REVIEW ARTICLE

Drugs 1998 Sep; 56 (3): 337-344
0012-6667/98/0009-0337/$08.00/0



# Disease-Modifying Antirheumatic Drugs

## Using Their Clinical Pharmacological Effects As a Guide to Their Selection

*Christopher G. Jackson*[1] and *H. James Williams*[2]

1 University of Utah School of Medicine, Salt Lake City Veterans Affairs Hospital, Salt Lake City, Utah, USA

2 Thomas E. and Rebecca D. Jeremy Presidential Chair for Arthritis Research, University of Utah School of Medicine, Salt Lake City, Utah, USA

## Contents



## Abstract

Rheumatoid arthritis is a disease of unknown aetiology characterised by persistent joint swelling, functional disability and increased mortality. No curative therapy exists at present but some therapeutic agents, commonly referred to as disease-modifying drugs, offer the potential for suppression of the inflammatory activity and attenuation of the disease process.

Since the precise mechanism of action of most disease modifying drugs is uncertain, the selection of a particular therapy must at present be based on the pharmacologic properties of each available agent, appropriately individualised for each clinical setting. The toxicity of disease-modifying agents often limits the dose and/or duration of therapy and makes careful monitoring mandatory.

No consensus exists as to the order in which disease-modifying agents should be employed. Less toxic disease-modifying drugs such as auranofin, hydroxychloroquine, minocycline, and sulfasalazine are usually used in early and mild disease. Azathioprine, penicillamine (D-penicillamine), methotrexate and parenteral gold are usually considered to be more toxic and are most often used in the setting of progressive disease while the most toxic agents, such as chlorambucil and cyclophosphamide, are reserved for life-threatening manifestations such as vasculitis.

Newer therapeutic approaches presently under study include the use of existing drugs in combination and novel biologic agents which selectively inhibit lymphocyte and cytokine activity. These strategies offer the hope of more efficacious and less toxic therapy in the future.

Despite an increasing understanding of the immune and inflammatory mechanisms which underlie its clinical manifestations, the aetiology and precise pathogenesis of rheumatoid arthritis (RA) remain unknown. Delineation of the influence of genetic background on susceptibility, and the host/environment interactions which permit autoimmune stimuli to endlessly trigger the inflammatory cascade, continues to be the major thrusts of present research. The clinical hallmark of RA is persistent synovial inflammation of diarthrodial joints which results in some degree of irreversible joint damage in the majority of patients. The course of the disease in each individual patient, however, is highly variable, ranging from spontaneous remission in some to relentless progression in others, resulting in joint deformity, functional disability and increased mortality.[1]

There is as yet neither a cure for RA nor any preventive strategies which reduce the risk of contracting the disease. Lacking the capacity to terminate the pathological process, present therapy can only attempt to reduce symptoms and attenuate joint damage by controlling inflammatory activity. All current treatment is empirical in origin and selection of the most appropriate therapeutic intervention is determined by the activity and stage of the disease as well as the pharmacological profile of each agent and treatment regimen. The varying nature of the disease, both from patient to patient and longitudinally within the same patient, together with the wide array of unrelated but concomitant medical problems, requires that the clinician individualise therapy for each patient and clinical setting.

## 1. Current Treatment Options

The currently available treatments for RA are usually divided into 2 categories, one being those agents which afford only symptomatic relief [aspirin (acetylsalicylic acid), nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids] and the other being those agents which may affect disease modification. This latter group are also referred to as 'slow-acting' antirheumatic drugs because of their relatively protracted onset of action. Some prefer to call them 'second-line' agents, feeling that actual disease modification has yet to be unequivocally demonstrated. While an agent that provides symptomatic relief alone may be sufficient for early or mild disease, a disease-modifying agent or regimen will give most benefit in association with concurrent symptomatic therapy unless a contraindication to their combined use exists.

### 1.1 Diagnosis

The process of determining when second-line drug therapy is appropriate begins with the establishment of an accurate diagnosis and assessment of the most likely prognosis. The clinical manifestations of early RA can be extremely subtle and no single clinical finding or laboratory abnormality by itself is diagnostic. A firm diagnosis becomes possible only when a sufficient number of clinical findings have appeared and established diagnostic criteria are satisfied.

A distinctive pattern of joint erosion can be seen radiographically but such a pattern is rarely present in early disease and is, therefore, of little help diagnostically. Because these erosive changes in reality represent the very damage that disease-modifying therapy is intended to limit, uniformly delaying the institution of second-line therapy until characteristic x-ray changes appear is conceptually a self-defeating approach. Nevertheless, the clinical appearance of RA does become more distinctive as the disease evolves and initiation of a second-line agent should ordinarily be delayed until the diagnosis is no longer in doubt.

### 1.2 Prognosis

Determining the most likely clinical course for patients with early RA is difficult and requires careful longitudinal observation combined with thoughtful integration of clinical, laboratory and radiographic data. Three broad patterns of clinical disease activity, often referred to as 'long clinical remissions', 'intermittent disease' and 'progressive disease', generally emerge early on in the RA population. It is patients who develop the pattern of 'progressive disease' as well as those with more severe 'intermittent disease' who require the efficacy of disease-modifying drug therapy and in whom their associated toxicities can best be justified.

Demographic features which portend a worse prognosis in early RA include a younger age at the time of onset and the patient's sex, women generally having a poorer prognosis than men of comparable age.[2] The actual significance of the individual's genetic makeup remains unclear but certain HLA alleles, most notably DR-4, have been associated with more serious disease.[3] The presence of rheumatoid factor and the appearance of rheumatoid nodules are also associated with a poorer outcome, as is the presence of thrombocytosis and an elevated acute phase reactant such as the erythrocyte sedimentation rate or the C-reactive protein.[4] No finding is more ominous, however, than the persistence and worsening of synovial proliferation (the increase in synovial tissue mass that occurs with chronic inflammation due to the formation of synovial villi with dense cellular infiltrates), which underscores the importance of careful longitudinal joint evaluation.

### 1.3 Timing

The optimal time to initiate disease-modifying therapy is after a clinical pattern of aggressive inflammation becomes evident but before irreversible mechanical damage is inevitable. This may, in fact, be a very small window in time and the early identification of aggressive disease remains at present a very difficult and subjective determination. When initiating or changing disease-modifying therapy in the patient with more advanced RA who has some degree of mechanical joint abnormality, the clinician must be sure that a reasonable potential for favourable response to treatment exists, i.e. a reduction in synovial inflammation will only result in significantly improved joint function if the mechanical integrity of the joint is sufficiently intact.

## 2. Criteria for Drug Selection

With present therapies, the most important pharmacological consideration in selecting a particular disease-modifying agent is an analysis of the probable efficacy versus possible toxicity. A selection based on the mechanism of action of a particular agent is regrettably not possible at present because neither the pathogenesis of the disease nor the actual biological effect of most agents is well enough understood. It is hoped that continued research will allow this to become the basis of selection in the not too distant future.

The efficacy and toxicity of current disease-modifying regimens are roughly equivalent, less efficacious agents being generally less toxic while more efficacious agents are usually more toxic. This characteristic heightens the importance of an accurate clinical assessment so that the therapy instituted will have the needed potency but will not expose the patient to unwarranted toxicity. For example, the efficacy of an alkylating agent may be needed if potentially life-threatening disease is present but its considerable toxicity renders it unacceptable in more mild disease. Conversely, the safety of an antimalarial agent makes it appropriate for mild disease but its relative lack of efficacy renders it insufficient in life-threatening disease. Thus, the selection of any agent or regimen can only be considered appropriate if the anticipated efficacy is sufficient to control the inflammatory activity and the probable toxicity does not exceed in severity the morbidity of the untreated disease.

While most rheumatologists prefer to use a less toxic agent initially and reserve agents with more serious toxicity for patients who demonstrate refractory disease, there is certainly no consensus as

to which second-line agent (or agents) should be used first or in what subsequent order. Further, suboptimal clinical outcomes are sufficiently common that more aggressive strategies which employ the early institution of more potent (and more toxic) agents either singly or in combination have been proposed. The actual efficacy and toxicity of these regimens in early disease are not fully known and most would agree that their use should be confined to formal clinical investigation for the present time.

The available disease-modifying agents can be divided into 3 categories on the basis of their potential for toxicity, namely, those which are 'more safe', those which are 'more toxic', and those which are 'very toxic'. Combinations of existing second-line agents as well as regimens which add new agents to existing therapy should be considered in the 'very toxic' group until more complete efficacy and toxicity data are available. While some second-line agents have yet to receive formal approval for use in the treatment of RA from regulatory agencies such as the FDA in the US, all the regimens discussed below have been shown in controlled trials to be efficacious and have fairly well understood toxicity profiles. Nonetheless, the need to appropriately individualise each therapeutic decision cannot be overemphasised.

## 2.1 'More Safe'

Those second-line agents usually included in the 'more safe' group include auranofin, hydroxychloroquine, minocycline, and sulfasalazine.

### 2.1.1 Auranofin

Auranofin is the only gold-salt preparation which can be taken orally. Sulfhydryl-containing organic gold compounds have been used in the treatment of RA with benefit since the 1920s. Gold metabolism is complex and yields several metabolites which vary in concentration in different tissues but no specific site or mechanism of action has been conclusively identified. Compared with parenteral gold, auranofin is less toxic but probably less efficacious as well, as evidenced by a comparative study where injectable gold but not auranofin appeared to reduce the rate of bony erosions.[5] The time to clinical response for auranofin ranges from 3 to 6 months after initiation of therapy, somewhat longer than is typically seen with parenteral gold. Diarrhoea is not uncommon but generally responds to a reduction in dose. Mucosal ulcerations and skin rashes occur with a frequency similar to that seen with injectable gold while bone marrow dysfunction and proteinuria are distinctly less common.[5] A monthly complete blood count (CBC) and urinalysis are required for adequate monitoring. Institution of auranofin is most often considered in the patient with mild disease and a favourable prognosis who is not adequately controlled with NSAIDs alone.

### 2.1.2 Hydroxychloroquine

Hydroxychloroquine is an antimalarial compound which may exert its beneficial effect in RA by suppression of lysosomal enzymes and inhibition of interleukin (IL-1) release. It is generally very well tolerated, with the most worrisome toxicity being ophthalmological. The potential for irreversible retinopathy appears to increase with the size of the daily dose and the duration of therapy. Ophthalmological screening on an annual basis has been recommended for those patients receiving a daily dose greater than 6.5 mg/kg or those with a duration of therapy longer than 10 years,[6] and may not be necessary for patients who have normal renal function, a daily dose less than 6.5 mg/kg, and a cumulative dose under 200g.[7] Hydroxychloroquine is usually considered for patients with more mild disease but should be used with caution if a concurrent ophthalmological condition exists which might obscure early retinal toxicity.

### 2.1.3 Minocycline

Minocycline is an antibiotic of the tetracycline class which was recently studied in a large, multicentre trial and appeared to be efficacious in a patient population with very early and mild disease.[8] A mechanism of action in RA is not clear but, in addition to their well known antimicrobial properties, the tetracyclines have demonstrated anticollagenase activity.[9] Minocycline is generally well tolerated although dizziness is not uncommon and

abnormal liver function tests have been observed. Until this drug has been studied in a population with more severe disease, the use of minocycline should probably be restricted to patients with early and mild RA.

#### 2.1.4 Sulfasalazine

Sulfasalazine was specifically developed as an antirheumatic drug but its actual mechanism of action is unknown and may well be different in RA from that in inflammatory bowel disease. It comprises anti-inflammatory [mesalazine (5-aminosalicylic acid)] and antibacterial (sulfapyridine) moieties with the antimicrobial portion probably responsible for the efficacy seen in RA.[10] Sulfasalazine-induced changes in the faecal flora are of uncertain clinical significance as are very modest effects on polymorphonuclear leukocyte (PMN) migration and lymphocyte response.

Sulfasalazine appears to be comparable with parenteral gold in efficacy but is much better tolerated.[11] However, one-quarter of all patients still develop adverse reactions severe enough to discontinue therapy, with gastrointestinal complaints being most common and leukopenia most serious. Recommended monitoring consists of a CBC and transaminase determinations every 2 to 4 weeks for the first 3 months of treatment and at least quarterly thereafter. Most rheumatologists prefer to use sulfasalazine in mild to moderately severe disease and in Europe it has become the disease-modifying agent most often prescribed in this clinical setting. The relatively infrequent monitoring requirements make it particularly useful when logistical constraints such as distance or restricted insurance coverage make access to healthcare difficult.

### 2.2 'More Toxic'

The disease-modifying agents included in the 'more toxic' group include azathioprine, penicillamine (D-penicillamine), methotrexate and parenteral gold.

#### 2.2.1 Azathioprine

Azathioprine is an oral purine analogue which inhibits lymphocyte proliferation, presumably by disrupting the incorporation of adenosine and guanine in DNA synthesis. Its efficacy in the treatment of RA is comparable with that of parenteral gold and penicillamine but with greater toxicity.[12] Nausea, vomiting and diarrhoea are not uncommon and the potential for bone marrow suppression and hepatic inflammation make a CBC and transaminase determinations necessary on a monthly basis. The most serious toxicity concern, however, is the development of lymphoproliferative cancers. Uncertainty exists as to the actual risk, as a recent and ongoing observation has failed to identify any increase in malignancy – which contrasts with previous data.[13,14] Most rheumatologists prefer at present to reserve the use of azathioprine for patients with progressive disease which has proven refractory to other second-line agents of comparable potency.

#### 2.2.2 Penicillamine (D-Penicillamine)

Penicillamine is a chelator of divalent cations which is structurally similar to cysteine. While it has been shown to impair antigen presentation, to diminish globulin synthesis and to inhibit PMN myeloperoxidase, no certain mechanism of action is known. Comparable with gold in efficacy, the use of penicillamine is often limited by toxicity.[15] In addition to immune complex–induced glomerulonephritis and bone marrow suppression, a number of autoimmune syndromes are also seen.[16] Monthly monitoring is required and consists of a CBC, a urinalysis and careful clinical evaluation. The use of penicillamine has decreased considerably, particularly in the US, with the advent of agents such as methotrexate and sulfasalazine which have comparable potency with better tolerability.

#### 2.2.3 Methotrexate

Methotrexate is an antimetabolite which impairs DNA synthesis by competitively inhibiting folic acid metabolism. Recent studies have additionally demonstrated an anti-inflammatory action which is mediated through adenosine and appears to decrease the secretion of proinflammatory cytokines such as tumour necrosis factor (TNF) while increasing the secretion of IL-10.[17] Supporting

this putative mechanism of action in RA is the observation that adenosine receptor antagonists appear to reverse the beneficial effect of both methotrexate and sulfasalazine in animal models of inflammation.[18]

Low dose pulse administration of methotrexate has proven to be extremely well tolerated, especially in comparison with other second-line agents of similar potency.[19] Stomatitis is not uncommon but often responds to folic acid supplementation with no reduction in control of the joint disease. Bone marrow suppression is infrequent at the dosages employed for RA. A hypersensitivity pneumonitis has been well described and should be considered in any patient who develops cough or dyspnoea. The toxicity of greatest concern, however, continues to be liver dysfunction but uncertainty remains as to the actual frequency of hepatic fibrosis and the relative risk of cumulative methotrexate dose, obesity, alcohol (ethanol) intake and diabetes mellitus. Published guidelines recommend that a CBC be obtained every 4 weeks and transaminase levels determined every 8 to 12 weeks.[20] In the US and elsewhere, methotrexate has become the agent most preferred by many rheumatologists for the treatment of patients with moderate to severe disease.

#### 2.2.4 Parenteral Gold

Parenteral gold has been demonstrated to affect the activity of B and T lymphocytes as well as PMN function. Injectable gold was the first second-line agent to have its benefit in RA established in a clinical trial,[21] and still represents an important standard for comparing the efficacy of other second-line agents. However, newer therapies, namely methotrexate and sulfasalazine, are equally efficacious but less toxic, making the current use of parenteral gold much less frequent. Bone marrow dysfunction and proteinuria from membranous glomerulonephritis require that a CBC and urinalysis be obtained before every injection. While these more serious toxicities as well as stomatitis and rash limit the number of patients who can tolerate parenteral gold long term, gold salts should still be considered in the patient with progressive disease, especially when other second-line agents have not been beneficial.

### 2.3 'Most Toxic'

Those second-line agents considered to be 'most toxic' include cyclosporin and the alkylating agents chlorambucil and cyclophosphamide. As noted above, combination therapy and biological agents also belong in this category until more complete efficacy and toxicity data are available.

#### 2.3.1 Cyclosporin

Cyclosporin is a fungal peptide which impairs the function of B and T lymphocytes by suppressing the synthesis and release of IL-1 and IL-2.[22] It appears to have efficacy comparable with that of other second-line agents but is less well tolerated due to hypertension and nephrotoxicity which are common and usually dose-related. For this reason, cyclosporin may have its greatest utility in combination with other, better tolerated second-line therapies where a smaller and less toxic dose of it can be employed.

#### 2.3.2 Chlorambucil and Cyclophosphamide

Chlorambucil and cyclophosphamide interrupt DNA and RNA metabolism, resulting in cell death and decreased numbers of B and T lymphocytes. Clinical improvement can be dramatic but chromosomal damage leads to an increased risk of malignancy, especially haematological. Other toxicities seen with some frequency include bone marrow suppression, increased risk of infection and disruption of gonadal function. Most agree that the use of alkylating agents can only be justified in the setting of life-threatening disease such as vasculitis.

## 3. Combination and Biological Therapy

The notion that agents could be combined to achieve improved efficacy without a corresponding increase in toxicity has been present for some time. Interest in this approach has continued to grow with the recognition that present single-drug regimens fail to induce a remission, or even acceptable control, in a significant number of patients. The rationale for which agents to use together and

for how long is empirical. Various combinations have been reported but seldom have the trials been of sufficient size or design to permit conclusive evaluation.

A meta-analysis in 1994 of the published experience with combination therapy suggested no benefit in comparison with single-drug therapy.[23] A recent, randomised trial has evaluated the combination of methotrexate-sulfasalazine-hydroxychloroquine against the combination of sulfasalazine-hydroxychloroquine as well as methotrexate alone.[24] After treatment for 2 years, statistically significant improvement was greater in the 3-drug arm than in the 2-drug arm, and greater in the 2-drug arm than with methotrexate alone. No increase in withdrawals due to toxicity was seen in the arms employing combination therapy. However, further study is needed to corroborate these results and identify the most appropriate patient population as well as the optimal time for initiation of therapy.

Another approach to combination therapy employs the addition of a second agent when response to an initial single agent has been incomplete. In a 6-month trial of patients with active disease despite therapeutic doses of methotrexate, the addition of cyclosporin produced significant improvement versus placebo without incurring additional toxicity.[25] While these results need to be confirmed and extended, the adjunctive use of low dose cyclosporin in the patient with incomplete response to methotrexate appears to be a promising approach.

A newer form of therapeutic intervention uses biological agents which are specifically designed to target elements important to the immune and inflammatory responses. These agents seem to offer the potential for greatly improved efficacy with decreased toxicity. The initial experience with monoclonal antibodies directed against lymphocyte subsets proved discouraging in that significant lymphocyte depression was achieved but did not produce meaningful clinical improvement.[26] However, recent pilot studies with agents directed against cytokines and cytokine receptors have been somewhat more promising.[27] Much of the interest at present centres around the proinflammatory cytokines TNF-$\alpha$ and IL-1. Several controlled trials which are currently under way are using antagonists to these cytokines and/or their receptors either as sole therapy or in addition to an established agent such as methotrexate. No biological therapies have yet been released for use other than in an approved clinical trial.

## 4. Conclusion

Continuing advances in both basic and clinical research will, it is to be hoped, allow treatment decisions in the near future to be based on the pathogenesis of RA and well understood mechanisms of drug action rather than empiricism. In the interim, however, the appropriate selection of a disease-modifying regimen in RA must rely on a careful efficacy/toxicity analysis of the available treatment options individualised for each patient. Fundamental and indispensable to this analysis is a thorough understanding and thoughtful consideration of both the clinical setting and the pharmacological properties of each disease-modifying agent.

## References

1. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously: predictive markers, socioeconomic status and comorbidity. J Rheumatol 1986; 13: 841-5
2. Wolfe R, Hawly DJ. Remission in rheumatoid arthritis. J Rheumatol 1985; 12: 245-52
3. Walport MJ, Ollier WER, Silman AJ. Immunogenetics of rheumatoid arthritis and the Arthritis and Rheumatism Council's national repository. Br J Rheumatol 1992; 31: 701-5
4. Masi AT, Maldonado-Cocco JA, Kaplan SB, et al. Prospective study of the early course of rheumatoid arthritis in young adults: comparison of patients with and without rheumatoid factor positivity at entry and identification of variables correlating with outcome. Semin Arthritis Rheum 1976; 5: 299-326
5. Ward JR, Williams HJ, Egger MJ, et al. Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1983; 26: 2446-9
6. Levy GD, Munz SJ, Paschal J, et al. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. Arthritis Rheum 1997; 40: 1482-6
7. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. Ann Rheum Dis 1997; 56: 188-90
8. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis: a 48 week, double blind, placebo controlled trial. Ann Intern Med 1995; 122 (2): 81-9

9. Greenwald RA, Golub LM, Lavietes B, et al. Tetracyclines inhibit human synovial collagenase *in vivo* and *in vitro*. J Rheumatol 1987; 14: 28-43
10. Pullar T, Hunter JA, Capell HA. Which component of sulphasalazine is active in rheumatoid arthritis? Clin Res 1985; 290: 1535-8
11. Williams HJ. Comparisons of sulfasalazine to gold and placebo in the treatment of rheumatoid arthritis. J Rheumatol 1988; 15: 9-13
12. Berry H, Liyange SP, Durance SA, et al. Azathioprine and penicillamine in treatment of rheumatoid arthritis: a controlled trial. BMJ 1976; I: 1052-4
13. Hickey A, Urowitz M. The rheumatoid arthritis azathioprine registry – interim analysis of malignancy and mortality. Arthritis Rheum 1996: 39: S1521
14. Silman AJ, Petrie J, Hazleman B. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow-up study. Ann Rheum Dis 1997; 47: 988-92
15. Paulus HE, Williams HJ, Ward JR, et al. Azathioprine versus D-penicillamine in rheumatoid arthritis patients who have been treated unsuccessfully with gold. Arthritis Rheum 1984; 27 (7): 721-7
16. Jaffe IA. Induction of auto-immune syndromes by penicillamine therapy in rheumatoid arthritis and other diseases. Semin Immunopathol 1981; 4: 193-207
17. Cronstein BN. Molecular therapeutics: methotrexate and its mechanism of action. Arthritis Rheum 1996; 39: 1951-60
18. Gadangi P, Longaker M, Naime D, et al. The anti-inflammatory mechanism of sulfasalazine is related to adenosine release at inflamed sites. J Immunol 1996; 156: 1937-41
19. Pincus T, Marcum SB, Callahan J. Long-term drug therapy for rheumatoid arthritis and in seven rheumatology private practices. II. Second line drugs and prednisone. J Rheumatol 1992; 19: 1885-94
20. Kremer JM, Alarcon GS, Lightfoot Jr RW, et al. Methotrexate for rheumatoid arthritis – suggested guidelines for monitoring liver toxicity. Arthritis Rheum 1994; 37: 316-28
21. Kean WF, Forestier F, Kassam Y, et al. The history of gold in rheumatoid arthritis. Semin Arthritis Rheum 1985; 14: 180-6
22. Shevach EM. The effects of cyclosporin A on the immune system. Annu Rev Immunol 195; 3: 397-423
23. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis: a meta-analysis. Arthritis Rheum 1994; 37: 1487-91
24. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996; 334: 1287-91
25. Bensen W, Tugwell P, Roberts RM, et al. Combination therapy of cyclosporine with methotrexate and gold in rheumatoid arthritis (2 pilot studies). J Rheumatol 1994; 21: 2034-8
26. Olsen NJ, Brooks JJ, Cush PE, et al. A double-blind, placebo-controlled study of anti-CD5 immunoconjugate in patients with rheumatoid arthritis. Arthritis Rheum 1996; 39: 1102-8
27. Campion GV. The prospect for cytokine base therapeutic strategies in rheumatoid arthritis. Ann Rheum Dis 1994; 53: 485-7

Correspondence and reprints: Professor *H. James Williams*, Division of Rheumatology, University of Utah, 50 North Medical Drive, Salt Lake City, UT 84132, USA.