

Drug regimens for RHEUMATOID ARTHRITIS

By SUE PARKINSON, D_{IP}C_{LIN}PHARM, MRPHARMS and ANDREW ALLDRED, D_{IP}C_{LIN}PHARM, MRPHARMS

There is now a tendency for drug treatment of rheumatoid arthritis to be aggressive. The options available are discussed here

The goals of rheumatoid arthritis (RA) management are to relieve pain and inflammation, prevent joint destruction, preserve or improve functional ability, and maintain a patient's normal lifestyle.

A multidisciplinary approach to treating RA patients is important. Physiotherapists, occupational therapists, clinical nurse specialists, podiatrists, social workers and pharmacists all have a crucial role. Education of patients is an important aspect of treatment because patients should have

knowledge of the disease process and prognosis, as well as treatment strategies, in order to improve compliance.

There has been a major shift in the treatment of RA over the past decade. Traditionally, the therapeutic pyramid was employed, whereby initial treatment was conservative, using non-steroidal anti-inflammatory drugs (NSAIDs) for several years and only progressing to disease-modifying antirheumatic drugs (DMARDs) when the disease was not controlled. This approach has been replaced by early treatment with DMARDs, because there is evidence that most patients develop joint destruction within the first two years of their disease.¹ The classes of drugs used in RA treatment are discussed below.

ANALGESICS

Paracetamol, paracetamol combinations and dihydrocodeine are all useful for simple pain relief. Although they have no anti-inflammatory properties, and do not affect the disease process, they do have a place in both the early and late stages of the disease. They may help with referred pain associated with muscle weakness and the general soreness associated with RA.

NSAIDs

The major pharmacological agents for the relief of pain and inflammation in rheumatic diseases are NSAIDs. Although NSAIDs come in a variety of chemical structures, they all have similar pharmacological

Ms Parkinson is the lead pharmacist for rheumatology at the Leeds Teaching Hospitals NHS Trust, a post previously held by Mr Alldred, who is now pharmacy procurement manager at the same trust

properties, that is, antipyretic, anti-inflammatory and analgesic actions.

Patient response to NSAIDs is highly variable, and therapeutic trials with several NSAIDs may be necessary to determine the best agent. It is estimated that 60 per cent of patients will respond to any one NSAID. Despite numerous clinical trials, differences between NSAIDs, using objective measurements of efficacy, have not yet emerged. It is recommended that the drug should be changed after one week if there has been no response and an analgesic effect is the desired outcome, or after three weeks if an anti-inflammatory effect is desired. Approximately 10 per cent of patients will not find any NSAID beneficial.

There is no evidence of synergism or reduced toxicity with the use of more than one NSAID. In fact, there is evidence that two NSAIDs may increase the risk of gastrointestinal (GI) toxicity.² Only one agent should therefore be prescribed at a time, although a short-acting drug may be used during the day with a longer-acting preparation at night.

GI adverse reactions GI adverse reactions range from superficial damage with minor symptoms (dyspepsia, abdominal pain, and diarrhoea) to duodenal and gastric ulceration, and potentially fatal complications. Patients generally complain of nausea and indigestion, but some of those presenting with bleeding or perforation will have no history of dyspepsia or peptic ulceration. The prevalence of symptomatic ulcers has been reported to be between 14 and 31 per cent, with gastric ulcers being most prevalent.

The options for reducing gastric side effects due to NSAIDs are:

- 1 Using simple analgesics instead of NSAIDs
- 1 Using an NSAID with the lowest associated GI side effects and at the lowest possible dose
- 1 Prescribing a gastroprotective agent or a selective cyclo-oxygenase (COX)-2 inhibitor

Misoprostol, omeprazole, lansoprazole and ranitidine have all been shown to be effective in the prevention of NSAID-induced gastroduodenal ulceration. In clinical trials, proton pump inhibitors have been shown to be more effective than misoprostol in preventing gastric and duodenal ulcers associated with NSAIDs.³⁻⁵ Ranitidine has been shown to protect against duodenal ulceration but has little effect in preventing gastric ulceration.^{6,7} From these studies, it would appear that proton pump inhibitors are the most effective agents for the prevention of GI complications associated with NSAID use.

COX enzyme selectivity The main mechanism of action of NSAIDs is believed to be the inhibition of the COX enzyme. COX converts the fatty acid arachidonic acid into endoperoxidases, prostaglandins and thromboxanes in a cell-specific manner. These prostanoids have a variety of physiological functions, including protection of the GI tract, renal homeostasis, platelet aggregation, and uterine smooth muscle contraction. Prostanoids are also widely implicated in pathological states associated with inflammation.

In the past decade, it has been shown that there are two isoforms of COX — COX-1 and COX-2. COX-1 is believed to function mainly by producing the prostaglandins that are critical for maintaining normal renal function, gastric mucosal integrity and haemostasis. COX-2 is virtually undetectable in most tissues under physiological conditions, but is induced by certain inflammatory stimuli.

NSAIDs act by direct inhibition of COX-1 and COX-2, via blockade of the COX enzyme site. The subsequent inhibition of prostaglandins reduces inflammation but also has collateral effects on platelet aggregation, renal homeostasis and gastric mucosal integrity. In an effort to reduce the side effects of NSAIDs, particularly GI side effects, agents were developed that selectively blocked COX-2, with minimal effect on COX-1.

There are four COX-2 selective agents available: etodolac, meloxicam, celecoxib and rofecoxib. Etodolac and meloxicam inhibit COX-2 up to 50 times more than COX-1, and newer agents celecoxib and rofecoxib are even more COX-2 selective.

The National Institute for Clinical Excellence has recently issued guidance on the use of COX-2 selective agents in the treatment of osteoarthritis and rheumatoid arthritis.⁸ In the guidance, there was no distinction between the different agents. COX-2 selective agents are recommended for use in patients that are at high risk of developing GI side effects but they are not recommended for routine use. Those at high risk are:

- 1 Patients over 65 years of age

- 1 Patients who are taking medicines known to increase the likelihood of upper GI side effects (for example, steroids and anticoagulants)
- 1 Patients with serious co-morbidities such as cardiovascular disease, renal or hepatic impairment, diabetes and hypertension
- 1 Patients requiring prolonged treatment with high doses of NSAIDs

There have been concerns raised over the cardiovascular safety of the coxibs, that is, rofecoxib and celecoxib. In the VIGOR study,⁹ which compared rofecoxib to naproxen in patients with rheumatoid arthritis, there was a higher incidence of cardiovascular side effects in the rofecoxib group, although the clinical significance of this is unclear. This trend was not repeated in the CLASS study,¹⁰ which compared celecoxib to diclofenac in patients with osteoarthritis. In this study, patients on low dose aspirin were allowed to continue taking it, unlike in the VIGOR study.

NICE has concluded that, based on current evidence, there is no justification for using a coxib and low dose aspirin together, because the aspirin appears to reduce the benefit of the coxib. NICE also concluded that there is no justification for prescribing a COX-2 selective agent in combination with gastroprotective agents.

Other adverse events Most NSAIDs can reduce creatinine clearance and produce a non-oliguric renal failure, probably as a result of inhibition of prostaglandin synthesis in the kidney. This effect is usually minor, reversible and associated with long-term therapy. Elderly patients, as well as those with impaired renal function, hepatic cirrhosis, and circulatory volume depletion are most at risk. Indometacin is the most commonly reported cause of NSAID-induced renal failure, and fenoprofen is the NSAID most commonly associated with interstitial nephritis and nephrotic syndrome.

Asthmatic patients can develop wheezing following the administration of NSAIDs, and aspirin will provoke or worsen asthma in approximately 5 per cent of patients.

DMARDs

DMARDs currently used in clinical practice include methotrexate, sulfasalazine, injectable or oral gold, antimalarials, ciclosporin, penicillamine, azathioprine and leflunomide. The choice of DMARD by individual clinicians depends upon the balance between adverse effects and efficacy. All the DMARDs possess a slow onset of action, and response to treatment is usually expected between four and six months. The dose of a DMARD should generally be titrated upwards as long as side effects allow.

In practice, the initial treatment of RA is

generally with a single agent. In many cases, if a satisfactory response is not achieved after a three to six months trial with monotherapy, combination treatment is then deployed. This is most likely to be a combination of sulfasalazine and methotrexate. Patients who fail to respond to such a combination will be offered other therapeutic options, such as leflunomide, before finally being offered tumour necrosis factor (TNF) blockade therapy.

Sulfasalazine and methotrexate are generally regarded as first line therapies due to their improved efficacy profile (approximately 40 per cent response rates) and high continuation rates compared to the other DMARDs.

Mechanism of action The precise mechanism of action of these drugs is unclear. All the DMARDs inhibit the release of, or reduce the activity of, inflammatory cytokines. Activated T-lymphocytes appear to be particularly important in this process and it is known that methotrexate, leflunomide and ciclosporin all inhibit T-cells. Cytokines, which appear to be important in the inflammatory cascade, include TNF, interleukin (IL)-1, IL-2, and IL-6. There is good evidence that DMARDs inhibit these cytokines *in vitro* and *in vivo*. Leflunomide has also been shown to inhibit the proliferation of B-cells, causing a reduction in antibody production.

Use of DMARDs The British Society for Rheumatology has published its recommendations on monitoring of DMARDs (see Table).

Patient information sheets and booklets are recommended for patients taking DMARDs. Counselling should reinforce the need to comply with monitoring requirements, the expected onset of action, and the potential toxicity and action to take in the event of adverse effects. Recently, there have been moves towards a shared care approach to managing patients receiving DMARDs. Medication may be supplied by a general practitioner but responsibility for monitoring and dosing remains with a hospital consultant. The aim of such schemes is to ensure that all patients receive adequate monitoring and specialist input without the inconvenience of frequent hospital visits.

Sulfasalazine is one of the most commonly prescribed DMARDs because it has a low risk of serious adverse effects and has been shown to slow disease progression. It is often used in mild to moderate disease. The monitoring requirements are less arduous than most other DMARDs, which is of significant benefit for patients. In order to reduce nausea, the dose is usually titrated from 500mg daily, increasing at weekly intervals up to 1g twice daily.

Methotrexate usage is increasing in the UK, and it is fast becoming first line therapy in most centres. It is generally used in patients with moderate to severe disease,

especially those with poor prognosis. It has a relatively rapid onset of action of four to six weeks and is easy to administer as a single weekly dose, given orally or by intramuscular or subcutaneous injection.

Hepatic fibrosis and liver toxicity can occur in a significant proportion of patients receiving methotrexate. Patients should be encouraged to avoid alcohol while on methotrexate, or at the very least, restrict it to special occasions. Liver function tests (LFTs) should be monitored frequently (see Table). Severe alveolitis can be a serious and sometimes fatal adverse event with methotrexate therapy, and requires urgent medical treatment. Patients should be advised to seek immediate medical attention and stop taking methotrexate if they experience worsening dyspnoea.

Nausea and stomatitis can be managed by the addition of folic acid to methotrexate therapy. The optimal dose has yet to be discovered but ranges from 5mg weekly to 5mg daily. A number of centres omit the folic acid on the day methotrexate is administered.

Bone marrow suppression is also a concern for patients receiving methotrexate therapy and can be related to either too high a maintenance dose or accidental overdose. This has occurred in patients who have inadvertently taken methotrexate daily rather than weekly or due to confusion between the 2.5mg and 10mg tablets, which is not uncommon in the elderly population.

Table: Dosage, side effects and monitoring guidelines for some DMARDs

Drug	Dosage	Side effects	Monitoring requirements*
Sulfasalazine	Initially 500mg once daily, increasing in weekly steps of 500mg to 1g twice daily	Nausea, reversible male infertility, rashes, marrow suppressions, hepatitis	FBC fortnightly. LFTs every four weeks for 12 weeks, then every three to six months
Methotrexate	5mg to 25mg once weekly	Rashes, nausea, stomatitis, marrow suppression, hepatitis, pneumonitis	FBC fortnightly for 12 weeks then LFTs monthly
Sodium aurothiomalate	10mg test dose, then 50mg weekly until signs of remission, then reduce frequency to monthly	Rashes, stomatitis, marrow suppression, proteinuria	FBC and urinalysis prior to each injection
Penicillamine	250mg to 750mg once daily (on empty stomach)	Rashes, taste disturbance, nausea, myositis, proteinuria, myasthenia, marrow suppression	FBC fortnightly until stable dose, then monthly. Weekly urinalysis
Ciclosporin	2.5mg per kg per day	Hirsutism, gingival hyperplasia, hypertension, renal impairment	Fortnightly U&Es, blood pressure and urinalysis for two months, and then monthly thereafter. Use baseline creatinine to alter dose
Leflunomide	Loading dose 100mg daily for three days, then maintenance dose of 10mg to 20mg per day	Gastrointestinal disturbances, alopecia, liver abnormalities, hypertension, marrow suppression	FBC, U&Es, LFTs and blood pressure monthly or more frequently (for example, fortnightly) during first six months, then at least every eight weeks thereafter
Azathioprine	1.5 to 2.5mg per kg per day	Nausea, hepatitis, cholestatic jaundice, marrow suppression	FBC, U&Es and LFTs fortnightly for two to three months, then every one to two months

*FBC = full blood count, LFT = liver function test, U&Es = urea and electrolytes

Patients must be strictly counselled on how many tablets to take and to take them once a week on the same day. Patients should be advised to seek medical help if they experience any signs of infection, such as unexplained fever or sore throat, and also to avoid contact with people who may have chickenpox.

Sodium aurothiomalate, or injectable gold, is an established DMARD that is effective in the treatment of RA, although its use is limited by its side effect profile. Compared with other DMARDs, patients are most likely to stop therapy with this drug due to toxicity. Important adverse events include rashes, stomatitis, proteinuria, leucopenia and thrombocytopenia. Despite this, injectable gold can provide benefit to some patients for many years and it can be useful in those with progressive disease which has failed to respond to other therapies.

Patients can be taught how to test their urine for proteinuria. If a significant amount of protein is detected, the gold therapy should be withheld, urinary tract infection excluded and the proteinuria quantified by means of urine collection over 24 hours. Patients on gold injections should also be asked to report any new side effects, such as rashes or mouth ulcers, to their general practitioner or rheumatology centre.

Auranofin, or oral gold, is a completely different drug entity to sodium aurothiomalate and, although less toxic, is also generally less effective than injectable gold. Adverse effects are similar to those of injectable gold but less frequent. The troublesome diarrhoea experienced with oral gold may be improved by taking a diet rich in fibre.

Penicillamine is now seldom used due to problems with toxicity and poor long-term efficacy. There is no evidence that penicillamine reduces joint erosions. It is initiated at a daily dose of 125mg, with monthly increases until a response is demonstrated. There is little benefit to be gained from increasing the dose above 750mg as the efficacy appears to have a "ceiling". Penicillamine should be taken on an empty stomach as absorption is reduced by up to 50 per cent when taken on a full stomach. The common adverse events include thrombocytopenia, proteinuria, taste disturbances and rashes. A less common side effect is neutropenia and rarely, there are autoimmune side effects (myositis, drug-induced lupus).

Cyclosporin is an immunosuppressive agent recently licensed for use in RA. It has proven efficacy in early and late disease but long-term data on reducing joint destruction is lacking. The lack of data and its potential toxicity means that cyclosporin is reserved for patients who have failed to respond to conventional therapies. Cyclosporin can cause nephrotoxicity and hypertension, which may have significant long-term consequences, and patients with a history of these conditions are generally

excluded from therapy. Treatment is initiated at a dose of 2.5mg per kg per day, and increased up to a maximum of 4.5mg per kg per day, depending on the patient's tolerance to the drug. There is no requirement to monitor ciclosporin blood levels in RA. Before commencing therapy, patients must have baseline blood pressure and creatinine measured, and both should be carefully monitored. Other side effects include hirsutism, tremor and gum hyperplasia.

The antimalarial agents (mainly hydroxychloroquine) are the least toxic of all the DMARDs. However, they are also the least effective and are generally reserved for less severe forms of the disease, or in combination regimens. Hydroxychloroquine generally requires little monitoring, and gastrointestinal toxicity is the main adverse effect. It seems that the retinopathy associated with this drug occurs only after high cumulative doses, and the need and frequency for eye tests is still being debated. The typical dose is around 400mg per day, although this has been increased to 800mg per day to achieve earlier efficacy.

Azathioprine is postulated to have a steroid-sparing effect and is of particular use when treating RA refractory to other agents. Cyclophosphamide, a potent cytotoxic agent, can be used either orally or as intravenous pulse therapy. It is used mainly in the management of rheumatoid vasculitis. Both azathioprine and cyclophosphamide have the potential to cause infertility and the development of malignancies. The risks of their use must therefore be carefully balanced against the intended clinical improvement.

Leflunomide is a relatively new DMARD that has both anti-inflammatory and immunomodulatory properties. It acts by inhibiting the synthesis of pyrimidine nucleotides in immune response cells, particularly T-cells. It reduces the pro-inflammatory cytokines TNF and IL-1. It is at least as effective as sulfasalazine and methotrexate, and there is some evidence that quality of life measures may be superior with leflunomide. It has a rapid onset of action (four weeks) and is well tolerated.

Leflunomide is given as a loading dose of 100mg daily for three days followed by 10mg to 20mg daily, although there may be local variations to this loading regimen.

The most common side effects are GI disturbances, reversible alopecia, rash and hypertension. There have been reports of serious liver reactions after treatment with leflunomide. LFTs should be checked at the initiation of treatment and at monthly intervals for the first six months of treatment and every eight weeks thereafter. If the enzyme alanine transferase (ALT) increases to more than twice the normal range then the dose can be reduced to 10mg daily and the LFTs monitored weekly. If the ALT level rises to three times the normal range, leflunomide should be discontinued.

Combination therapy There is some evidence that combination therapy with different DMARDs is more likely to achieve clinical improvement of the disease.¹¹ Combination therapy may offer better symptom control, particularly when agents with different modes of action are combined. To date, evidence supporting the efficacy of combination therapy is conflicting. In some studies, there have been no improvements in efficacy compared with monotherapy, and toxicity has been higher.^{12,13} Others have shown impressive benefits.¹⁴ A triple regimen of hydroxychloroquine, methotrexate and sulfasalazine has shown significant improvements compared with monotherapy using the individual agents.¹⁵ This combination regimen was also well tolerated.

A "step-down" approach, where DMARDs are given as combination therapy from the outset of treatment and then tapered down, has shown improvements in disease activity. Sulfasalazine, methotrexate and prednisolone have been used in this way with some success. A more common approach in the UK is to use the "step-up" regimen. Here, treatment is commenced with monotherapy, and a second agent added if the first is ineffective or if there is a partial response. Methotrexate with ciclosporin has been shown to be effective in this way, as has methotrexate with sulfasalazine.

— STEROIDS

Systemic corticosteroids have long been used in the management of RA and were the first drugs to result in reversibility of the disease. However, their place in therapy is still controversial.

Corticosteroids suppress cytokines and produce a rapid improvement in signs and symptoms of the disease. They have a potent anti-inflammatory effect and recent studies have suggested a slowing of radiological progression.¹⁶ Unfortunately, the side effects associated with long-term, high-dose therapy, (for example, osteoporosis, diabetes mellitus, hypertension) have severely limited the long-term role of corticosteroids in RA. Therefore, details such as the dosage and duration, as well as the stage of disease that corticosteroids should be used in, are still open to debate.

Place in therapy Oral prednisolone can be used to provide temporary relief until a DMARD becomes effective, or in patients with aggressive disease who cannot be adequately controlled with a combination of DMARDs ("step-up" or "step-down" approach). Once commenced, systemic corticosteroids can be difficult to withdraw, as the disease tends to flare with dose reductions.

In order to minimise side effects, a daily

maintenance dose of 7.5mg of prednisolone or less, given as a single dose in the morning, should be used. Prophylaxis against osteoporosis is recommended in patients likely to be on long-term therapy.

Intra-articular steroid administration can effectively relieve pain, increase mobility and reduce deformity in one or more joints. Examples of drugs that are given via this route are methylprednisolone acetate, triamcinolone acetonide and triamcinolone hexacetonide. The duration of response to intra-articular steroids is variable, and triamcinolone hexacetonide may produce the greatest response. The dose used is dependent upon the joint size. Methylprednisolone acetate 40mg or triamcinolone hexacetonide 20mg are suitable for use in large joints (for example, knees). The frequency with which injections can be given is controversial, but repeated injections are usually given at intervals of one to five weeks or more, depending on the degree of relief obtained from the first injection. Intramuscular steroids may be useful in patients with an acute flare of disease, and intravenous pulses of methylprednisolone are particularly helpful in controlling rheumatoid vasculitis.

TNF BLOCKADE

At the present time, agents for TNF blockade are only used in patients that are resistant to, or fail conventional disease-modifying treatment. This approach may change in the future if current trials demonstrate a benefit of using these agents earlier in disease.

There are currently two TNF-alpha blocking agents available. Infliximab (Remicade) is given by infusion and etanercept (Enbrel) by twice-weekly subcutaneous injections. The third article, which begins on page 16 of this special feature, discusses these new agents in more detail.

Anakinra Anakinra is expected to become available early next year. While TNF-alpha is believed to mediate inflammation in RA, IL-1 appears to mediate bone and cartilage destruction.

Anakinra is an IL-1 receptor antagonist. The likely place in therapy for IL-1 receptor antagonists such as anakinra is in cases where TNF blockade fails. However, further

research is required to identify the role of these agents.

SUMMARY

The treatment of RA has changed significantly over the past decade. Treatment is now more aggressive in early disease, with disease-modifying agents being introduced much earlier in treatment. There have also been many developments both in the treatment of disease and control of symptoms. New agents such as leflunomide and TNF-alpha blockers have increased treatment options for patients.

There are many products currently undergoing research, and undoubtedly, research into RA will continue to develop. This is expected to be of considerable benefit for patients, but there will also be significant cost for health care providers.

REFERENCES

1. Fuchs HA, Kaye JJ, Callahan LE, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first two years of disease. *J Rheumatol* 1989;16:585-91.
2. Corte LC, Caselli M, Castellino G, Bajocchi G, Trotta F. Prophylaxis and treatment of NSAID-induced gastroduodenal disorders. *Drug Safety* 1999;20:527-43.
3. Hawkey CJ. Progress in prophylaxis against non-steroidal anti-inflammatory drug associated ulcers and erosions. Omeprazole NSAID Steering Committee. *Am J Med* 1998;104: 67S-74S, 79S-80S.
4. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ et al. For the omeprazole vs misoprostol for NSAID-induced ulcer management (OMNIUM) study group. *N Engl J Med* 1998;338:727-34.
5. Rose P, Huang B, Lukasik N, Collis C. Evidence that lansoprazole is effective in preventing NSAID-induced ulcers. *Gastroenterology* 1999;116:A295.
6. French PC, Darekar B, Mills JG, Wood JR. Ranitidine in the prevention of non-steroidal anti-inflammatory drug associated ulceration in arthritic patients. *Eur J Gastroenterol Hepatol* 1994;6:1141-7.
7. Koch M, Dezi A, Ferrario F, Capurso I. Prevention of non-steroidal anti-inflammatory drug induced gastrointestinal mucosal injury. *Arch Intern Med* 1996;156:2321-32.
8. Technology Appraisal Guidance Number 27. Guidance on the use of cyclo-oxygenase (COX) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. London: National Institute for Clinical Excellence;2001.
9. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B et al. Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in patients with Rheumatoid Arthritis. For the VIGOR study group. *New Engl J Med* 2000;343:1520-8.
10. Silverstein FE, Faich G, Goldstein JL, Simon L S, Pincus T, Whelton A et al. Gastrointestinal toxicity with celecoxib versus non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomised controlled trial. *JAMA* 2000;284:1247-55.
11. Machold KP, Eberl G, Leeb BF, Nell V, Windisch B, Smolen JS. Early arthritis therapy: rationale and current approach. *J Rheumatol* 1998;25(Suppl 53):13-9.
12. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. *Arthritis and Rheum* 1994;37:1487-91.
13. Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double-blind 52-week clinical trial of sulfasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;58:220-5.
14. Verhoeven AC, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. *Br J Rheumatology* 1998;37:612-9.
15. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Laasonen L et al. Comparison of combination therapy with single drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999;353:1568-73.
16. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;333:142-6.