

Treatment of Rheumatoid Arthritis and Osteoarthritis

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Highlights / Hoogtepunte

- The multidisciplinary team approach to the management arthritis patients.
- Practical guidelines for initiating disease-modifying drugs (DMARD's) in both OA and RA.
- The role of intra-articular injections and surgery in arthritis.
- Die multidisiplinêre spanbenadering tot die hantering van artritis pasiënte.
- Praktiese riglyne vir die inisiëring van siekte modifiserende geneesmiddels vir OA en RA.
- Die rol van intra-artikulêre inspuitings en chirurgie.

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The assessment of any arthritis disease requires clarification of the specific disease as well as evaluation of the stage and activity of the disease and of function of the joint involved. In doing so, one can assess prognosis and adjust the patient's therapy accordingly. This can be classified as symptomatic therapy, specific disease modifying therapy and rehabilitation with restoration of function.

Non-pharmaceutical therapy is an essential part of treatment, and a multidisciplinary approach is ideal. This encompasses physiotherapy, occupational therapy and patient education, all aimed at empowering the patient to understand the chronic disease process.

Osteoarthritis (OA) is perhaps the model degenerative disease, whilst rheumatoid arthritis (RA) is a classic inflammatory arthritis. Both diseases warrant symptomatic therapy, consisting of anti-inflammatory therapy and analgesic therapy. However, in addition, a disease modifying approach is applicable to both diseases. This is particularly so for RA, where it is now demonstrated to have revolutionised treatment and improved outcome in patients.

Ideally treatment of these diseases should occur by or in consultation with a rheumatologist, but this is not always

possible. The general practitioner should be seen as part of the team, and should endeavour to acquire skills of diagnosis and a sound understanding of disease modifying drugs and their potential side effects, as well as requirements for monitoring.

NON PHARMACOLOGICAL THERAPY

This is provided by physiotherapists, nurses, educators, occupational therapists, orthotists, dieticians, social workers, and the families and patients themselves.

The Physical Therapist plays a role in assessing function and activity and implementing a program to facilitate pain relief initially and rehabilitation in the long term. Acute management includes resting or immobilising acutely inflamed joints, and maintaining joint range of movement by active movement and passive stretch exercises. Heat, laser and ultrasound provide relief to the soft tissues. Hydrotherapy plays a role in mobilisation and provides exercise in a non-impact, buoyant environment to restore muscle tone and power. As the joints become less inflamed, movement is encouraged with active exercise against progressive resistance.

The Occupational Therapist looks at the function of the patient in the context of his or her disability. They teach and provide joint protection advice. They also provide assistive devices and splints. Resting splints are used during the acute phase. Thereafter, serial splints are used with semi-static, resting splints with progression to dynamic splints. The use of assistive devices and education about the activities of daily living is invaluable.

The Dietician provides advice regarding a balanced diet and weight control, a major problem especially in disease of large weight bearing joints, especially in OA. There is no specific diet for arthritis. However, red meat is reduced and fish and vegetable intake is encouraged. In some patients aggravation by certain foodstuffs may be noted, and advice is given to avoid these in individual cases.

The Orthotist provides a vital service especially by providing devices, such as arch supports for ankle and subtalar disease and metatarsal domes for metatarsal disease.

PHARMACOLOGICAL THERAPY

Symptomatic therapy is useful to relieve discomfort. However, other than helping

to maintain mobility and joint range of movement, it has no influence on actual disease control or influence on outcome. Analgesia was previously seen as first line therapy in disease, but recent advances have changed the classical teaching. In RA, the early use of disease modifying drugs (DMARDs) has changed disease outcome. It is not considered sufficient to treat RA with analgesics or anti-inflammatories alone. In OA, the first line approach of analgesics has also been challenged. Evidence suggests that OA is a heterogeneous condition with significant inflammation present, and not a simple mechanical or degenerative disease. Evidence suggests that anti-inflammatories are more efficacious than analgesics in OA. Previous guidelines for therapy of OA, advocating analgesia as first line, have been heavily influenced by the side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). The advent of specific COX-2 inhibitor drugs have made effective, safer, use of anti-inflammatories possible, even in the higher risk elderly patient population seen in OA.

ANALGESIA

Analgesics are used in a stepwise fashion, titrated according to severity of pain. Mechanical problems are worse through the day and with activity, and analgesics may be used "as required". They include paracetamol, paracetamol-codeine combinations and stronger medications such as tramadol and dextropropoxyphene. Advantages of the analgesics include relative sparing of gastric ulceration, but increasing problems with constipation as well as renal and hepatic impairment have been reported.

ANTI-INFLAMMATORIES

These include the older, non specific COX inhibitors and the newer COX-1 sparing, COX-2 specific drugs. These provide an increased safety profile by sparing the gastric mucosa, reducing ulceration and also maintaining platelet function. Anti-inflammatory drugs are best used in patients who are manifesting symptoms of inflammation: swelling, stiffness and local heat in the joints.

The concern that NSAIDs damage human cartilage is not confirmed, although indometacin may accelerate deterioration in OA of the hip.

COXIB drugs, including celecoxib (Celebrex®), rofecoxib (Vioxx®), valdecoxib and etoricoxib, and lumiracoxib, are more expensive than non-specific NSAIDs, but have been shown to be less toxic to the gastric mucosa. They constitute a whole new class of NSAIDs. They have altered the approach to early use of NSAIDs as analgesic therapy, especially in at risk population groups, such as the elderly, previous peptic ulcer disease and co-use of corticosteroids. Unfortunately health funders, perhaps inappropriately, view these as too expensive for general use. However complications, including bleeding and transfusion requirements, are reduced. In addition, the platelet sparing effect make their use in the perioperative environment much more desirable than the older NSAIDs, which were associated with increased bleeding and haematoma formation. Since osteoarthritis occurs in the elderly, COXIBs allow safer early use of anti-inflammatory therapy.

Other strategies to reduce gastric side effects of the older NSAIDs, include co-use with proton pump inhibitors or misoprostol. Some of the older NSAIDs, (including meloxicam, diclofenac and ibuprofen), have a more selective COX-2 to COX-1 ratio than other NSAIDs (such as piroxicam or ketoprofen). They are, however, NOT specific COX-2 inhibitors.

DISEASE MODIFYING DRUGS

In RA, there is a new recognized need for disease modifying drugs early on in the disease. In fact rheumatologists now support the use of DMARDs as soon as the diagnosis is made. The concept of the pyramid approach to therapy is no longer applicable in RA, and the pyramid approach is now inverted. (Fig. 1.)

DMARDs are used either alone or in combination. Some rheumatologists advocate a step up approach, adding or replacing should response be incomplete. The aim is remission of disease. (Table 1, 2) This is only rarely achieved, although amelioration of the disease is experienced in the majority. Evidence suggests that even short term exposure to DMARDs will improve long term prognosis.

Rheumatologists advocate ongoing DMARDs, as long as there are no side effects and efficacy is continuous. Without the drugs the result will be recurrence within approximately three

1.	Reduction of pain
2.	Reduction of inflammation
3.	Prevent joint destruction
4.	Preserve of joint function
5.	Return to a productive life
6.	Remission

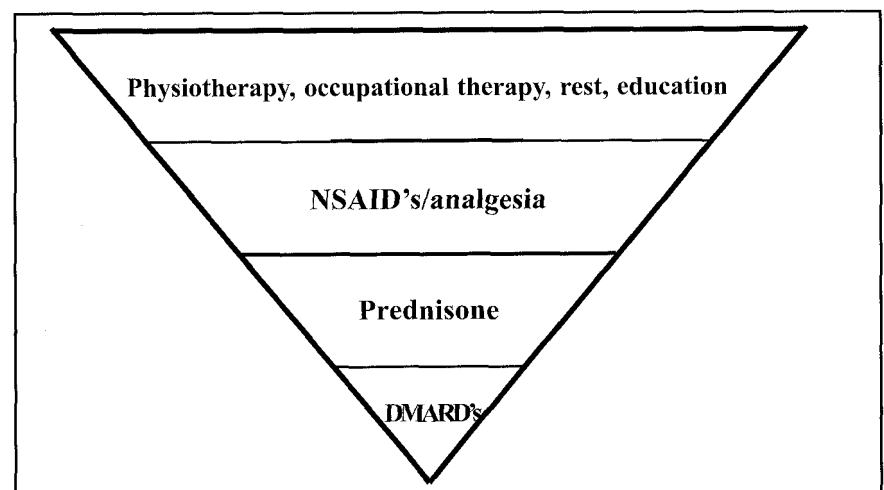


Figure 1: The new inverted pyramid approach to Rheumatoid arthritis

Table 2: Criteria for remission

1.	Duration of morning stiffness not exceeding 15 minutes.
2.	No fatigue.
3.	No symptoms of joint pain.
4.	No joint tenderness or pain on motion.
5.	No soft tissue swelling in joints or tendon sheaths.
6.	ESR < 30 (female) and <20 (male)
NB Require 5 or more criteria for at least 2 consecutive months. There must be no clinical manifestation of active vasculitis, pericarditis, pleuritis, or myositis or unexplained recent weight loss or fever attributable to rheumatoid arthritis.	

Table 3: Relative strengths of DMARD.

Drug strength	Rank order	Weak
Auranofin (oral gold)	1	•
Hydroxychloroquine / Minocycline	2	•
Chloroquine	3	•
Sulphasalazine / Intramuscular gold / D-Penicillamine	4	•
Methotrexate / Leflunomide	4/5	Strong

weeks. Patients are thus advised NOT to stop their medication.

There is a rank order of efficacy (Table 3) and generally, stronger drugs have a greater side-effect profile. Side effects and monitoring are therefore drug dependent. In practical terms, the gold standard DMARD is methotrexate, but most rheumatologists also use sulphasalazine and antimalarials (hydroxychloroquine, chloroquine sulphate, chloroquine phosphate). Gold and penicillamine are not frequently used any longer, due to their toxicity profiles. Newer DMARDs now developed include leflunomide (Arava®).

For resistant disease drugs such as azathioprine or cyclosporine were used in the past, but biological agents against cytokines, especially tumour necrosis factor, and IL-1 which promote disease, have been developed. Anti-TNF agents include etanercept (Enbrel®), infliximab (Revellex®, Remicaide®) and adalimumab. These have provided dramatic advances in treating resistant disease, but are limited by cost and risk of side effects, especially reactivation of tuberculosis. Other biological therapeutic agents include anakinra (IL-1 receptor antagonist). These drugs should remain for specialist usage.

Methotrexate is given as an injectable or oral preparation. It is used at night and the usual recommended starting dose is 7.5-10 mg per week with an increasing dose versus response to 20 mg/week. The drug takes approximately 4-6 weeks for a response to develop.

It cannot be used in patients with established or active liver disease, renal impairment, significant lung disease and excessive alcohol abuse. A history of hepatitis should be determined prior to therapy and a chest X-ray should be performed. Urine analysis is required every 3-6 months.

The side-effects include nausea, diarrhoea, rashes, alopecia, mouth ulcers and stomatitis.

More severe effects include bone marrow suppression, liver toxicity and pulmonary toxicity (pneumonitis).

To prevent nausea, doses should be administered in the evening.

The use of folic acid with the drug can also reduce side effects. In South Africa it is common practice to use 5mg per day. Folic acid does not interfere with drug activity.

Liver biopsy is not considered essential for baseline assessment or for routine follow up after a predetermined total dose. Guidelines are now available for follow up and need for biopsies.

Routine monitoring must be done using blood count and liver function assessments (AST, ALT, GGT and full blood count). Blood tests must be done at baseline, at one month, and thereafter every 2 months. If levels are persistently increased 50% above normal, consider biopsy if the drug is to be continued.

Pregnancy: Teratogenicity is reported and therefore, males and females on methotrexate should be taken off the drug for 3 months before conception. The drug is also contraindicated in lactation.

Sulphasalazine consists of two agents – a sulphur (sulfapyridine) and a salicylate component, (5 amino salicylic acid). The drug is introduced slowly over the first month to avoid problems of nausea and gastrointestinal irritability - starting with 0.5 g daily for one week, then 1 g daily for one week, then 1.5 g daily for one week, and thereafter 2 g per day. Response takes between 1-6 months.

Adverse events are reported more often in the first three months of use and have a generally low profile with no long term effects reported. The drug is generally well tolerated. Dose reductions are usually effective for minor side effects.

- Gastrointestinal discomfort, with nausea, vomiting, loss of appetite, and abdominal pain.
- Skin rashes and allergic manifestations are common.
- Headaches, mood alterations.
- Reduced sperm counts may be seen, but this is reversible.

- Marrow suppression.
- G-6-PD deficiency manifesting as anaemia with haemolysis.
- Nephrotoxicity.
- Hepatotoxicity.
- Pulmonary toxicity.
- Major allergic rashes - including Stevens-Johnson syndrome.

Monitoring requires baseline blood count and liver function assessment, including eAST, ALT, GGT and Urine analysis. The monitoring must be done monthly for 3 months and then three to six monthly.

Pregnancy: No teratogenicity is reported from over 2000 reports of pregnant patients using the drug, (mainly in inflammatory bowel disease patients). But, it is generally advised that the drug be discontinued in pregnancy unless considered essential because of severe disease. The drug is considered safe during lactation, with little sulphasalazine in the milk and sulfapyridine levels 40% of plasma levels.

3. Antimalarials

These are chloroquine salts/hydroxychloroquine. They are generally seen as milder drugs.

The use of chloroquine is generally for milder disease or in combination therapy and it takes about three to six months to demonstrate efficacy. Hydroxychloroquine has, on meta-analysis review, been shown to be slightly weaker but less side-effect prone than chloroquine.

Side effects:

Minor side effects include:

- Nausea.
- Rash and photosensitivity. Skin pigmentation in sun-exposed areas may develop.
- Diarrhoea
- Neuromyopathy is reported rarely.

Serious side effects:

The main problems are ophthalmological. Prolonged therapy has been associated with fundal defects with maculopathy, especially loss of peripheral vision and reduced night vision. Therefore regular ophthalmological assessment is required on a six monthly to yearly basis. Baseline assessment is required within the first six months. Early examination may reveal dose-related corneal deposits, necessitating dose reduction. Retinal changes are a consequence of an excessive daily dose, and not thought to be from accumulation.

Dose recommendations - Chloroquine - 4mg / kg. Hydroxychloroquine - 6.0-6.5 mg/kg.

These are calculated according to the amount of chloroquine base in the drug. Dose reductions must be considered in the elderly. Once the condition has been stabilised, dose reductions can be considered by decreasing the frequency of administration.

It is advised that the drug be taken with food to improve bioavailability and reduce nausea.

Pregnancy:

Little information is available, as fewer than 100 reports exist of pregnancy in rheumatoid arthritis patients on antimalarials. However, amongst these there are no reports of adverse fetal effect. The drug should be stopped, unless absolutely necessary.

4. Minocycline

Antibiotic therapy has been controversial but some studies now suggest that there is a response to minocycline. It is seen as an option in milder disease.

Trials have been contradictory but the balance showed benefit. Radiological progression has not been slowed by use of the drug.

Dose recommended is 100mg twice daily.

Effectiveness takes approximately 3-6 months to be established.

Side effects:

- Nausea, vomiting, taste disturbance in 30%.
- Hyperpigmentation and tooth discoloration.
- Skin rash, photosensitivity.
- Headaches.
- Hypersensitivity pneumonitis.
- Hepatotoxicity.
- Drug induced SLE and antinuclear factor (ANF) positivity.

Pregnancy and lactation: contraindicated.

5. Leflunomide

This is metabolized to active metabolites that inhibit dihydro-oroate dehydrogenase. This is the rate-limiting enzyme in pyrimidine nucleotide synthesis. In rheumatoid arthritis, the activation and proliferation of T cells is therefore impaired. Clinical trials show a reduction in joint counts and improvements in physician and patient

global assessment and function. Trials suggest efficacy is sustained. Comparison with methotrexate suggests equivalent efficacy, as well as an improvement when compared to placebo. There is also evidence for reduction in erosions. Trials are ongoing regarding combination therapy, including with methotrexate.

Side effects:

- Gastrointestinal symptoms, (diarrhoea).
- Skin rash.
- Alopecia (reversible).
- Elevation of liver enzymes.
- Severe teratogenicity.

Serious adverse events in trials are seen in approximately 20 % of patients, requiring stopping the drug in 15% of patients. If there are side-effects, drug levels can be reduced or eliminated by cholestyramine.

Pregnancy is absolutely contraindicated (for male and female patients) and there is a minimum three year recommendation off the drug before initiating a pregnancy. Alternatively the drug can be eliminated, but the drug level should then be measured to ensure complete elimination prior to stopping contraception.

SYSTEMIC CORTICOSTEROIDS

These have their place in inflammatory arthritis, in low doses in articular disease but in high doses for systemic extra-articular involvement of RA.

For articular disease, the dose should be kept low at or below 7.5mg per day of prednisone. It should be taken in the morning. Alternate day use is not well tolerated by RA patients, as the disease is sensitive to small changes in dose.

Systemic corticosteroids are particularly useful for the treatment of stiffness and swelling whilst DMARDs are being initiated, prior to effect. Thereafter the prednisone should be reduced and possibly stopped, where possible, over 2-3 months.

DMARD therapy in Osteoarthritis

Tremendous research is ongoing in

osteoarthritis, and the disease is seen as several subcategories including an inflammatory subtype associated with early onset, genetic background and swelling and a soft tissue component on examination.

Glucosamine Sulphate

There is some accumulating evidence that glucosamine sulphate has efficacy in osteoarthritis, with trials showing pain relief but also chondroprotection. Three and five year follow up in patients treated for osteoarthritis of the knee show a slight increase in joint space, compared to loss in placebo groups. Glucosamine sulphate is made from shrimp and crab shells and consists of the building block of the glycosaminoglycans, the ground substance of cartilage. It has been shown to increase proteoglycan synthesis. It is absorbed well and is excreted in the lung and kidneys. The recommended dose is 1500mg/day.

The consumer is faced with a large choice of products. Unfortunately there is no quality control regarding the bioavailability of the active ingredient. Most studies showing efficacy are based on the SULPHATE moiety, and there is no evidence that the CHLORIDE product is as efficacious. Similarly, studies of chondroitin sulphate are not definitely conclusive and this constituent, derived from bovine sources, adds considerably to the price.

Diacerhein

This is a compound derived from rhubarb and is the acetylated form of anthraquinone, rhein. The drug has been shown in some trials to reduce symptoms as well as reduce the inflammatory response of IL-1 in chondrocytes. There is evidence that it may reduce cartilage loss in OA of the hip, compared to placebo. The product is not yet available in South Africa.

Other disease modifying therapies in OA

Trials of tetracycline and antimalarial therapies are in the process. Tetracycline blocks synthesis of nitric oxide as well as metalloproteases involved in cartilage destruction.

INTRA-ARTICULAR INJECTIONS IN RA AND OA

Corticosteroid Injections

If a joint is swollen and out of phase with the rest of the disease activity, it is frequently useful to inject that joint directly. Joint injection techniques require skill and should be done as a sterile, non-touch technique in the clinic setting. They should NOT be painful. A painful injection may suggest the injection has been incorrectly administered. Similarly, tendon and soft tissue injections are very useful, but require precise diagnosis and anatomical location of the abnormality.

Whereas systemic corticosteroids have little place in the treatment of OA, there is no doubt that intra-articular steroids control symptoms in patients with OA. However, the benefit is short lived, lasting only a few weeks or months.

Side-effects other than infection are mild, with flushing, skin discolouration and local fat atrophy, especially if the injection is misplaced. Diabetic control may also require monitoring.

Injections should be limited to 3-4 times per year in weight bearing joints. They must be only an adjunct in the control of the underlying disease.

Hyaluronan

This is given as an injection of linear glycosaminoglycan into the joint. It supplements endogenous hyaluronan, which is reduced in the OA joint. It is made from Rooster comb, with chemical modifications to increase half life and increase claimed efficacy. It does not work as a simple lubricant, as it is cleared rapidly from the joint. Efficacy is due to its influence on synovial cytokines. The trials do not show definite long term efficacy, and widespread use is not justified. However some patients do seem to benefit from symptomatic relief lasting months. They therefore may be used in patients who require, but do not want, surgery and who fail to respond to corticosteroid injection.

Surgery

Surgery plays a special role in patients who have mechanical joint problems that impair daily life activity and are not

responding to medical and conservative therapy.

The advent of replacement arthroplasty (joint replacement), has been a major advance in the treatment of rheumatic disease. Survival rates of total hip replacement (THR) and total knee replacement (TKR) is 10-15 years. Age is not a contraindication to surgery. Anaesthetic techniques and anticoagulation have reduced perioperative complications. Late complications include infection, loosening, osteolysis, periprosthetic fracture and wear of the prosthesis.

Timing of joint replacement therapy is delayed until conservative therapy fails. However, if there is a problem of regional osteoporosis and loss of bone stock, delay may be harmful in some patients.

In addition, it is important to address the underlying disease, especially in RA, as active disease will limit rehabilitation.

Arthroscopy has also been revolutionary in management of internal derangement of joints, especially relating to meniscal tears and foreign bodies in the knee. Other forms of arthroscopic lavage and debridement of osteoarthritic joints, however, are more controversial and recent trials show no benefit from the procedures.

Decisions regarding surgery must have appropriate indications, and whilst it may offer a quick solution, surgery should be considered as an adjunct to and not a replacement for medical therapy.

Chondral defects can also be managed arthroscopically using osteochondral autografts or by cartilage cell transplant or periosteal grafts, both of which are performed in open surgery. However, these procedures remain experimental at this time.

RECOMMENDATIONS FOR SOUTH AFRICAN PRIMARY CARE PRACTITIONERS FOR USE OF DMARD IN RA: SUMMARY

1. Confirm the diagnosis as early as possible. Whilst classification criteria exist, these are NOT diagnostic criteria. (Table 4)

2. Assess degree of activity by assessing degree of stiffness and swelling/joint counts.
3. Assess risk factors. (Genetic subsets with HLA typing, especially shared epitope, identifies severe disease and has been used by O'Dell to predict the response to combination therapy. However, this is not felt to be practical for the South African situation.) **(Table 5)**
4. Monitor the patient for efficacy and side-effects. **(Table 6)**
5. Refer where possible to a rheumatologist or specialist with an interest in rheumatology. Encourage a team approach with the specialist

A PERSONAL RECOMMENDATION FOR DMARD USE

- Early active disease presenting with symptoms / features of rheumatoid arthritis but little synovitis on examination and low risk factors: suggest management with COXIBS/NSAIDs and consider early introduction of disease modifying therapy if still active at three months after onset of symptoms (recommendation to start sulphasalazine or hydroxychloroquine). If inadequate response or progression by one to three months on DMARD, add methotrexate.
- Early active disease presenting with features of rheumatoid arthritis with mild to moderate synovitis and risk factors: suggest management with COXIBS/NSAIDs/low dose steroids with introduction of methotrexate. If inadequate response by three months: add a second disease modifying drug (sulphasalazine or hydroxychloroquine).
- Early active disease presenting with features of rheumatoid arthritis with moderate to severe synovitis: initiate dual therapy early in combination low dose corticosteroids. Dual therapy includes methotrexate with hydroxychloroquine or sulphasalazine. Specialist referral desirable.
- Early active disease presenting with features of rheumatoid arthritis with severe synovitis and risk factors: initiate triple therapy early in combination low dose corticosteroids. Triple therapy includes methotrexate

with hydroxychloroquine and sulphasalazine. Specialist referral desirable.

- Intolerance to methotrexate but

normal liver function, consider leflunomide. However this requires specialist referral.

- If established rheumatoid arthritis

Table 4: 1988 revised ACR criteria for classification of RA: Arnett FC, Edworthy SM, Block DA, et al: The American Rheumatism Association 1987 criteria for the classification of Rheumatoid arthritis (abstr). Arthritis Rheum 1987;30:S17	
1.	Morning stiffness for longer than 1 hr and longer than 6 weeks duration
2.	Swelling in 3 or more joints for longer than 6 weeks duration
3.	Swelling MCP or PIP for longer than 6 weeks duration in wrist
4.	Symmetrical joint swelling
5.	Rheumatoid nodules
6.	Serum rheumatoid factor
7.	Hand X-ray changes – erosions or decalcification
Require	4 or more for classification

Table 5: Factors suggesting poor prognosis	
1.	Early age at onset
2.	High titre rheumatoid factor
3.	Young female
4.	Elevated ESR / CRP
5.	Elevated platelet count
6.	Swelling >20 joints
7.	Extra-articular disease
8.	Shared epitope positivity - HLA-DRB1 typing
9.	Radiological detection of erosions

not responding or intolerant to triple therapy: consider the use of leflunomide, and if still no response consider azathioprine. Specialist attention considered mandatory.

- Established rheumatoid arthritis not responding to any therapy: consider etanercept/infliximab, depending on availability. Specialist attention considered mandatory.
- Remember that all patients require individualized therapy, and this article provides only a guideline. Where possible, referral to a rheumatologist is strongly recommended. □

Please refer to the CPD questionnaire on page 53.

Table 6: Measurement of response to therapy	
1.	Duration of morning stiffness
2.	Severity of fatigue
3.	Joint swelling scores (tender / swollen joint counts)
4.	Visual analogue scores for pain and stiffness.
5.	Physician assessment visual analogue scores.
6.	Evidence of disease progression on examination - loss of motion / deformity
7.	Patient global assessment visual analogue scores.
8.	Basic functional assessment scores- in particular the Stanford health assessment questionnaire – HAQ score.
9.	ESR, CRP, platelet count
10.	Radiological damage