Fortnightly Review

Medical management of rheumatoid arthritis

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Rheumatoid arthritis is a chronic, disabling disease associated with substantial morbidity, increased mortality, and a poor prognosis in severe cases.¹ In this review we will discuss the medical management of joint disease in rheumatoid arthritis, but we emphasise that such management cannot be practised in isolation. Rheumatoid arthritis is a systemic disorder affecting many organs but space does not permit a discussion of subjects such as rheumatoid lung disease. Effective management also requires a multidisciplinary approach, with input from orthopaedic surgeons, occupational therapists, physiotherapists, nurses, orthotics and prosthetics departments, social workers, and chiropodists. One of the rheumatologist's most important roles is to coordinate these resources to minimise the impact of the disease on patients' lives. Drug treatment is also important, however, and continues to be a complex and controversial issue.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are effective in reducing the pain and stiffness associated with rheumatoid arthritis, and this can result in improved functional capacity. These drugs may be associated

Non-steroidal anti-inflammatory drugs

- Prescribed to most patients with rheumatoid arthritis
- Effective in reducing pain and stiffness
- Caution needed in patients at high risk of toxicity: elderly patients, smokers, patients with history of ulcer or renal impairment, patients taking oral anticoagulants, patients with asthma or congestive cardiac failure

with considerable toxicity, and recent evidence suggests that they are as toxic as second line drugs.² A plethora of non-steroidal anti-inflammatory drugs is available to clinicians, and although the drugs vary in efficacy and incidence of side effects (table), there is no consensus on which ones have the best risk to benefit ratio. The choice of non-steroidal anti-inflammatory drugs is also influenced by prescribing cost and pharmaceutical considerations—for example, many sustained release preparations are currently available, permitting once or twice daily administration. It is sensible for clinicians to become well acquainted with several non-steroidal anti-inflammatory drugs and to restrict their prescribing to them in most cases.

Although non-steroidal anti-inflammatory drugs may be associated with many side effects, the main concern is gastrointestinal side effects.³ Long term use is associated with the development of gastric, duodenal,

Summary points

- Non-steroidal anti-inflammatory drugs are effective in reducing the pain and stiffness of rheumatoid arthritis
- A gastroprotective agent may also be prescribed to reduce the gastrointestinal side effects of these drugs
- Second line drugs should be prescribed to slow disease progression—for example, hydrochloroquine, sulphasalazine, intramuscular gold, methotrexate—and their effects monitored
- Treatment with a combination of second line drugs is not justified
- Oral corticosteroids should be used sparingly, but they may be used more freely in very elderly patients or patients with terminal illness
- Intra-articular steroid injections should be limited to a maximum of four injections into any one joint in one year

and small bowel ulceration, which may result in gastrointestinal haemorrhage, perforation, and death. It is a testament to the efficacy of non-steroidal anti-inflammatory drugs that they continue to be almost universally prescribed to patients with rheumatoid arthritis, despite such side effects. H₂ receptor antagonists and misoprostol treatment are both effective in reducing peptic ulceration. There is an argument that all patients receiving long term treatment with non-steroidal anti-inflammatory drugs should also be prescribed prophylaxis against the gastrointestinal side effects, but such an approach is as yet unproved and

Ranking of non-steroidal anti-inflammatory drugs on basis of adverse reactions and deaths per million prescriptions

Serious gastrointestinal		Total serious		Deaths	
Drug	Rate	Drug	Rate	Drug	Rate
Azapropazone*	67.0	Azapropazone*	87.9	Azapropazone*	9.9
Piroxicam*	58.7	Fenbufen*	69.4	Fenoprofen*	6.6
Fenbufen*	35.7	Piroxicam*	68.1	Piroxicam*	6.2
Diffunisal*	33.5	Sulindac*	54.3	Naproxen*	5.6
Ketoprofen	33.2	Diffunisal*	47.2	Sulindac*	5.1
Naproxen*	32.8	Fenoprofen	43.7	Fenbufen*	4.5
Fenoprofen	32.3	Naproxen*	41.1	Diffunisal*	3.5
Flurbiprofen	27.4	Diclofenac	39.4	Flurbiprofen	3.3
Sulindac*	23.9	Ketoprofen	38.6	Diclofenac	3.1
Diclofenac	20.9	Flurbiprofen	35.8	Ketoprofen	1.6
Ibuprofen	6.6	Ibuprofen	13.2	Ibuprofen	0.7

*Long plasma half life.

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BMJ 1993;307:425-8

cannot be recommended. It would seem reasonable, however, to use prophylaxis in subgroups of patients at high risk of developing gastrointestinal toxicity.⁴

Second line drugs

Although non-steroidal anti-inflammatory drugs (first line drugs) are effective in ameliorating the symptoms of rheumatoid arthritis, they have no effect on the progression of the disease. In contrast, the primary aim of second line drug treatment is to reduce the activity of the disease and thus slow progression. Initial optimism about the success of this strategy has had to be tempered with realism: despite the use of second line drugs many patients have a poor outcome, with evidence of continuing joint destruction (fig 1).¹

FIG 1—Hand radiographs of the same patient showing radiological deterioration of rheumatoid arthritis after an interval of five years

What is the evidence that second line drug treatment has an effect on disease progression? Short and medium term controlled trials have clearly shown that these drugs are effective in reducing a number of parameters of disease activity such as erythrocyte sedimentation rate, C reactive protein, and titre of rheumatoid factor; these changes are paralleled by clinical improvement in the duration of morning stiffness, the number of swollen or tender joints, and functional ability.⁵ Controlled trials have also shown that intramuscular gold and cyclophosphamide slow the development of radiological erosive change when compared with placebo.^{6,7} Evidence from comparative drug trials also shows that sulphasalazine⁸ and methotrexate⁹ slow the progression of erosive disease.

Thus evidence suggests that many of the available second line drugs can slow the progress of rheumatoid arthritis but in practice the patients' prognosis remains poor. Why should this be so? The reasons are twofold. Firstly, the effect on disease progression is probably moderate at best. Patients given maintenance treatment with methotrexate show continuing radiological

deterioration in the long term,¹⁰ and methotrexate is probably as effective as any of the second line drugs. How much second line drugs slow disease progression over the long term is not known, and it is probably not possible to answer this question.¹¹ Secondly, only a minority of patients manage to continue taking any second line drug (with the possible exception of methotrexate)¹² long term because of the side effects.¹³ None the less, it is possible to give most patients maintenance treatment with one of the second line drugs over many years.¹⁴ It might be helpful to draw an analogy with the rationale behind long term control of hypertension—which drug is used to control blood pressure is probably not important, but the better the control of blood pressure over the years the greater the reduction in morbidity. In conclusion, second line drugs are partially effective, but patients' disease will progress despite continuing to take them.

Second line drugs—Which patients? When?

The selection of patients for second line drug treatment should be made carefully because all of the available drugs have clinically significant side effects. Only patients who are likely to benefit from treatment should therefore be exposed to the associated risks. Second line treatment should be considered in patients with active synovitis, radiological evidence of erosive disease, or rapid function decline. It should not be withheld in elderly patients or in patients with chronic destructive disease who show evidence of ongoing disease activity. Second line treatment is unlikely to be beneficial in patients with inactive disease even when there is evidence of previous erosive damage that has resulted in a lot of mechanical pain.

Second line drug treatment

For patients with high risk of progressive disease:

- Active synovitis
- Erosive radiological change
- High erythrocyte sedimentation rate or C reactive protein
- Seropositive for rheumatoid factor
- Deteriorating function

Traditionally, the timing of second line treatment in rheumatoid arthritis has been based on a therapeutic pyramid (fig 2). It was proposed that all patients should be given non-steroidal anti-inflammatory drugs and then second line treatment if the response, as measured by symptomatic control or disease progression, was considered to be inadequate. Immunosuppression with cytotoxic agents was reserved for patients in whom second line drug treatment had failed.

Recently there has been a lot of concern that such an approach is inappropriate and that the pyramid should be remodelled¹⁵ or abandoned.¹⁶ The main thrust behind this argument is that the traditional pyramid approach has failed to stop disease progression in many patients and that erosive change progresses fastest in the early stages of the disease¹⁷—thus, perhaps earlier, more aggressive treatment would be more effective. The challenge is to identify patients with a poor prognosis and to institute second line treatment at an early stage. Unfortunately, the prognostic markers available are unable to distinguish accurately the patients at high risk of disease progression from those with non-aggressive disease, and whether to use second line drug treatment is still largely decided on the basis of clinical examination, radiographic appearances, and simple laboratory investigations.

FIG 2—Pyramidal approach to the treatment of rheumatoid arthritis

Which second line drug?

The choice of second line drugs to use and in which order is to some extent dependent on fashion and personal preference. Methotrexate is rapidly increasing in popularity in the United States, where sulphasalazine is not licensed for use. In the United Kingdom sulphasalazine remains a favourite with many rheumatologists, although intramuscular gold, penicillamine, and methotrexate are all widely used. There is evidence that these four drugs are of similar efficacy.¹⁸ Hydroxychloroquine and auranofin, and possibly azathioprine, may be less powerful—sulphasalazine, intramuscular gold, and methotrexate result in a faster, and probably greater response than auranofin¹⁹⁻²¹; sulphasalazine is more effective than hydroxychloroquine⁸; methotrexate compares favourably with azathioprine in some trials.²²

Which second line drugs?

- Hydroxychloroquine—good choice in mild disease because of mild side effects
- Sulphasalazine—commonly first choice in Britain for more severe disease
- Intramuscular gold—effective and still widely used despite side effects
- Methotrexate—increasingly used, although concerns about long term and life threatening toxicity remain
- Penicillamine—unfashionable because of side effects
- Azathioprine, cyclosporin, cyclophosphamide—for patients with resistant disease

Drug efficacy cannot, therefore, always help in formulating a prescribing policy, and drug toxicity needs to be considered. Here we discover one of the major problems associated with the use of second line drugs. Several studies have shown that only a few patients tolerate being given a second line drug long term, principally because of toxicity. One of the reasons for the dramatic increase in the use of methotrexate in the United States has been evidence that its long term tolerability is better than that of gold, sulphasalazine, or penicillamine.²³ This may be the case, although not all studies support this finding.²⁴ Furthermore, reservations must remain about the widespread use of methotrexate until the risks of long term toxicity from hepatic disease, pneumonitis, and opportunistic infection have been fully evaluated.

The choice of second line drug in an individual patient can sometimes be dictated by other factors—for example, methotrexate should be avoided in patients with hepatic, respiratory, or renal disease, and gold or

Side effects

- Hydroxychloroquine—retinal toxicity is rare if dosage guidelines are adhered to
- Sulphasalazine—nausea (try oral prochlorperazine), skin rash (try desensitisation), and mouth ulcers are common. Leucopenia is usually reversible but agranulocytosis occurs rarely
- Gold/penicillamine—mouth ulcers and rash are common. Reversible proteinuria also common. Leucopenia and thrombocytopenia can occur and be life threatening
- Methotrexate—nausea and mouth ulcers occur, but the main concern is development of chronic liver disease, pneumonitis, and opportunistic infections. Folic acid supplements may reduce the incidence of side effects

Monitoring treatment

- Hydroxychloroquine—ophthalmology examination every six months
- Sulphasalazine—full blood count every two weeks for three months, every month for three months, and every six weeks thereafter; liver function tests every six weeks
- Penicillamine—full blood count and urine analysis every two weeks for three months and monthly thereafter
- Intramuscular gold—full blood count and urine analysis before every injection
- Methotrexate—urea and electrolyte measurements full blood count, and liver function tests every 2-4 weeks

penicillamine therapy cannot be safely monitored if the patient already has proteinuria or leucopenia. Alternatively, parenteral gold or methotrexate may be chosen in patients in whom compliance is a problem.

Because of the high incidence of side effects associated with the use of second line treatment, it has become accepted practice to monitor patients closely while they continue with treatment. The effectiveness of such monitoring is debated, and the regimen used is to some extent arbitrary.

Combination treatment

The perceived failure of traditional second line drug treatment and the success achieved by combination chemotherapy in treating haematological malignancies has led rheumatologists to contemplate the use of second line drugs in combination.²⁵ Encouraging early reports were all from small, open uncontrolled studies, but unfortunately, this early encouragement has not been matched by results from controlled clinical studies. Some combinations, such as gold and hydroxychloroquine, have been quite widely prescribed. One study of gold and hydroxychloroquine treatment suggested a trend (although significance was not achieved except with one variable) towards increased efficacy of the combination (compared with gold alone), matched by increased toxicity.²⁶ Even this mild effect has not been confirmed in other studies.²⁷ Trials of combinations of sulphasalazine and penicillamine and of methotrexate and auranofin have also failed to show any benefit.²⁸ In conclusion, there is currently no evidence to support the use of combinations of second line drugs. It is still possible that combination treatment might have a role in severe, refractory rheumatoid arthritis, but such treatment regimens must be validated by prospective, controlled trials before they can be recommended.

What is the role of corticosteroids?

When corticosteroid treatment was introduced in the 1950s it was hailed as the answer to the treatment of rheumatoid arthritis.²⁹ Unfortunately, it has become clear that this is not the case. Oral corticosteroids have an undoubted effect on disease activity, although whether they have an effect on disease progression remains unknown. The dosage required to control disease activity in the long term is, however, too high in most patients and is associated with unacceptable long term toxicity—for example, increased infection, osteoporosis (and hence fractures), diabetes, hypertension, and myopathy. Is there still a role for steroids? Low dose prednisolone (5.0-7.5 mg/day) continues to be used by some rheumatologists as an adjunct to second line drug treatment, and it is hoped that the side effects become acceptable by limiting the dose in this way.

Ongoing clinical trials into the use of low dose prednisolone should provide further information on its role in treating rheumatoid arthritis. There is evidence, however, that even at low doses, corticosteroid use is associated with osteoporosis, even in men.³⁰ In patients with terminal illness and in very elderly patients corticosteroids can be used more freely because much of their toxicity occurs after long term use.

Local injection of the joint with a long acting corticosteroid is a simple, quick procedure that can be performed on inpatients or outpatients. Injections can improve pain and reduce synovitis and effusion in the joint for several weeks. Repeat injections into an individual joint are possible, although injections done too often or too frequently may accelerate joint damage. Most rheumatologists therefore limit the number and frequency of joint injections to a single joint, a good rule of thumb being a maximum of four injections into any joint in one year.

Other second line drugs

It is not possible to discuss in detail the use of all the available treatments. In addition to those mentioned above, cytotoxic drugs such as cyclophosphamide and chlorambucil are sometimes used, but concerns about the possible development of malignancy caused by prolonged use limits their role. Cyclosporin has been shown to be effective in rheumatoid arthritis³¹ but is not yet widely used, largely because of fears about long term renal toxicity.

New biological treatments

The explosion of interest, knowledge, and techniques in molecular biology have opened up new possibilities for treating rheumatoid arthritis, which are, as yet, only in the early stages of evaluation. From a therapeutic point of view, the development of techniques for producing monoclonal antibodies has been most exciting. It has proved possible to produce chimaeric or humanised monoclonal antibodies against several T lymphocyte cell surface antigens (for example, CD4, CD7, CDW52); administration of these antibodies result in profound lymphopenia and temporary improvement in disease activity,³² although the precise mechanism of action remains obscure because disease recurrence often precedes the return of the lymphocyte count to normal. Repeated courses of treatment would probably be needed to control rheumatoid arthritis in the long term, and the major concern is whether inducing lymphopenia for prolonged periods would be associated with an increased risk of opportunistic infection. Research is also underway using monoclonal antibodies directed against cytokines such as tumour necrosis factor α , and early results are quite encouraging.³³ Other approaches include T cell vaccination and the use of blocking synthetic peptides to disrupt the presentation of the putative antigen in the peptide binding groove of the HLA DR4 molecule.

Conclusions

Most patients with rheumatoid arthritis require non-steroidal anti-inflammatory drugs to reduce pain and stiffness. Consideration should be given to also prescribing a gastroprotective agent in patients at high risk of the gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs. Second line treatment should be considered in patients with active synovitis or erosive disease to try to slow disease progression. Combination treatment cannot be justified on the evidence available. Despite these approaches, many

patients have continuing decline in function and new, more effective treatments are desperately needed.

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