

Reviews

The use of suppressive agents for the treatment of rheumatoid arthritis

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Rheumatoid arthritis (RA) has a prevalence of approximately 2% in our community. The aetiology of RA is complex but involves amongst other things interactions between Class II antigens on synovial cells and activated T lymphocytes.¹ The initiating factors for the inflammation in RA are not known but a variety of infectious agents have been implicated. The inflammatory process triggered by this initiating event involves a large number of different types of cells and mediators which interact together to produce joint destruction and subsequent disability. Some of the cells and mediators involved in RA are shown in Table 1. Since we are at present unable to identify the cause of RA, therapy must be directed at these cells and the mediators in an effort to reduce or prevent joint damage. From Figure 1 it can be seen that there are a number of different pathways by which joint destruction can occur. These processes are complex and interacting and it is unlikely that a single pharmacological intervention will suffice to control this process.² However, if we are going to treat RA we should try to use drugs which suppress that inflammation and therefore attempt to prevent subsequent disability.

Although this paper addresses the issue of slow-acting anti-rheumatic drugs (SAARDs) used in the management of RA it cannot be done in isolation from other treatment modalities such as non steroidal anti-inflammatory drugs (NSAIDs) and physical therapies. Prostaglandins have significant effects on immune responses and thus NSAIDs which interfere with prostaglandin production may produce mild immunomodulation.³ It is now clear that NSAIDs have many effects other than merely interfering with prostaglandin synthesis, including modifying lymphocyte function, leukotriene production and other cell membrane activity.³ In the past NSAIDs

were used as the initial treatment of RA with SAARDs being used after a trial of NSAIDs had failed to suppress inflammation. Most rheumatologists now use SAARDs at a very early stage in the disease in an effort to control synovitis. When considering the issue of SAARD use in RA we need to consider three questions.

- ① When do we use SAARDs?
- ② How do we choose a SAARD?
- ③ How often and what do we monitor?

To these questions can be added other issues such as how do we know that a SAARD is working and when or should we stop a SAARD. This review will first address prognosis in RA because it is on this that many of the principles of SAARD use are justified. Individual SAARDs will then be discussed from the point of view of their pharmacokinetics and pharmacodynamics, their adverse reactions and practical prescribing issues. An important feature to realise about the choice between SAARDs is that it is empirically based because controlled trial evidence of comparative efficacy is not available or demonstrates no difference between agents. This is often due to a type 2 error in the trial design but within the trials individual patients show marked variability in response.

PROGNOSIS

Up until the last decade it was generally accepted that RA was in many cases a mild disease with frequent remissions.⁴ Recently, however, it has become apparent that RA does have considerable mortality and morbidity. In a 20 year follow-up of 112 patients with RA 35% of the patients were dead and 19% severely disabled despite the use of SAARDs.⁵ Mitchell *et al.*⁶ demonstrated a median reduction in life span of four

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TABLE 1
Cells and Mediators Involved in RA

| Cells | Mediators |
|------------------------------|-----------------------------|
| macrophages | prostaglandins |
| lymphocytes | leukotrienes |
| polymorphonuclear leucocytes | cytokines |
| platelets | kinins |
| fibroblasts | platelet activating factors |
| mast cells | lysosomal enzymes |
| chondrocytes | oxygen radicals |
| endothelial cells | |

years in men and ten years in women with RA and this increased mortality has been confirmed by other groups. Increased morbidity with a significant effect on work capacity has also been reported. Yelin *et al.*⁷ have shown that 50% of RA patients were unable to work ten years after diagnosis. From these data it would seem clear that the prognosis of RA is not good and that patients with definite RA rarely remit.⁸

The development of cartilage and bone erosions have been a major diagnostic and prognostic feature of RA. Brook and Corbett⁹ showed that if bony erosions occur in RA they do so in the majority within the first two years of disease onset. Bony erosions progress in many patients but there is some suggestion that the number of new erosions will level off after the first year

although the area of an individual erosion may continue to increase.¹⁰ If one accepts that a principal role of SAARDs is to reduce synovitis and subsequent bony erosion then it is obvious that they have to be used early in the treatment of RA rather than late, in an effort to decrease subsequent bone erosion. The problem is that the evidence for SAARDs, as currently used, to reduce erosions is slight. The traditional pyramidal approach to the management of RA where one commences with NSAIDs and then moves to the SAARDs using corticosteroids (either intra-articularly or orally) for flares as demonstrated in Figure 2 is currently being challenged. With the advent of SAARDs which work more rapidly with fewer serious side-effects it is being suggested that SAARDs be used at a very early stage in the management of RA.^{11,12} With this strategy SAARDs and steroids are used early and then withdrawn as the disease (hopefully) comes under control. Although this concept has not been universally adopted, appreciation of the increased mortality and morbidity of RA is encouraging more rheumatologists to adopt the principles of early SAARD therapy.

Over the last decade, an increasing number of SAARDs have become available (Table 2). This has enabled less toxic SAARDs to be used early in the disease without significant anxiety regarding serious

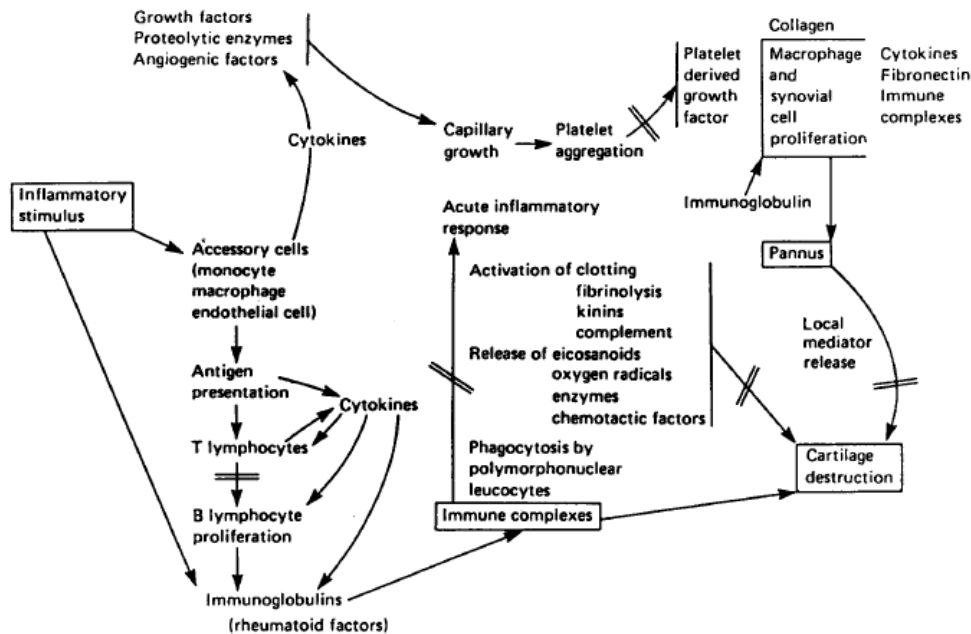


Figure 1: Pathways to joint destruction in rheumatoid arthritis from Forrest and Brooks 1988² with permission.

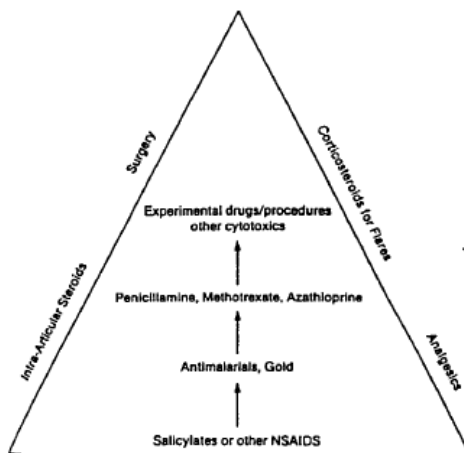


Figure 2: Traditional pyramidal approach to the therapy of rheumatoid arthritis from Wilske and Healey 1989¹¹ with permission.

adverse drug reactions. It has also created dilemmas as to which SAARD to use in any given situation although patients seem to respond individually to these drugs both in terms of efficacy and side-effects. More recently we have seen the use of combinations of SAARDs rather than single agents. This has been based on the hope that drugs having different mechanisms of action and spectrum of side-effects might produce an additive effect on the inflammatory disease without increasing toxicity.

A great deal of the debate regarding treatment of RA is now shifting from the specific question of which drug should be used to a more general issue of different strategies. This would include early use of SAARD within three months of polysynovitis commencing, or use of combination therapy. Although these questions are fundamental to our understanding of the management of RA it should be appreciated that these strategies have not yet been adequately assessed.

The individual SAARDs will now be reviewed.

TABLE 2
Slow-Acting Anti-Rheumatic Drugs

| Group 1 | Group 2 | Group 3 |
|--------------------|--------------------|------------------|
| oral gold | intramuscular gold | corticosteroids |
| hydroxychloroquine | d-penicillamine | azathioprine |
| sulphasalazine | methotrexate | cyclophosphamide |
| | | chlorambucil |
| | | cyclosporin A |
| | | experimental |
| | | immunotherapies |

Efficacy, side-effects and difficulty in managing therapy tend to increase from group 1 to group 3. The selection of drugs for each group is purely arbitrary and based on the clinical experience of the author.

SUPPRESSIVE AGENTS FOR TREATING RHEUMATOID ARTHRITIS

ANTI-MALARIALS

Hydroxychloroquine and chloroquine have been used for the treatment of RA since the 1950s.¹³ Both drugs are characterised by linear pharmacokinetics and extremely long plasma half-lives. This is because of their avid binding to tissues including erythrocytes and pigment cells. Because of their long half-lives it may take three to four months before steady state plasma concentrations are reached and this may explain their delayed effect. Frisk-Holmberg *et al.*¹⁴ have proposed a therapeutic plasma concentration range of chloroquine in RA of between 700-2,100 ug/mL but recent data would suggest that the majority of patients with RA treated with hydroxychloroquine do not have plasma concentrations within that range.¹³ This has important implications for the use of hydroxychloroquine since it is considered to be a relatively weak (but safe) SAARD. Alteration of the dose might well improve efficacy but perhaps at the expense of safety.

Anti-malarials bind strongly to DNA, inhibit lymphocyte responsiveness, chemotaxis, phagocytosis and superoxide production by PMNs and macrophages and stabilise lysosomal membrane. Anti-malarials also reduce the production and release of interleukin-1. Anti-malarials have been shown to be better than placebo but slightly less efficacious than other anti-rheumatic drugs. Recent trials comparing hydroxychloroquine with sulphasalazine¹⁵ have shown an earlier response to sulphasalazine in 60 patients with RA never exposed previously to SAARDs. In this study sulphasalazine was found to slow development of erosions in the hands and feet¹⁵ in comparison to the hydroxychloroquine group, but relatively low doses of hydroxychloroquine were used.

The major concern with hydroxychloroquine treatment is that of retinopathy. It is relatively common to find patients complaining of minor visual disturbances, such as a difficulty in accommodation, during the first few weeks of treatment. These features invariably settle with continuing therapy. Concern regarding long-term retinopathy should be allayed, since very few if any cases of permanent visual disturbance have been reported using recommended doses of hydroxychloroquine.¹⁶ It is standard practice, however, in most countries to advise fundoscopy and visual field charting (particular red field) at four to six monthly intervals. No studies to validate this practice have been carried out. Other screening procedures such as the AMSLER grid and retinal photography may also provide a simple and less expensive way of detecting early retinal changes although they remain to be validated. In view of the increasing cost of monitoring this therapy some review of these practices should be carried out.

GOLD COMPLEXES

Gold complexes used in the treatment of RA fall into two major groups — the water-soluble thiolates

(sodium thiomalate and thioglucose) and the fat-soluble phosphine auranofin.¹⁷ Metabolites of gold circulate in the blood bound primarily to plasma proteins but significant concentrations of gold are also found within the red cells. Injectable gold complexes are rapidly absorbed after intramuscular injection although maximal plasma gold concentrations are slightly delayed with the more oily aurothioglucose. Peak plasma concentrations of gold during long-term treatment with aurothiomalate show considerable patient variation but are approximately 25 uM(5 mg/L) on 50 mg/week. Gold is eliminated slowly from the body and has been found in tissues over 20 years after the last dose. Approximately 25% of auranofin is absorbed orally, the major route of elimination being in the faeces. The half-life of gold with auranofin in the body is less than after administration of injectable gold complexes. Both intramuscular gold salts and auranofin are widely distributed through the body and there is some evidence that they are concentrated within the inflammatory tissues and, in particular, macrophages. Gold complexes have a wide variety of effects on inflammatory cells and mediators. Their principal effects seem to be on monocytes and lymphocytes but *in vitro* effects depend very much on the concentration and conditions utilised in experiments. Auranofin would seem to have more of an effect on PMNs inhibiting phagocytosis, the oxidative burst and the release of lysosomal enzymes. The major clinical trials involving gold complexes have been reviewed recently by Champion *et al.*¹⁷ Since their introduction by Forrester in the 1920s, injectable gold complexes have been used as the major reference standard for SAARD therapy. Injectable gold complexes have been shown to be better than placebo but the changes in end points such as functional capacity, grip strength and active joint count are relatively modest.¹⁸ The optimum dose of injectable gold complexes have not been clearly established with doses as low as 10 mg/week being no different from 50 mg/week which in turn is as effective as 150 mg/week. In comparison to other SAARDs, gold complexes show a similar efficacy to d-penicillamine (600-1800 mg/day). Sulphasalazine (2-3 g/day), show a similar efficacy to d-penicillamine (600-1800 mg/day), sulphasalazine (2-3 g/day), azathioprine (2-2.5 mg/kg/day) and methotrexate (10-12.5 mg/week). Although it is standard practice to continue gold injections, albeit at a reduced frequency, there is little data in the literature which addresses this question and long-term follow-up shows the majority of patients commenced on gold treatment have ceased it three to five years later because of lack of efficacy or side-effects.¹⁹ In their recent survey of efficacy of injectable gold complexes Champion *et al.*¹⁷ conclude:

- ① Doses in the range of 10-50 mg (weekly/monthly) for one to two years are more effective than placebo.
- ② Dose-response relationship in the range of 10-150 mg/week has not yet been established.
- ③ Clinical responses occur in between 10-35% of patients and peak at 6-12 months but only half of these patients maintain this response after 12 months. Long-term remissions are rare.
- ④ Gold complexes retard the development of joint erosions.
- ⑤ Even when dosage is reduced to maintenance levels, only about 20% of patients continue treatment after four years. As the incidence of toxicity declines, terminations due to loss of efficacy continue to rise (see Figure 3).

A number of workers have tried to predict therapeutic efficacy and toxicity to gold complexes. Although a multi-variate combination of HLA-A3, the absence of HLA-DR4 and depressed haemoglobin provide a discriminate function predictive of therapeutic response,²⁰ this function has not been applied widely and at present there does not seem any simple means of assessing patients' response. Although auranofin is superior to placebo it is less efficacious than aurothiomalate, d-penicillamine and methotrexate and causes fewer adverse reactions.

Adverse reactions to gold complexes are important as these are major reasons for discontinuation of therapy. Auranofin has few serious side-effects although diarrhoea is dose-related and mucocutaneous reactions, proteinuria and thrombocytopenia are also seen. The major adverse reactions are well documented.¹⁷ They include skin rashes, proteinuria, blood dyscrasias and the rare problems of enterocolitis, peripheral neuropathy, pneumonia and bronchiolitis obliterans. In most clinical studies approximately 20% of patients have to cease gold treatment because of side-

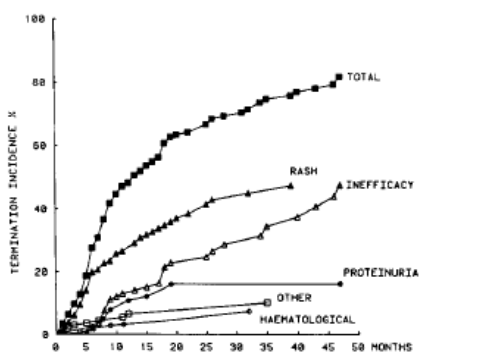


Figure 3: Termination on aurothiomalate treatment from Sambrook *et al.* 1982.¹⁹

effects while up to 40% may experience adverse reactions. Mild pruritic skin rashes and transient proteinuria are common but some patients go on to develop severe exfoliate dermatitis or membranous glomerulonephritis. Eosinophilia is common in patients with RA but has been described in up to 50% of patients taking gold and does not seem to correlate well with toxicity. The most severe adverse reactions with gold salts are those of neutropenia or aplastic anaemia. A significant number of patients who develop blood dyscrasias on gold therapy show a progressive fall in their white cell count or platelet count prior to aplastic anaemia occurring. This emphasises the importance of careful and continuing evaluation of blood parameters. There are, however, some cases where the fall in blood parameters can be precipitous and without warning. Aplastic anaemia has a high mortality rate but this can be reduced by aggressive treatment with high dose corticosteroids, chelating agents and even bone marrow transplantation.²¹

Monitoring of gold treatment is important since adverse events need to be identified as early as possible to prevent severe or even fatal sequelae. There is still wide variation in the practice of rheumatologists regarding monitoring strategies although the majority check the full blood count prior to each injection at least for the first three months.²² Liang and Fries²³ have recommended the following as a strategy that takes into account the cost of monitoring:

- Patient to fill in questionnaire on side-effects prior to each injection
- Weekly white cell and platelet count with monthly full blood count
- Dipstick urinalysis for blood and protein (performed by patient) before each injection
- Monthly review by the medical practitioner.

Although relatively intensive, the consequences of missing early bone marrow depression or glomerulonephritis can be devastating.

D-PENICILLAMINE

The use of d-penicillamine in RA has been reviewed recently.²⁴ D-penicillamine has three functional groups, an amino, a carboxyl group and a sulphhydryl group. These groups determine the pharmacokinetics and biological activity of d-penicillamine. Peak plasma concentrations of d-penicillamine occur between 1.5 and four hours after oral ingestion and the terminal elimination half-life has been estimated at between one and 7.5 hours. D-penicillamine binds to tissues and to plasma albumin and dissociates slowly. Most d-penicillamine is transformed to disulphides by oxidation. D-penicillamine acts as a metal chelator and interactions with zinc, copper and iron may be important in RA. *In vitro* and *in vivo* effects of d-penicillamine include reduction of immunoglobulin

synthesis by monocytes and lymphocytes, alteration in T-lymphocyte function and inhibition of myeloperoxidase enzyme within PMNs. D-penicillamine may also influence mediator production such as eicosanoids and cytokines and may protect joint tissue from oxygen radical damage.²⁴

D-penicillamine has been shown to be significantly better than placebo in doses of between 600 and 1500 mg daily. Response rates are usually in the order of 50% but about one quarter of patients will withdraw during the first six months of therapy due to an adverse event.

Efficacy and toxicity of d-penicillamine in RA have been compared to other SAARDs but many of these trials are of insufficient power to detect differences between treatment groups. However, d-penicillamine appears to be slightly more efficacious than hydroxychloroquine and auranofin and of similar efficacy to azathioprine. There are conflicting data as to whether d-penicillamine retards joint erosions in RA but with SAARDs slowing of erosions often occurs after 12 months of treatment²⁵ and may be missed if the studies are not continued into the second year.

D-penicillamine produces a similar spectrum of side-effects to intramuscular gold. Certain differences do, however, occur such as bullous pemphigoid and autoimmune disturbances such as induction of antinuclear antibodies, systemic lupus erythematosus, myasthenia gravis, Goodpasture's syndrome and poly/dermatomyositis being occasionally seen.²⁴ It has been reported that those patients who are poor 'sulphoxidisers' have an increased overall rate of toxicity and there may also be an association with the HLA antigens DR3 and B8. From a practical point of view, d-penicillamine should be commenced at a low dose (125-250 gm/daily) and the dose then increased to 500-750 mg/daily over a period of a few months. The patients need to be monitored carefully for the development of skin rashes and renal and haematological side-effects with regular full blood counts and urinalysis. In some situations where thrombocytopenia and proteinuria occur d-penicillamine may be continued at a lower dose as long as the abnormalities revert quickly to normal. Once the disease has been controlled the dosage of d-penicillamine may be reduced but in most instances where it is ceased an exacerbation of RA occurs.²⁶

SULPHASALAZINE (SASP)

Sulphasalazine was first developed in the 1930s as an antibacterial agent and subsequently established its place in the management of inflammatory bowel disease.²⁷ Over the last ten years, however, it has become recognised as a SAARD in the management of RA. SASP is poorly absorbed with the delivery of most of the dose into the large bowel where it is split by colonic bacteria into 5 amino acetyl salicylic acid

(5 ASA) and sulphapyridine. 5 ASA is poorly absorbed and primarily excreted unchanged in the faeces while sulphapyridine is absorbed and metabolised in the liver. The active component of SASP in RA would seem to be sulphapyridine but it is significantly more toxic than SASP.²⁸

The mode of action of sulphasalazine has not been clearly defined, with conflicting evidence of immunomodulation, particularly at concentrations achieved *in vivo*. Recent studies have suggested an effect of sulphapyridine on inhibition of synovial angiogenesis,²⁹ possibly as a consequence of LTB₄ suppression. Early placebo controlled trials had difficulty in showing significant differences between placebo and SASP but this in part was due to better than expected placebo response.²⁷ Later studies were, however, able to demonstrate a significant benefit of SASP over placebo and there is some suggestion that it may slow the development of erosions. Although a number of comparative studies of SASP against gold and d-penicillamine have been carried out, none have been of sufficient statistical power to demonstrate differences.²⁷ Although up to 50% of patients may develop side-effects with SASP, in less than half of those cases will the reaction be severe enough to stop treatment. Side-effects include nausea and abdominal pain, skin rashes, transaminitis, CNS disturbances and blood dyscrasias.²⁷ Bodily secretions commonly become discoloured and those wearing plastic contact lenses should be warned that their view of the world will be tinged yellow. The most potentially serious side-effects are haematological but a large study by Donovan *et al.*³⁰ has demonstrated that these are most likely to occur in the first four months of treatment. Oligospermia is a common accompaniment of SASP therapy and although these changes revert on ceasing treatment SASP should not be prescribed to those wishing to have a family.

Since Donovan *et al.*³⁰ have demonstrated that the majority of serious side-effects will occur within the first three months of SASP treatment, it is during this period when vigilance has to be at its highest. It is recommended that the full blood count and liver function tests be monitored each fortnight for the first three months and then at six weekly to three monthly intervals after that.

CORTICOSTEROIDS

Since the Nobel Prize winning work of Hench and his colleague in 1949,³¹ corticosteroids have played a major role in the treatment of RA. The major effects of corticosteroids in RA have been reviewed recently by George and Kirwan³² and include:

- Increased synthesis of lipocortin and subsequent inhibition of phospholipase A2

- Reduced production of cyclooxygenase and other inflammatory enzymes
- Inhibition of both T and B lymphocyte function
- Reduction in Fc receptor expression
- Alteration in white cell traffic increasing circulating neutrophils, decreasing margination of cells and producing lymphopenia.

Cortisol is tightly bound to the alpha-2-globulin transcortin while a small amount is bound to albumin and a further 10% remains free. The free cortisol diffuses into the cells where it binds to a specific receptor protein in the cytoplasm of glucocorticoid responsive tissues. This 95-kD phosphorylated protein has now been cloned and sequenced. The corticosteroid/receptor complex undergoes conformational change and moves to the nucleus where it binds reversibly to specific sites on DNA. The action of corticosteroids in humans is produced by the proteins induced from the messenger RNAs and in particular lipocortin. Lipocortin inhibits phospholipase A2 and prevents the conversion of membrane phospholipids to arachidonic acid with a reduction in prostaglandin, leukotriene and oxygen radical formation. Glucocorticoids also modulate the production of a variety of cytokines including the interleukins, interferons and tumour necrosis factors. A variety of lymphocyte functions including proliferation and antibody synthesis are suppressed by corticosteroids and they also influence the trafficking of white cells producing a decrease in peripheral lymphocytes, eosinophils and monocytes and an increase in circulating neutrophils. There are a variety of synthetic analogues of cortisol available for use which diffuse more completely into tissues since they are not as strongly bound to plasma albumin.

The commonly used oral corticosteroids prednisolone and prednisone are absorbed rapidly from the gastrointestinal tract and have half-lives of approximately one hour although their action in tissues last much longer. Prednisolone and prednisone are the most appropriate oral steroids to use in RA because the smaller tablet size allows for small dosage adjustments. Corticosteroids are used in the treatment of RA in the following situations:

- As continuous low dose (< 10 mg daily)
- As short courses of rapidly decreasing dose for disease flares
- As large oral pulses (200 mg-1 gm)
- As intra-articular injections for particular problem joints
- As IV pulse therapy during a flare or as induction treatment with the commencement of other SAARDs.

The major clinical trials of corticosteroids in RA are summarised by George and Kirwan.³² Early studies showed them to be better than placebo and NSAIDs for management of pain and stiffness in RA. These

early studies also suggested that steroids might have disease-modifying properties by reducing the rate of bone erosion.³³ In a long-term review of 50 patients treated with rest, anti-inflammatory anti-rheumatic drugs with and without the addition of corticosteroids, Millon *et al.*³⁴ showed that patients treated with the combination of steroids and exercise had a more favourable outcome. Although the list of potential complications of corticosteroid therapy is long,³² low dose therapy (up to 7.5 mg/daily) does not seem to be a risk factor for the development of peptic ulcer³⁵ or significant osteoporosis.³⁶

Intravenous pulsed methylprednisolone (1 gm/day for three days) has been showed to be useful in rapidly controlling synovitis although erosions continue.³⁷ Our group³⁸ has shown that methylprednisolone (1 gm/daily for three days) is equivalent to oral prednisolone (1 gm/day for three days) in suppressing disease activity in RA but the effects of both treatments only last for about six weeks. Doses of methylprednisolone as low as 100 mg and 320 mg have been shown in well designed studies to be as useful as 1,000 mg in patients with RA.³⁹ Recently, methylprednisolone pulsing has been shown to increase the speed of response and reduce side effects in patients commencing gold therapy.⁴⁰

Corticosteroids are extremely effective anti-inflammatory agents although whether they have significant disease modifying activity is still unclear.³² From a practical point of view, they should be used judiciously trying to aim for a maintenance dose of 7.5 mg daily or less. Larger oral or parenteral doses may be used during acute exacerbation or when other SAARDs are being commenced. Cost consideration should be made when deciding on which preparations to use and further studies should be carried out to determine relative efficacy of the various preparations.

Corticosteroids are often injected into joints or other inflammatory lesions and can suppress pain and inflammation. Significant concentrations of corticosteroids are found in the plasma following intra-articular injection explaining why patients have a general response.

Joints requiring injection more than three times per year should raise the question as to whether other local (i.e. radionuclide synovectomy or surgery) or general therapeutic change (i.e. alter SAARDs) should be considered.

In summary, glucocorticoids play an important role in the management of RA and used carefully can significantly reduce symptoms and possibly slow the progression of erosive disease. The real issue is whether the potential benefits are worth the potential long-term risks of tissue breakdown and infection. Prospective studies are still required to address these issues but the physician commencing corticosteroid therapy must be eternally vigilant.

AZATHIOPRINE

Azathioprine is an oral purine analogue converted to active metabolites which inhibit synthesis of DNA and RNA. It acts as a general immunosuppressive, particularly on rapidly dividing cells.⁴¹ Approximately 50% of the oral dose is absorbed and the plasma half-life varies from 60-90 minutes resulting from renal excretion, cellular uptake and metabolism. Azathioprine has significant steroid-sparing effect in RA and seems comparable to gold and hydroxychloroquine and d-penicillamine.⁴¹

Currey *et al.*⁴² compared azathioprine, cyclophosphamide and gold in 121 patients with severe RA. At 18 months all drugs showed similar efficacy but azathioprine and cyclophosphamide allowed greater steroid reduction. The effects of azathioprine are significantly greater with a dose of 2.5 mg/kg per day than with 1.25 mg/kg per day.⁴³ Short term toxicity with azathioprine is relatively low with approximately five to ten episodes per 100 patients of nausea, vomiting or diarrhoea and about four episodes per 100 patients' years of leukopenia.⁴⁴ Toxic effects leading to withdrawal include bone marrow suppression and gastrointestinal reactions including hepatitis. The concern with azathioprine, particularly with long-term use is the increased incidence of neoplasia. Silman *et al.*⁴⁵ have demonstrated a twofold increase in lymphoma risk with a 20 year follow-up of over 200 patients treated with 300 mg azathioprine daily.

METHOTREXATE

Methotrexate is an analogue of folic acid and aminopterin. It was first used for the treatment of RA in the early 1950s but did not achieve widespread acceptance until the 1980s.⁴⁶ Methotrexate inhibits dihydrofolate reductase and impairs DNA synthesis. It is now used commonly in a once weekly dose for the treatment of RA. Methotrexate is rapidly absorbed from the gut and the parent compound and metabolites circulate bound to serum albumin. The drug is oxidised to an active 7-hydroxymethotrexate and both this and the parent compound accumulate in the liver as polyglutamates. Methotrexate is eliminated from the body by renal excretion and by biliary excretion in the faeces. Although NSAIDs significantly interfere with the excretion of high dose methotrexate there is no evidence that this is an important interaction at the low doses used in RA.^{46,47} Methotrexate reduces lymphocyte proliferation and rheumatoid factor production by lymphocytes. Methotrexate also reduces PMN chemotaxis possibly by inhibiting specific methylation reactions and may influence cytokine production.⁴⁶ A major advantage of methotrexate is that it has not been associated with oncogenicity – a fact that gives it a distinct advantage over azathioprine, chlorambucil and cyclophosphamide.⁴⁶

Methotrexate in doses of between 7.5 and 15 mg weekly has been shown to be better than placebo and equal to or slightly better than azathioprine, injectable gold, auranofin, d-penicillamine and hydroxychloroquine.⁴⁸⁻⁵⁰ Tugwell *et al.*⁵¹ have demonstrated in a meta-analysis that patients on methotrexate have a 26% reduction in pain and that this occurs relatively quickly (within one to two months) and reaches a maximum in six months. Recent studies suggest that patients will remain on methotrexate for a longer period of time than other SAARDs.⁵⁰ The effect of methotrexate on radiographic changes is still unclear with some studies showing a slowing of erosion rates and others not.⁴⁶ The major concern with methotrexate is its side-effects.⁴⁶ Anorexia and nausea particularly in the 24 hours after dosing are relatively common. This may be reduced or eliminated by co-prescription of folic acid without affecting the anti-inflammatory effects of methotrexate.⁵² Transient, mild elevation of liver enzymes occur in up to 60% of cases but do not correlate with the development of hepatic fibrosis.⁴⁶ Hypersensitivity reactions including rashes, fever and pneumonitis have also been reported. The true incidence of pneumonitis is not known but seems to be of the order to 3-7%. The major concern with methotrexate therapy is that of hepatic fibrosis and cirrhosis. Kevat *et al.* demonstrated an incidence of moderate fibrosis in 0.5% of 714 patients and an incidence of cirrhosis of 0.1%.⁵³ It does seem, however, that this is a relatively rare complication and, although liver biopsy has been recommended when the cumulative dose reaches 1.5-2 gm,⁵¹ some studies of repeat liver biopsies over a ten year period have failed to demonstrate a significant incidence of cirrhosis.⁵⁴

However, recent data have suggested that serial liver biopsies in patients on methotrexate did show an increase in pericellular and portal tract collagen with time that was not related to total dose of methotrexate⁵⁵ but did correlate with the concentration of methotrexate and polyglutamate metabolites in hepatic tissues.⁵⁶ Patients over the age of 65 do not seem to have significantly increased adverse events and respond in a similar fashion to younger patients.⁵⁷ A small study has suggested that patients on methotrexate may have an increased risk of postoperative infection after prosthetic joint surgery suggesting that the drug should be discontinued around the time of surgery.⁵⁸ Further studies are required to determine if, and for how long, methotrexate treatment should be ceased in this situation.

Methotrexate is a very easy drug to use in the treatment of RA. It does have significant side-effects but these can be kept to a minimum, at least in the short term, by monitoring liver function tests and full blood count at monthly intervals for the first three months of treatment and three monthly after that.

Methotrexate should not be used in those patients with a previous history of hepatic injury unless they are willing to have a liver biopsy to assess liver architecture. Alcohol intake should be kept to a minimum and the patient warned not to take antibiotics with trimethoprim-sulfamethoxazole and to report any persistent cough not settling with standard therapy. The question of when or if to biopsy the liver when using methotrexate has still not been adequately answered. The decision has to be made in each individual patient and will be determined by previous hepatic disease, length of time on and dose of methotrexate and the coexistence of other risk factors for cirrhosis.

CYCLOPHOSPHAMIDE

Cyclophosphamide is a derivative of nitrogen mustard and can be used orally or intravenously for treatment of severe RA. Cyclophosphamide has a plasma half-life between two and ten hours and is metabolised primarily by the liver.⁴¹ Cyclophosphamide itself is inactive but is converted into an active metabolite which produces immunosuppressive effects and also toxicity. The active metabolites are toxic to both resting and dividing cells by interfering with the DNA repair mechanisms. Low dose oral cyclophosphamide seems to have more of an influence on cell-mediated responses while high dose intermittent therapy predominantly affects humoral immunity.⁴¹ The first open study of cyclophosphamide in RA was carried out by Fosdick *et al.* in 1968⁵⁹ and this demonstrated clinical improvement in 75% of cases and significant steroid reduction. The Cooperating Clinics Study⁶⁰ shows that cyclophosphamide 150 mg/daily was significantly better than 15 mg/daily with a slowing of radiographic change. High dose intravenous pulse therapy with cyclophosphamide has been shown to be of some benefit in small numbers of patients⁶¹ but recent studies⁶² have failed to confirm any benefit from the use of this treatment for severe synovitis and its main use in rheumatoid disease has been for the systemic complications of RA such as vasculitis.

CHLORAMBUCIL

Chlorambucil has been used in the treatment of severe RA primarily by the French. It acts as an alkylating agent and has both anti-inflammatory and immunosuppressive effects.⁴¹ Hatchuel⁶³ demonstrated clear superiority over placebo in a three-month study of 48 patients in a dose of 0.2 mg/kg per day. A number of open studies using between 0.1 and 0.2 mg/per kg/day have shown efficacy but the side-effects are significant, particularly in the long-term. Patients taking chlorambucil long-term have a significantly increased risk of the development of leukaemia and duration of treatment with this drug should be kept to a minimum.

CYCLOSPORIN A

The new immunomodulating agent cyclosporin A inhibits the production of both interleukin-1 and interleukin-2 – important mediators in RA. Open studies⁶⁴⁻⁶⁶ have demonstrated the drug to be of benefit in patients with active RA; a comparison with d-penicillamine⁶⁷ and azathioprine⁶⁸ also showed it to be beneficial. These studies, however, were associated with a relatively high incidence of renal toxicity. Recently, Tugwell *et al.* have reported a six-month comparison with placebo in 144 patients with severe RA.⁶⁹ In this study the initial daily dose of cyclosporin A was 2.5 mg/kg with a cautious increase to a mean stabilisation dose of 3.8 mg/kg. The major outcome measurements of active joints, pain and global score all showed a greater than 20% reduction. Although the serum creatinine increased in those patients taking cyclosporin A these increases were controlled in the vast majority of patients by simple dose adjustment without withdrawal from the study. The major problem with cyclosporin A is that it requires fairly intensive monitoring and that it is often taken with other potential nephrotoxins such as NSAIDs. Although it is obviously a difficult drug to use in RA it may be helpful for patients 'resistant' to other forms of therapy.

NOVEL APPROACHES

The new therapeutic approaches to RA are shown in Table 3 but these compounds are only in early clinical trial in humans. Use of molecular therapies such as monoclonal antibodies have been reviewed recently by Kirkham and Panayi.⁷⁰ Uncontrolled studies using murine antibodies directed at different T-lymphocyte antigens have shown conflicting results. Herzog *et al.*⁷¹ reported significant improvement in five of seven patients lasting up to five months using seven daily infusions of CD4 monoclonal antibody. Kirkham and Panayi⁷⁰ on the other hand showed transient responses in only two of six RA patients treated with CD7 monoclonal antibody. Clearly these molecular approaches offer the chance of controlling disease activity in RA but their true benefit must await properly controlled clinical trials.

COMBINATION THERAPY

Over the last decade an increasing number of combinations of SAARDs have been used in the management of RA. This topic has been the subject of a number of recent reviews^{72,73} which point out that very few of these studies have been conducted in a controlled fashion. Of over 30 reports in the literature on the use of combination therapy for the treatment of RA, only three of these are randomised double blind studies.⁷³ In these studies gold and d-penicillamine together resulted in an earlier response than gold or

TABLE 3
Experimental Therapies for Rheumatoid Arthritis

| | |
|---|----------------------|
| Cytokine inhibitors | |
| IL-1 | Tenidap Romazarit |
| Monoclonal antibodies | |
| CD4 | monoclonal antibody |
| CD7 | monoclonal antibody |
| Monoclonal + toxin | |
| Ricin A + CD ₃ monoclonal antibody | |
| Interferon | |

d-penicillamine alone, while the combination of gold and hydroxychloroquine was more effective than gold alone. Although a number of other combinations of SAARDs seem promising from non-blinded studies, they are all of relatively short duration with small numbers. As pointed out,⁷³ it is very important to conduct controlled studies with a sufficient number of patients before combinations of SAARDs are adopted as normal practice.

The rationale for combination therapy would seem to be logical in that SAARDs with a different mechanism of action and a different spectrum of side effects could be used in smaller than normal doses providing added efficacy without added toxicity. Given that we now have a range of SAARDs available, it is to be hoped that properly controlled studies will be organised utilising these drug combinations in an effort to provide better control of RA in the near future.

CONCLUSION

For a long time now we have accepted that there is little to choose between NSAIDs in the management of arthritis although variability in response to these agents may lead to significant individual preferences. We seem to be rapidly approaching this point with SAARDs as an increasing number of these agents become available. There is little doubt that these drugs do play a significant role in suppressing disease activity in RA. There is also little doubt that few of them (if any) will continue to suppress disease activity over long periods of time. If we accept this premise then it would seem important to monitor patients very closely from the point of view of disease activity and to serially change the SAARD at regular intervals when outcome variables decline.⁷⁴ There is a need to develop simple measures of disease outcome and to standardise them internationally so that trials done in different countries can be compared.

We should now be putting the treatment of RA on a much more scientific footing. To this end, Fries⁷⁴ has enunciated six principles to establish this strategy:

1. Early use of SAARDs before joint damage occurs.
2. One or multiple SAARDs used continuously through the disease.

3. Disability and other outcomes measures regularly monitored so that disease progression can be serially plotted.
4. Limits to disability set a priori such that decisions to change therapy can be planned.
5. SAARD therapy is serially changed to new agents alone or in combination at each decision point.
6. Analgesics and NSAIDs utilised as adjunctive therapy for symptomatic relief as required.

There are some data emerging from recent meta-analyses of SAARD trials in RA⁷⁵ which do provide some guidelines on overall efficacy and toxicity of these agents (Table 4). In this study Felson *et al.*⁷⁵ reviewed placebo-controlled and comparative studies of methotrexate, injectable gold, d-penicillamine, SASP, auranofin and anti-malarials for both efficacy and toxicity. From 66 clinical trials analysed for efficacy, auranofin was shown to be significantly weaker than methotrexate, injectable gold, d-penicillamine or SASP and slightly, but not significantly, weaker than anti-malarials. Interestingly, they found that none of the reported studies comparing methotrexate, injectable gold, d-penicillamine or salazopyrine contained enough patients (170 per treatment group) to successfully differentiate between these drugs. In 71 clinical trials assessed for toxicity, 30% of patients dropped out and in half of these the reason was an adverse drug reaction. Injectable gold had the highest rate of toxicity while anti-malarials and auranofin the lowest.

Although adverse reactions are a major reason for cessation of anti-rheumatic therapy there seems no way of predicting whether an individual patient is going to develop a side-effect to a SAARD⁷⁶ HLA-DR3 may predispose to development of side-effects with parenteral gold and d-penicillamine. Although it has been suggested that biochemical factors such as sulfoxidation status may influence the development of adverse reactions to gold or d-penicillamine it is not clear whether this is a useful predictor of subsequent development of side-effects.

Most patients who respond to a SAARD will do so within six months⁷⁷ and, if they do not, then it is important to either change the SAARD or add another one in an effort to try to suppress disease activity.⁷⁴

With close monitoring of both clinical efficacy and adverse reactions, significant benefits can be provided to most patients with RA by SAARDs' treatment without producing major adverse reactions. The treatment of RA is one of the many areas of medicine where the 'science' does not always provide the answer. Practitioners of the 'art' can still help patients significantly and by defining the research questions to be answered, design the trials that will significantly benefit patients with RA.

There are still many issues to be resolved regarding the treatment of RA but emphasis should be put on

TABLE 4

| | Composite treatment effect | Total dropout rates % | Dropout rates due to toxicity % |
|-----------------|----------------------------|-----------------------|---------------------------------|
| Placebo | 0.15 | 25 | 5 |
| Anti-malarials | 0.58 | 22 | 8 |
| Auranofin | 0.45 | 28 | 11 |
| Injectable gold | 0.7 | 40 | 30 |
| Methotrexate | 0.74 | 17 | 15 |
| D-pen | 0.75 | 30 | 18 |
| SASP | 0.76 | 29 | 22 |

Comparative treatment effect and dropout rates from metaanalysis of anti-rheumatic drug trials modified from Felson *et al.* 1990.⁷⁵ The comparative treatment effect is the mean of 'standardised change' in the tender joint count, erythrocyte sedimentation rate and grip strength.

measuring (and improving) the quality of life. It is still not clear whether early use of SAARDs brings about substantially more remissions or whether combinations of SAARDs are any better than either drug alone⁷⁸ despite the fact that some SAARDs have been used for over half a century. We are still not clear as to their exact mechanism of action. We do have some idea of how to measure disease activity, however crude, and we have the epidemiological skills to design appropriate clinical trials to try to answer some of these questions. ■

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