like the neck of a swan. Mild swan neck deformities can be seen in persons with benign hypermobility. Severe swan neck deformities can also occur in SLE.

- In others a flexion deformity occurs, called a Boutonniere deformity. This can cause considerable functional problems with a finger permanently flexed.

- As a result of synovitis at the metacarpo-phalangeal joints of the hands, subluxation of these joints leads to a drift of the fingers to the ulnar side leading to the typical deformity of ulnar deviation of the fingers. Although very typical of rheumatoid arthritis it may also be seen in patients with systemic lupus erythematosus (SLE).

N.B. Severe ulnar deviation of the fingers also occurs in SLE.
Destruction of the distal radioulnar joints leads to a dorsal protrusion of the ulna head at the wrist. If you palpate the ulnar head at the wrist, it can be felt to move up and down, as its anchor ligaments have been destroyed. This is called the piano key sign.

Destruction of the carpal bones leads to wrist instability causing severe functional problems. No matter how good the fingers may still be, a strong wrist is needed in many hand actions. Tenosynovitis of extensor, and more often flexor tendons of the hand, are common and very important. It left untreated this synovitis will with time invade and destroy the tendons, leading to tendon rupture. This of course has catastrophic effects on hand function.

Compression of the median nerve in the carpal tunnel (the carpal tunnel syndrome) as a result of synovitis of the wrist may be presenting symptom.

Inability to make a fist or pinch thin objects, as well as loss of grip strength, are important functional consequences of severe hand involvement.

Hand changes:

- swelling of proximal finger joints
- swan neck deformity
- boutonniere deformity
- ulnar deviation of the fingers
- piano key sign at the wrist
- wrist instability
- tenosynovitis/tendon rupture
- carpal tunnel syndrome

**Elbow**

Involvement of the elbow is a major problem in 10 to 20% of patients. Pain and flexion contracture are typical findings. Pro- and supination are painful as a result of synovitis and destruction of the radial head of the elbow.
Shoulder

The shoulder joints are very frequently involved with synovitis and destruction of the glenohumeral and acromioclavicular joints. The sternoclavicular joint is also occasionally involved. Inflammation of the rotator cuff occurs and can lead to complete rupture of the cuff. Subacromial bursitis is very common.

Foot

Involvement of the foot is very common and in 10% of patients the first erosions is seen at the metatarsophalangeal joints. Swelling and tenderness of these joints, and with time deformities in the form of claw toes and hammer toes, occur. With further destruction the toes may over ride each other. Bunion formation is very common as well as bunionette (a bunion at the 5th toe).

Joint destruction is also seen in the ankle between the distal tibia, fibula and talus as well as the subtalar joint.

The supporting ligaments of the feet, and in particular the tibialis posterior and peroneus tendons, develop a tendonitis with stretching and occasionally rupture of the involved tendon.

The result of bony destruction at the ankle together with involvement of the tendons result in collapse of the medial foot bridge, leading to pronation of the foot and ever increasing pain and difficulty with walking.

Knee

Involvement of this joint occurs in 80% or more of all patients. Synovitis is usually easy to identify by tenderness and swelling around the patella. Large effusions are common. The knee joint communicates with bursae in the fossa poplitea. With large knee effusions they become very enlarged, forming a Baker's cyst. This Baker's cyst can leak with synovial fluid seeping down into the calf. This synovial fluid is highly
irritating causing swelling of the calf and pain. It may easily be mistaken for a deep-vein thrombosis.

The natural course of long-standing knee involvement is often valgus instability, flexion contracture, and inability to walk.

**Hip**

Hip joint involvement is not as common as the knee and usually a late manifestation. However, once started the arthritis leads to severe disability, with pain on weight bearing and limitation of motion, in particular of abduction and rotation. Pain from soft tissue inflammation, and in particular from the bursa over the greater trochanter of the femur, can be mistaken for hip arthritis. Local tenderness over the trochanter is typical. Infiltration with local anaesthetic and corticosteroids gives immediate relief.

**Cervical spine**

The cervical spine is involved in up to 70% of patients with severe or long standing rheumatoid arthritis, and in particular patients treated with corticosteroids. The dominating symptom is occipital pain, sometimes made worse by movement although many have little pain. Destruction of the anchoring ligaments of the odontoid process of the 2nd cervical vertebra allows the odontoid process to sublux posteriorly and press on the spinal cord during flexion of the neck.

This in turn can lead to catastrophic neurological complications. Long tract signs of upper motor neuron lesions occur, but can be difficult to demonstrate in patients with destroyed joints. A Babinski reflex from upper motor neurone disease can be almost impossible to find if the big toe joints are destroyed.

A lateral radiographic view of the upper neck with the head in flexion is usually sufficient to make the diagnosis. The distance between the anterior odontoid process and atlas is measured. Once subluxation exceeds 10mm. pressure on the spinal cord when the patient flexes the neck is almost certain. A sharp jerk on the neck can be fatal. However, a slowly developing cervical myelopathy is the more common path,
due to the repeated pressure from the odontoid process on the cord. The symptoms include paresthaesia, numbness, weakness, spastic paralysis, sensory loss, loss of bladder control, faecal incontinence, and syncope, often when coughing. Subluxation may also occur at lower levels of the cervical spine.

N.B. A high index of suspicion of high spinal cord compression is needed in long standing disease, severe disease or cortisone treated patients.

**Temporomandibular joint**

This is affected in one-quarter of patients, usually symmetrically and causing no major disability. In severe destructive cases of rheumatoid arthritis however, attrition of joint cartilage and bone causes malalignment of the teeth with malocclusion pain with chewing.

**Synovitis of the cricoarytenoid joint**

This is well-recognized. The symptoms are laryngeal pain and hoarseness. Involvement of this joint can cause problems with intubation during anaesthesia.

**Rheumatoid nodules**

Rheumatoid nodules occur in 30 per cent or less of patients. The most common sites are the extensor areas of the forearm and pressure areas in any part of the body.

Although not specific for rheumatoid arthritis they are useful from both a diagnostic and prognostic point of view. Patients with nodules have, in general, a worse prognosis.

They may occur in internal organs such as the lungs, heart and gallbladder. The histological appearance is that of a central necrotic area surrounded by a row of fibroblasts, with occasional histiocytes and macrophages.
Non-articular manifestations

Rheumatoid arthritis is primarily a joint disease, but extra-articular manifestations can be detected in almost any organ system and may occasionally precede the onset of arthritis.

Lymph nodes

Lymph nodes are enlarged in a majority of patients but only rarely palpable. In a few cases, rheumatoid arthritis may start with widespread palpable lymphadenopathy and a histological picture similar to Hodgkin's disease.

Pulmonary involvement

Pleurisy is the most common but is frequently asymptomatic. It may be associated with pericarditis, more common in older men. Rheumatoid nodules in the lungs are asymptomatic, may be single or multiple and can cause diagnostic problems. Rheumatoid arthritis patients exposed to dust e.g. miners can develop huge nodules in the lungs. This is called Caplan syndrome. Diffuse interstitial fibrosis and fibrosing alveolitis are rare but serious manifestations.

Cardiac involvement

Pericarditis is a common finding at autopsy, but causes symptoms in only a few patients. These may range from pain with friction rubs to severe exudative pericarditis with cardiac tamponade requiring surgical intervention. Most cases are, however, benign and self-limiting.

Muscle involvement

Some degree of muscle atrophy is almost invariably present in rheumatoid arthritis, but true myositis is rare.
Bone

Generalized osteoporosis is closely associated with active rheumatoid arthritis. The use of corticosteroids can greatly aggravate the condition.

Skin

Palmar erythema is common, as is vasculitis that can manifest in a variety of forms. Involvement of the small arteries presents as digital gangrene or small infarcts around the nail folds. Occasionally medium sized arteries are involved, with skin ulcers that are often very painful. Vasculitis of the venules presents as purpuric papules. Leucocytoclastic vasculitis also occurs and is seen as a palpable purpura.

Ocular involvement

Dry eyes from Sicca syndrome is very common (see next section) and is part of the Sjögren's syndrome.

Other eye complications are rare but when they occur in aggressive form are very serious. The episclera of the eye is highly vascular and inflammation presents as an acute red eye. Unlike conjunctivitis there is no discharge. Scleritis causes severe ocular pain and a dark red discoloration. Again no discharge is present. With severe inflammation of this layer, the sclera can become very thinned with the black choroid layer becoming visible. Perforation of the eye can follow and is called scleromalacia perforans.

NB Ask for an ophthalmology opinion for any suspicious eye problem in the rheumatoid patient.

Secondary Sjögren 's syndrome

Secondary Sjögren's syndrome in rheumatoid arthritis is common and may start many years after onset of the joint disease. It is characterised by a dry mouth and dry eyes.
Artificial tears, careful oral hygiene to avoid an increase in caries, and bromhexin may help in the management.

7. **Disease Course**

Rheumatoid arthritis is extremely variable with regards to the severity and rate of progression. Early and permanent remission may occur in some cases, although this is rare once permanent joint damage has started. Cyclic types of disease with remissions and exacerbations, as well as a slow but relentless progression pattern, are well described. Long-term follow-up studies clearly show that functional deterioration occurs in most patients surviving 15 years or longer.

Once erosions are present, remission is very rare.

8. **Influence of Age, Sex, and Pregnancy**

The older the patient is with the onset of the disease, the poorer the prognosis is. In women, disease onset is on average 5 years earlier than in men, and clusters around the menopause.

About 70% of women with rheumatoid arthritis who become pregnant, will go into a remission during the pregnancy. Severe relapses are common in the post-partum period.

There are many theories for this phenomenon, one being the role of sex hormones. Oral contraceptives give a small but not statistically significant protective effect against rheumatoid arthritis and seem to reduce the risk for developing severe disease. Postmenopausal use of hormones does not confer protection and contraceptive hormones have no place in the therapy of established rheumatoid arthritis.

9. **Complications**

Infections
Patients with rheumatoid arthritis are more susceptible to almost all infections. Of great importance is the fact that rheumatoid joints are very susceptible to septic arthritis. Septic arthritis occurs more often in patients with long standing disease who are taking oral glucocorticoids. More than one joint may be involved. The usual signs of sepsis, such as fever and leucocytosis, may be absent, and the diagnostic delay may be weeks.

Septic arthritis may easily be overlooked in patients with much disease activity. The most frequent infecting organism is *Staphylococcus aureus*. The diagnosis may be confirmed by aspiration and a positive culture of the synovial fluid. However, negative cultures of aspirated fluids are not unusual, and cultures of biopsies of the synovium are a more sensitive and reliable diagnostic method.

N.B. Keep a high index of suspicion for septic arthritis.

**Neurological involvement**

The most common neurological complication is entrapment neuropathy secondary to synovitis, of which the most common is carpal tunnel syndrome. It often occurs very early in the disease and is often the presenting symptom of rheumatoid arthritis.

Rheumatoid arthritis is probably the most common single cause of median-nerve compression, causing carpal tunnel syndrome.

Entrapment of the ulnar nerve and rarely the radial nerve at the elbow; anterior and posterior tibial nerves at the fibular head and in the tarsal tunnel can occur.

Mononeuritis multiplex is rare, with bilateral sudden onset of motor neuropathy signs. It usually occurs in the legs of patients with rheumatoid vasculitis. It has a very poor prognosis.

Cervical subluxation at the atlantoaxial level is well described and a much feared complication (see above).
Osteoporosis

The inflammatory process in the joints causes osteoporotic changes in the bone next to the joint, so-called juxta-articular osteoporosis. A generalised osteoporosis occurs in patients with active disease and all patients receiving corticosteroid treatment are very vulnerable to severe osteoporosis.

Amyloidosis

Amyloidosis is a rare complication of severe rheumatoid arthritis. It should be considered in cases with proteinuria or decreased renal function.

Felty's syndrome

This is a condition where splenomegaly and a white cell count of less than 2000 /mm³ occur together with rheumatoid arthritis. Hepatomegaly and lymphadenopathy are also frequently found. Severe systemic infections are a major clinical problem. The management of Felty's syndrome is still controversial. The effect of splenectomy is not convincing and often transient at best. It confers no protection against sepsis. Aggressive treatment of the rheumatoid arthritis seems to be the best therapeutic path.

10. LABORATORY ABNORMALITIES

The chapter on laboratory changes must now be consulted.

N.B. The rheumatoid factor test is not diagnostic but rather of prognostic value. Other diseases associated with chronic inflammation can also make the test positive.

11. IMAGING

Radiographic changes are of major importance in the diagnosis and staging of the disease.
The earliest sign is periarticular soft tissue swelling, particularly of the small joints of the hands and feet. Although at first it may be asymmetrical, symmetrical involvement with time is almost always the rule.

N.B. When viewing an X-ray, start by examining the soft tissues around the joints for swelling.

Progressive joint space narrowing due to destruction of articular cartilage by the pannus is another hallmark of the disease. In large joints such as the knee, hip and shoulder, the cartilage loss occurs through the entire joint, as opposed to osteoarthritis, where only a part or single compartment of the joint is affected, eg lateral compartment of the knee.

Bony erosion is another hallmark of the disease. Marginal erosions occur at the edge of the joint cartilage. Typically these ‘bare’ areas of intra-articular bone not covered by cartilage, are the initial points of attack by the proliferating synovial tissue. The erosions appear as vague areas of loss of bone, that gradually enlarge with ultimately total joint destruction.

Another radiological picture is compressive changes due to collapse of the osteoporotic subchondral bone. This occurs in joints exposed to either strong muscular actions or to significant weight-bearing forces. In the hip it is called protrusio acetabuli, with the head of the femur protruding through the softened bone of the acetabulum. Another important site is the metacarpo-phalangeal joint, with collapse of the base of the proximal phalanx.

Subchondral cysts are frequently found in rheumatoid arthritis. They may be seen as small ill-defined subchondral translucencies, or as large obvious cysts adjacent to the involved joint.

12. **TREATMENT**

Several important facts have emerged from out-come studies on rheumatoid arthritis:
♦ No single therapeutic regimen has been shown to consistently halt the progression of the disease.
♦ In many, if not most, cases, irreversible loss of articular cartilage occurs very early in the disease.
♦ Patients treated early and aggressively tend to have a better long term outcome.
♦ A crude index of the individual patient’s outcome can be gauged by the degree and the intensity of the joint synovitis.

The challenge in treating rheumatoid arthritis is to begin early with therapy that is likely to down-grade the disease to a less destructive form of disease, without causing undue morbidity from the therapy.

Education and Arthritis

There is a strong correlation between education level and disease outcome. The reason for this is unknown. Also, the better the disease is explained to the patient, the better the outcome.

Always explain the disease to the patient and at each visit explain a little more.

Bed Rest and Other Modalities

A lack of physical activity or exercise leads to a rapid loss of muscle mass and results in muscle weakness. Weak muscles e.g. the quadriceps plays havoc with the associated joints. On the other hand, excessive exercise can lead to accelerated joint damage. For this reason, resistance isotonic exercise is rarely appropriate for the patient with very inflamed joints. Isometric exercise has been shown to cause the least joint inflammation or increased intra-articular pressure. With very acute flare ups, splinting to immobilise the joint may be required. Removal of the splint twice a day to passively move the joint through its full range to movement is important to prevent contractures. The more typical patient with moderate synovitis requires a prescribed isometric programme, progressing to a well supervised resistance programme.
Diet and Rheumatoid Arthritis

Obesity is very harmful for weight-bearing joints. There is scientific rationale for eliminating those precursors of arachidonic acid from the diet that are pro-inflammatory and adding to the diet those that are anti-inflammatory. In practice this means a vegetarian diet supplemented with fish or fish oil capsules (containing omega 3 fatty acids). Some improvement with these supplements has been proven in several trials. It is difficult to manipulate patient’s diets and adding 6 fish oil capsules per day is probably the best one can do.

Pharmacotherapy

Pharmacological treatment must be divided into two groups namely:

- symptomatic relief
- disease suppression

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDS are the dominant group of drugs used to reduce inflammation and relieve pain as well as per se an analgesic effect. They offer reliable but limited symptomatic relief from pain and stiffness. There is no hard evidence that they affect long-term outcome in rheumatoid arthritis but there is, however, no doubt that they improve the quality of life in an important way in most patients.

Despite the exuberant claims of many manufacturers, there is no evidence that any one NSAID is better than another. Individual patient preferences are however, well known.

Combination NSAID's do not improve efficacy, but sharply increase the chance of serious complications. If the optimal dose of one NSAID has no satisfactory effect after 3 to 4 weeks, it is advisable to try another.

NB Never use more than one NSAID at a time
Adverse effects are very common, and may be life threatening. Awareness and careful patient education are essential. Gastrointestinal problems are to be taken seriously. Prophylactic regimens with sucralfate, H2-blocking agents, proton pump blockers or misoprostol, or the use of a cox-2 selective drug, should be considered for patients at special risk of gastrointestinal complications.

Patients at particular risk of gastrointestinal complications are:
- age over 60 years
- female sex
- previous peptic disease
- use of corticosteroids

All gastrointestinal complains in rheumatoid arthritis patients must be taken seriously.

Impaired renal blood flow is very common in patients with pre-existing kidney disease, and is believed to be due to reduced presence of procirculatory prostaglandins. NSAID's may worsen this. It is important to avoid dehydration, which may precipitate severe renal failure in patients taking NSAIDs.

Watch the kidney functions very carefully in this class of patient when starting start long term NSAID's.

In the elderly, and in particular those with marginal kidney function impairment, fluid retention is common. This is a little recognised cause of heart failure in these patients.

The effectiveness of thiazides and loop diuretics, B-blockers and ACE inhibitors is reduced by NSAID’s.

Drugs for the suppression of Disease
There is a second group of drugs that suppress the actual disease process. It is a slow process taking weeks before any clinical effect. This should be carefully explained to the patient, as they all are in continual pain and are looking for quick relief. It is seldom that complete disease remission can be achieved, but even partial suppression slows the disease process and will considerably relieve the symptoms.

NB Explain that disease suppression takes weeks or even months, but with the reduced disease activity there will ultimately be less pain.

**Chloroquine**

Chloroquine normally used as an anti-malarial, has a moderate disease-suppressive action in rheumatoid arthritis, and in the right dosage, very few adverse reactions. Safety and little need for routine laboratory tests make it an inexpensive first choice for low grade rheumatoid arthritis. The major risk is eye toxicity, but this is rare in patients without liver disease, provided that a dose of 4mg/kg/day for chloroquine (chloroquine sulphate 200mg tablets, one per day), is not exceeded. It is recommended to stop the drug for 4 weeks each year as a precaution. Nevertheless an ophthalmologic examination every six months is mandatory. These are specialised tests and not just a side room examination with an ophthalmoscope.

NB A proper examination of the macula by an ophthalmologist every six months is mandatory.

Tip: I Stop the drug every January for one month. Never stop over Christmas, for fear of a holiday flare up.

N.B. The patients must be wanted that should they enter a malaria area, they must not use mefloquine (Lariam) together with the chloroquine, because serious cross reactions may occur. Rather the chloroquine should be combined with another anti-malarial.

**METHOTREXATE (MTX).**
Low dose methotrexate is now established as the gold standard amongst slow acting disease modifying drugs for rheumatoid arthritis, and the best tolerated. It is distinguished by a rather rapid disease suppressing effect when given orally or parenterally, in doses ranging between 5 and 25 mg once a week. The usual starting dose is 7.5 mg per week. Decreased renal function increases blood levels. Probenecid increases Methotrexate levels by 400%. Co-trimoxazole must not be used with methotrexate, because there is increased bone marrow suppression with the combination.

N.B. Do not give Co-trimoxazole to patients on methotrexate.

Minor adverse events are common, only requiring temporary cessation or a dose reduction. The most common is nausea. Delayed wound healing post surgery is no longer a concern. Increases in the size of rheumatoid nodules have been documented, but can be alleviated by the co-use of chloroquine. Potentially more serious adverse effects are associated with age, diabetes, renal impairment and folate deficiency. Folic acid 5mg/day does not reduce the efficacy of methotrexate, but markedly reduces toxicity. Irreversible liver damage has been a big concern. Present guide lines are:

- Baseline liver functions and screening for hepatitis B and C.
- Patients with a history of hepatitis, alcohol abuse or known liver disease must have a liver biopsy first.
- Liver function tests every 4 or at the most 8 weeks.

Only transaminases and albumin need be done. If the transaminases are raised to more than double their normal values for more than 6 out of 12 months, liver biopsy or discontinuation of therapy is advised. Before this, reducing the methotrexate dose may be all that is required. A fall in serum albumin also requires lowering dosage until it has recovered.

Always add 5mg/day folic acid to any methotrexate prescription.
Hypersensitivity pneumonitis is a serious event, managed by stopping the methotrexate and using steroids. Baseline lung functions with diffusion are advisable before commencing methotrexate therapy. Any complaints of dyspnoea should be promptly investigated.

N.B. Promptly investigate any complaints of dyspnoea.

Bone marrow suppression is rare on low dosage, but routine blood counts are required.

TIP: The dosage of MTX is weekly. A number of fatal accidents have occurred by dispensing the dosage as daily. Always underline the weekly dosage on prescriptions.

**Sulphasalazine**

Several studies have shown sulphasalazine to be an effective disease-suppressing agent in rheumatoid arthritis, although the onset of effect is slow. There is a modest slowing of the radiographic progression of the disease. The most common adverse reactions are nausea, abdominal pain, dizziness, and headache, and these are only marginally improved by the use of enteric-coated tablets. An acute pneumonitis develops rarely, and then usually early in the course of treatment. Leukopenia, neutropenia and thrombocytopenia occur in 1-5% of patients, usually in the first 3 months of therapy. Serious bone-marrow toxicity is, however, rare. Routine blood counts must be done, at first every month but later every three months. Spermatogenesis can be affected, causing reversible subfertility. Skin rashes occur in about 5% of patients.

Dosage: 500mg tablets, 4 to maximum 6 per day.

Tip: The nausea from the drug can be very annoying. Start with a very low dose e.g. one tablet per day, and build up slowly over several weeks.
Leflunomide

This expensive disease modifying drug is for use by specialists only. It antagonises a mitochondrial enzyme critical for de novo biosynthesis of pyrimidines. The active metabolite persists for a long period and there are protocols available to wash out the drug in case of serious adverse events or prior to conception. Side effects include bone marrow and liver toxicity and careful monitoring is required.

Soluble gold salts

These have been given parenterally since the 1930s. Unfortunately serious and fairly common adverse reactions have sharply reduced the use of injectable gold compounds. Although still used in other parts of the world, it is not available in South Africa anymore.

The post-injection reactions, also called the nitritoid reaction, are quite frightening although not serious, with the patient complaining of weakness, dizziness, nausea, facial flushing. It is more common in patients taking ACE inhibitors for blood pressure. Agranulocytosis and thrombocytopenia are usually reversible.

Adverse reactions to injectable gold

Post-injection reaction (nitritoid reaction)

Skin and Mucous membranes
- Stomatitis
- Various skin rashes

Renal
- Proteinuria/nephrotic syndrome
- Membranous glomerulonephritis

Haematological
- Eosinophilia
- Neutropenia
- Thrombocytopenia
- Aplastic anaemia

Hepatitis

Colitis (especially with oral gold preparations)

Pulmonary
- Diffuse pneumonitis
- Bronchiolitis obliterans

Neurological
- Peripheral neuropathy

Monitoring for side effects is critical. At every visit a full blood count and urine examination for blood and protein is mandatory. If a skin rash occurs or mouth ulcers the drug must be stopped. Any proteinuria or hematuria requires the drug to be stopped. A fall in platelets or any of the other white cell elements must be viewed seriously and again the drug must be stopped. Over one third of patients started on gold salts will have to be withdrawn within the first year because of side effects.

An oral gold compound is available but considerably weaker than parenteral gold. The most common side-effects are diarrhoea and other mild gastrointestinal disturbances. Serious adverse reactions are unusual.

**D-Penicillamine**

D-penicillamine is as effective as the anti-malarials and injectable gold, but because of its toxicity and cost it is infrequently used. It is particularly useful in patients with vasculitis, Felty's syndrome, amyloidosis and rheumatoid lung disease. Objective signs of a decrease in the synovitis can take 6 months.
Dosage: start with one 125mg tablet per day, slowly increasing to a maximum of 500mg per day 1 to 2 hours away from food. Its absorption is hindered by food, iron and antacids.

Adverse effects are frequent and can be serious. Haematological toxicity is the most serious. Full blood counts must be performed every two weeks for three months then monthly. A white blood count below 3000cells/mm³ or a platelet count below 100,000 cells/mm³ requires the drug be stopped.

Nephropathy is usually due to immune complex deposition. Urine analysis must be done at the same time as the blood count. Proteinuria is an indication to stop therapy. An early and a late rash may occur. The late onset rash often requires discontinuation as it pruritic. D-penicillamine induced lupus erythematosus is well described and the drug must be promptly stopped. D-penicillamine is contraindicated in pregnancy owing to its teratogenic effects.

Azathiprine

The use of the purine analogue azathioprine, although reasonably effective, is declining due to short and long term toxicity. The dose is between 1.5 and 2.5 mg/kg/day, and the onset of action is slow. Bone marrow toxicity is the most common complication and the induction of lymphoma is a rare complication.

Biological agents

These drugs antagonise the effects of key cytokines in the inflammatory process. The most common agents act on tumour necrosis factor alpha (infliximab, etanercept, adalumimab), although other cytokines like inteleukin 1 (anakinra) have also been targeted. They all require parenteral administration and are potent immunosuppressants with the potential for life threatening infections. They are also dramatically effective in reducing the inflammation in most patients with rheumatoid arthritis and slow the progression of erosive damage. They are unfortunately very expensive.
Glucocorticosteroids (cortisone)

After more than 40 years of clinical use, there is still considerable debate as to the indications for cortisone use. Pain and stiffness are dramatically reduced with oral cortisone therapy, but should be used very carefully as the side effects can be difficult to overcome.

The main side-effects are:

♦ weight gain
♦ hypertension
♦ cataract
♦ diabetes mellitus
♦ arteriosclerosis
♦ osteoporosis

Some indications for oral cortisone are:

♦ ineffective response to adequate use of the disease modifying drugs
♦ acutely ill patients (for a limited time only)
♦ significant systemic disease
♦ serious social problems e.g. a bread winner possibly loosing his or her job.

Keep the dose as low as possible and if possible below 7,5mg prednisone per day.

High-dose systemic dosage may prevent formation of erosions but adverse effects preclude its uninhibited use.

Intra-articular use of depot-cortisone preparations is, however, both effective and rational, as it delivers the disease-suppressive drug to the involved site.
It is suggested that up to 4 joints can be injected at a visit, but that the same joint should not again be injected for three months. Another important place for injectable steroids is tenosynovitis. A low dose of depot product is injected into the tendon sheath, never into the tendon. This can dramatically reduce the synovitis of the tendons. If 2 injections have not cleared the synovitis, surgical synovectomy of the tendon sheath is required to prevent tendon rupture.

Iatrogenic septic arthritis is the big fear but is usually not a major problem when using a proper technique. Thoroughly clean the skin over the joint to be injected, use a mask and gloves and a thorough aseptic method in drawing up the steroid to be injected.

N.B. Warn the patient they might have a chemical reaction to the injected material, with pain a few hours after the injection. Should the pain persist or they feel feverish the next day, they must report back to exclude septic arthritis.

**Surgery in Rheumatoid Arthritis**

Despite all attempts are at reducing the inflammatory process in rheumatoid arthritis, patients often end up with severe joint destruction, significant disability and pain. In these instances surgery can have a major impact to improve function and the quality of life, with interventions ranging from synovectomy, nerve decompression, soft tissue realignment, arthroplasty and arthrodesis.