Management of inflammatory joint disease

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Chronic inflammatory arthritis refers to a large group of arthritis conditions of various aetiologies and clinical presentations, but with the common feature of synovial inflammation. Abnormal activation of the immunoreactive cells (T-lymphocytes, B-lymphocytes, macrophages, dendritic cells, leucocytes) both systemically and locally in joints leads to the hallmarks of joint pain, swelling, warmth and reduced mobility. The commonest forms of inflammatory arthritis (Box 1) in usual clinical practice also share the potential for joint damage and loss of joint function.

Rheumatoid arthritis is the commonest of the chronic inflammatory arthritides occurring in approximately 1% of most populations. It is a systemic inflammatory disease, but with cardinal features of synovitis and joint erosions that lead to joint damage. It is now clear that erosions occur early in its course – most occur in the first three years (Figure 1) and set the scene for subsequent joint destruction and disability.

This newer understanding of the pathophysiology and the course of the disease has led to the development of more aggressive and early treatment approaches, as retardation of joint erosions has been demonstrated with early treatment with DMARDs (Disease Modifying Anti-Rheumatic Drugs).[1,2] In parallel, the same principles have been extended to the treatment of other forms of inflammatory arthritis. It should be remembered that the broader aspect of treatment of inflammatory arthritis entails much more than DMARDs, and includes symptomatic treatments, physical and surgical treatments, orthotics, education and rehabilitation (Figure 2).

Anti-inflammatory agents

Anti-inflammatory agents have been an essential cornerstone in inflammatory arthritis management. Although they do not possess disease modifying properties, they reduce pain and swelling of joints and in turn can facilitate exercise and physical therapy which in turn improves joint function and reduces disability. As well as the conventional NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) there are now available the COX-2 specific agents. Their selective COX-2 inhibition not only allows COX-2 mediated anti-inflammatory activity, but only minimally inhibits important COX-1 mediated homeostatic functions such as maintenance of the gastroduodenal mucosal integrity (Figure 3).

COX-2 inhibitors (Coxibs) show their main advantage in considerable less potential for gastroduodenal ulceration. In large scale studies of celecoxib and rofecoxib[10,11] upper gastrointestinal ulcer rate was significantly reduced when compared with conventional NSAIDs . It should be remembered that non-ulcer dyspepsia and other gastrointestinal adverse events also occur commonly with Coxib use. There is not any conclusive evidence that the Coxibs are any less likely to exacerbate Inflammatory Bowel Disease (IBD), so that all anti-inflammatories should be avoided in active IBD, and used with

Box 1. Commoner inflammatory arthritis conditions encountered in clinical practice

Commoner forms of Chronic Inflammatory Arthritis

- Rheumatoid arthritis
- Seronegative spondylarthropathy group
  - Psoriatic arthritis
  - Ankylosing spondylitis
  - Reactive arthritis
  - Inflammatory bowel disease related arthropathy
  - Undifferentiated spondylarthropathy and enthesitis/oligoarthritis
- Early undifferentiated persistent polyarthritis
- Systemic lupus erythematosis

caution only in quiescent IBD. As therapeutic agents, the Coxibs are of equivalent but not of superior efficacy to conventional NSAIDs. Doses of anti-inflammatory agents often need to be at the high end of the dose range compared with their use in non-inflammatory arthritis (Table 1).

Regular daily dosing is preferred over irregular or pain contingent dosing in order to achieve a Steady State therapeutic level. This is more likely to consistently suppress the inflammatory aspects of arthritis. In selecting an anti-inflammatory agent, it is worthwhile trialling two to three different agents if at first there is little therapeutic response. There is no rule for the preferred first choice of agent as there are considerable inter-individual differences in response that cannot be predicted. A particular agent may be chosen having regard to the potential for toxicity to the patient. Thus for example a short acting agent in low dose might be preferred over a long acting agent in the elderly patient. The patient with higher upper gastrointestinal risk may be better suited to a Coxib or to a conventional NSAID plus a gastroprotective agent (e.g. proton pump inhibitor).

Disease modifying anti-rheumatic drugs (DMARDs)

The early initiation of DMARD therapy can lead to substantial improvements in disease and retard radiographic progression[1,2] (Figure 4). The commonest conventional DMARDs in use in New Zealand are hydroxychloroquine, sulphasalazine, methotrexate, and most recently leflunomide (Arava). Other less commonly used agents include the older intramuscular gold therapy, D-Penicillamine, minocycline, and immunosuppressive agents such as Neoral cyclosporine and azathioprine. Prednisone is also now regarded as having disease modifying properties and because of its rapid onset of action, can be used in a variety of clinical settings and therapeutic applications,

Figure 1. Most joint erosions occur early in the course of rheumatoid arthritis.

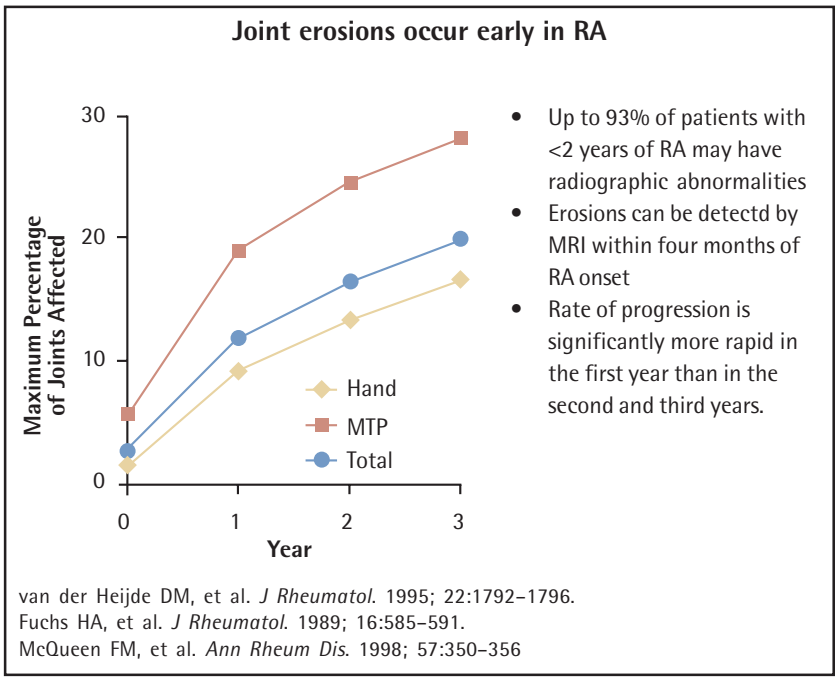

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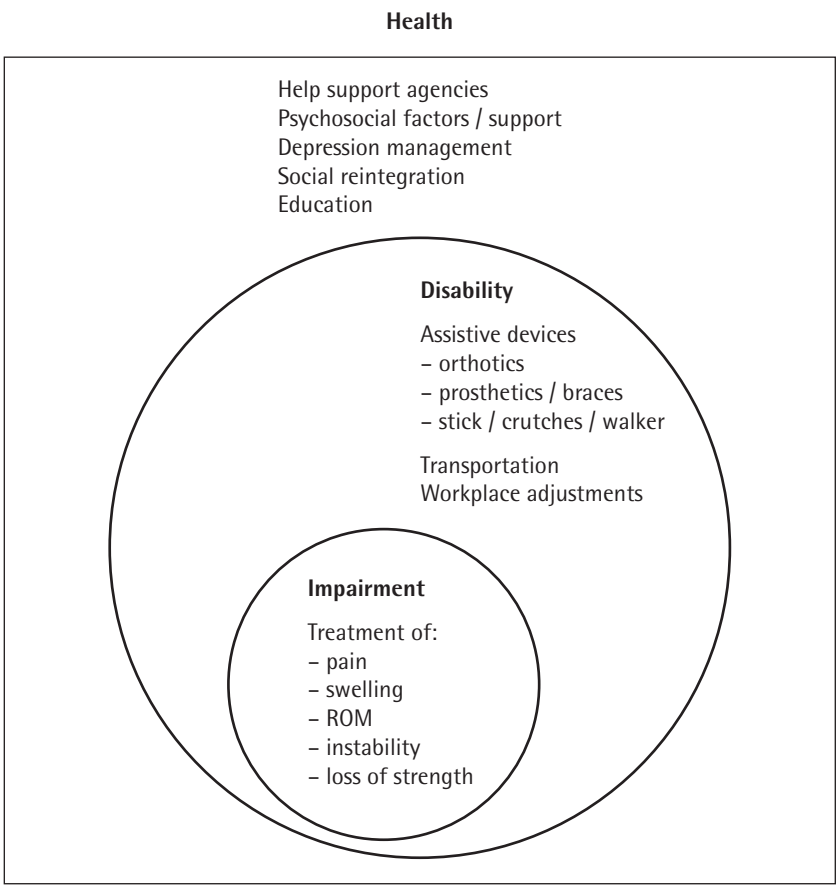
Figure 2. Relationship of impairment, disability and health in the management of arthritis.

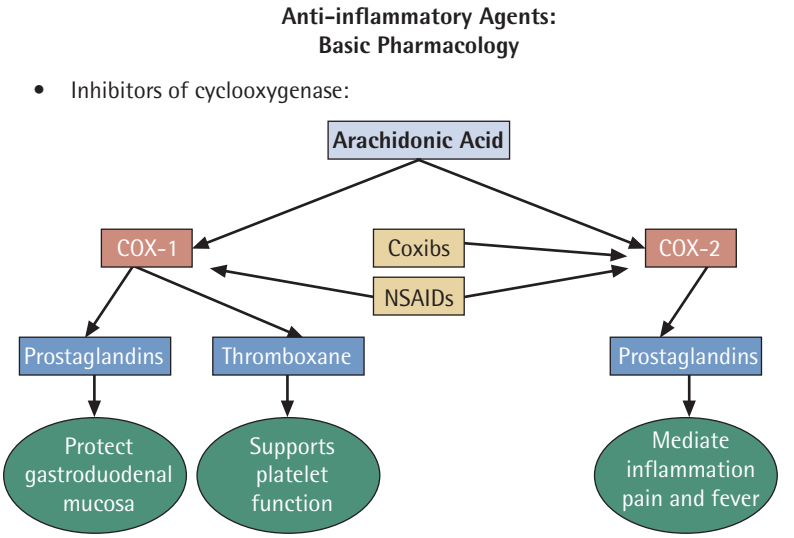


especially in those such as the elderly who may be intolerant of DMARDs (see later).

It is now perceived that the introduction of a DMARD should occur as early as possible after establishing a diagnosis of persistent chronic inflammatory arthritis where erosive disease is likely to occur – most commonly rheumatoid disease. In other forms of inflammatory arthritis such as the spondylarthropathies or in seronegative oligoarticular disease, the indication for routine early DMARD therapy is not as clear and is more likely determined by clinical indicators of moderate to severe disease inadequately controlled with anti-inflammatories, or appropriate corticosteroid joint injections in the case of oligoarticular disease.

One of the more difficult aspects is predicting which patients with early inflammatory arthritis will progress to persistent chronic disease compared with those who develop only mild or even self-limiting disease. While it is not desirable to commence a DMARD with its potential toxicities in the patient who does not need it because of mild/self-limiting disease, it is even less desirable to delay DMARD therapy in the patient until the groundwork (e.g. erosions) for permanent joint damage has already occurred. To find the ideal middle ground between these two adverse outcomes requires a careful assessment of the patient, and evaluation by a rheumatologist at this point is recommended. There are clinical indicators (such as Joint Swelling Counts, ESR, CRP, Rheumatoid Factors) and also Disease Activity Scoring systems[3] used in clinic settings that can assist in deciding who needs early DMARD therapy. Newer investigations such as selected joint MRI and Ultrasound have shown promise in the detection of early synovitis and erosive disease and will likely come into wider use.

Figure 3. Conventional NSAIDs inhibit both COX-1 and COX-2 mediated function whereas the Coxibs only inhibit COX-2, the target of prostaglandin mediated inflammation.



Hydroxychloroquine

Hydroxychloroquine (HCQ) is a commonly used DMARD of mild efficacy. It has a place in early rheumatoid arthritis and lupus arthritis, or added in combination therapy with other DMARDs such as methotrexate or salazopyrin in moderate to severe disease in which it would seldom be sufficient as monotherapy. Its long onset of action means that at least six months treatment should be trialled to assess efficacy. Used in dosages up to 6.5mg/kg/day – the usual daily dose is 200–400mg per day in the adult. It has relatively few adverse effects (nausea, skin rash and headaches being commonest) and does not require the same intensity of blood test monitoring as with other DMARDs. However, a baseline ophthalmology examination is required to screen for any pre-existing retinal disease, and periodic follow-up examinations to screen for the very rare instances of retinal toxicity. For practical purposes a 'baseline' examination could be performed in the first few months of therapy as retinal toxicity almost never occurs in the first six months at recommended dose.

Table 1. Suggested dose ranges for coxibs in OA (osteoarthritis), RA (Rheumatoid arthritis) and acute severe short-term arthritis conditions such as Gout. Similar relative dose ranges also apply to conventional NSAIDs.

Suggested Coxib dosing: (Pharmacia and MSD product information)			
	OA	RA	Gout or Acute
Celecoxib	100–200mg/day	200–400mg/day	400mg stat
Rofecoxib	12.5–25mg/day	25mg/day	50mg stat
Etoricoxib	60mg/day	90mg/day	120mg stat
Valdecoxib	10–20mg	20mg/day	40mg/d

Sulphasalazine (Salazopyrin EN)

In New Zealand salazopyrin is one of the commonest DMARDs initiated early in the course of rheumatoid disease and the seronegative spondy-

larthropathies. Like HCQ, the precise mode of action is unclear. The dose usually starts low at 500mg per day and is increased over three to four weeks to 1Gm twice a day. Doses above this are only occasionally more effective. The onset of action is relatively fast at four to eight weeks so a full three-month trial is recommended. Commoner adverse effects are headache, nausea and other gastrointestinal disturbance, occasional skin rashes, and rarer cytopenias (especially neutropenia). Regular blood test monitoring for haematology two to four weekly and liver enzymes four to six weekly is therefore required early in treatment, but the frequency can be reduced to as long as three-monthly with long-term therapy.

Methotrexate

Weekly oral methotrexate (MTX) is the most widely used DMARD in moderate to severe chronic inflammatory arthritis, either as monotherapy or in combination therapy. It is the agent most likely to provide a favourable response that is long-lasting and the most likely to be chosen by patients to continue for long periods of time.[4] MTX is usually commenced at 7.5mg as a single once a week dose, but increased over several weeks to 15mg per week. Further dose titrations up to 25mg per week are common, and occasionally higher doses are used by subcutaneous or intramuscular administration. Commoner adverse effects are nausea and other lower gastrointestinal tract symptoms, mouth ulcers, photosensitivity, with rarer pulmonary toxicity, cytopenias and liver enzyme elevations. Because of the rare potential for chronic hepatotoxicity such as hepatic fibrosis and cirrhosis, concomitant exposure to hepatotoxins such as alcohol and hepatotoxic drugs must be minimised. Alcohol intake should be no more than four to seven units per week, and avoided completely if serum transaminases become elevated. However, chronic liver disease is very rare where regular blood test monitoring is performed, as there is a well-defined ACR (American College of Rheumatology) protocol for the monitoring and management of abnormal liver tests. Folic acid supplements reduce the incidence of many of the adverse events. Avoidance or extreme care should be taken in the use of other medications that have antifolate activity (e.g. trimethoprim).

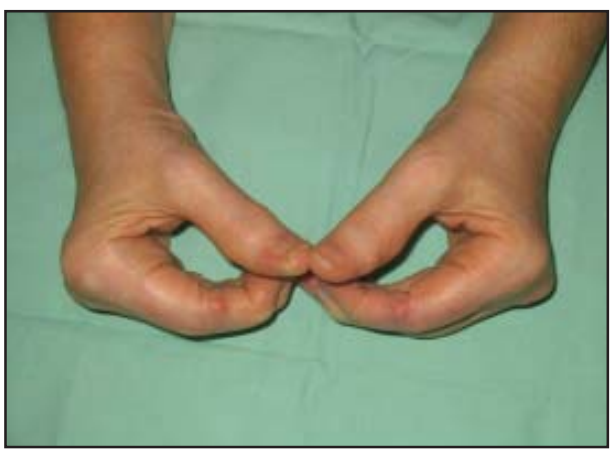
Leflunomide (Arava)

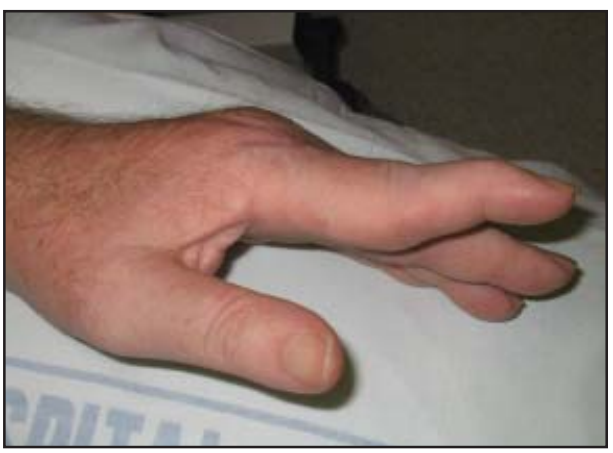
This agent is the most recent available subsidised DMARD in New Zealand for the treatment of rheumatoid arthritis. Its efficacy has also been demonstrated in the seronegative arthritides, especially psoriatic arthritis although it is currently not subsidised for these latter conditions. Leflunomide has a particularly long half-life of around two weeks and therefore takes several weeks after cessation of the drug for level to decline to minimal levels. It has approximately equal efficacy to moderate doses of methotrexate.[5] When used as sole DMARD therapy, an initial loading dose of 100mg per day for one to three days may be employed, followed by the maintenance dose of 20mg per day. If added to methotrexate therapy the loading dose is omitted and frequently a lower maintenance dose of 10mg daily is used. About two-thirds of re-

Key Points

- Chronic inflammatory arthritis requires a co-ordinated pharmacologic, physical, and social approach to management.
- Early diagnosis of an inflammatory arthritis and rheumatology referral are essential.
- Joint damage occurs early in the disease course.
- Treatment objectives now focus on early effective disease modifying therapies to prevent joint damage and disability.

Figure 4. The objective of early DMARD therapy is to prevent the deformity and loss of hand function in inflammatory arthritis





sponders do so by four weeks, and 90% by two months. Adverse events mainly relate to the gastrointestinal tract, but it also requires regular blood test monitoring for haematologic and liver toxicity. Because of its long half life, if serious adverse events occur, an elimination protocol over 11 days with cholestyramine or activated charcoal is required. If leflunomide is used in women of childbearing potential, pregnancy must be avoided for two years after cessation of the drug unless the elimination protocol is used and follow-up blood leflunomide levels are performed to ensure complete elimination.

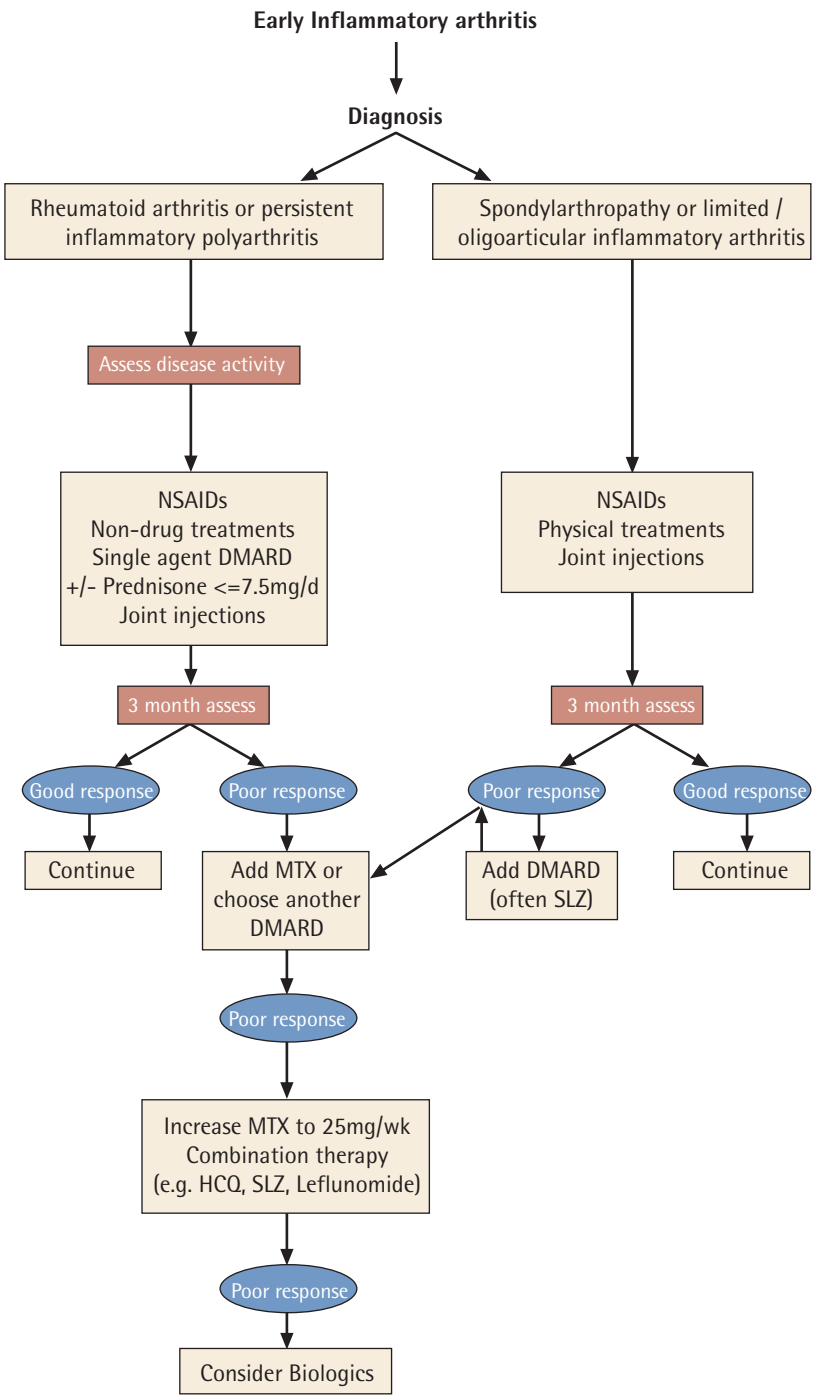
Combination DMARD therapy

Although single agent DMARD therapies produce good clinical response in the majority, remission or near remission is not commonly achieved. This has led to the use of combination DMARD therapy in the belief that there are additional or even synergistic effects. Several studies in the literature support the use of combination therapy, giving superior and more durable responses.[4] In New Zealand this has become commonplace especially with HCQ, SLZ and MTX. Methotrexate is the most common anchor in a combination regimen. Usually DMARDs are added sequentially according to clinical response, but occasionally combinations are used at the outset in more severe rheumatoid arthritis. Fortunately toxicity does not appear to occur any more commonly than with single agent therapy.

Oral and parenteral corticosteroids

Oral prednisone is being used increasingly in treating rheumatoid arthritis and other forms of inflammatory arthritis. A number of reviews[6,7] have demonstrated not only efficacy in rapidly reducing symptoms and signs of inflammatory arthritis, but also a reduction in the progression of erosions

Figure 5. Common treatment approach in inflammatory arthritis



This flow chart, in the opinion of the author, reflects the common clinical approach to treatment of inflammatory arthritis by New Zealand Rheumatologists. It is not intended to be used as a treatment protocol nor a clinical pathway. It is not formally endorsed by the NZ Rheumatology Association.

and joint damage when used early in the disease course (up to about two years from onset). With the use of lowest possible doses (2.5-7.5mg/day) and with the availability of effective anti-osteoporosis agents, side-effects can be significantly reduced. Prednisone can be employed in a number of ways:

- Short-term bridging therapy while awaiting DMARD onset of action
- Early DMARD therapy in its own right
- Treatment of disease flares
- Longer term therapy as DMARD or symptom control.

Intravenous or intramuscular corticosteroids may be used where short-term high doses of corticosteroids are needed such as in rapid induction of remission in severe disease, or for severe acute flares.

Intra-articular corticosteroids

Intra-articular corticosteroids play an essential adjunctive role in managing inflammatory polyarthritis, and central to management of large joint oligo- or mono-arthritis or oligo/monoarticular flares in polyarthritis. It may be the definitive management of specific problems such as carpal tunnel syndrome and flexor tenosynovitis. As there is appreciable systemic absorption from intra-articular injections, there is a useful short-term systemic corticosteroid effect especially where total doses of >/=40mg Depomedrol or triamcinolone are used. This systemic effect is usefully employed in DMARD bridging therapy and to assist in remission induction.

Biological agents

The newest developments are the biologic agents targeted against specific cytokines or immunoreactive cells (e.g. T and B-lymphocytes) central to the inflammatory process. TNF-alpha is one such cytokine essential to the perpetuation of the inflammatory response. Two anti-TNF agents have become available for limited use in New Zealand in selected patients: etanercept and infliximab. Adalimumab is the most recent agent currently being trialled in New Zealand as a multi-centre study of rheumatoid disease. These agents have approximate equal efficacy and have been shown to improve symptoms in patients already on methotrexate who have persistent active disease. Furthermore they have been shown to slow radiological progression.[8,9] They are also proving to be effective in psoriatic arthritis and the other spondylarthropathies. Rapid responses, even after days are seen. Infliximab is given by intermittent intravenous infusions every eight weeks after an initial six weeks of more frequent dosing. It requires co-therapy with methotrexate which reduces the production of anti-infliximab antibodies that would otherwise reduce its effectiveness. Etanercept is self-administered twice per week subcutaneously, and adalimumab subcutaneously every second week. Cost is a major limiting factor in New Zealand. These agents are not subsidised and can cost in the order of NZ$18,000–22,000 per annum. Commoner adverse effects include subcutaneous injection site reactions and infusion reactions (infliximab). With all agents there is a rare risk of serious deep tissue and opportunistic infections. As reactivation of latent tuberculosis is seen, screening for TB with a Mantoux test and chest x-ray is essential. In New Zealand the biologics are considered where progressive active disease persists despite adequate therapy with the currently available conventional DMARDs singly or in combination.

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