Dr Fahim Kahn*, discusses the successes and disappointments which are being experienced as the search for more effective and better tolerated rheumatoid arthritis therapies continues.

Rheumatoid arthritis: current and future high-tech therapies

Dr Fahim Khan

Rheumatoid arthritis is a multisystem autoimmune disease that usually takes the form of a chronic synovitis that progressively destroys bone and cartilage leading to an increased mobidity and mortality in affected individuals.

Current Therapies

Evidence is accumulating that early and aggressive disease suppression is the most likely route to a favourable outcome. The majority of patients who develop erosive and destructive rheumatoid arthritis begin to show radiological evidence of joint destruction within two years of disease onset. A window of opportunity may exist early in the disease process when switching off the inflammatory process will have its maximum impact on long-term outcome.

Modifying Disease

The majority of patients with rheumatoid arthritis are at some time treated with disease-modifying rheumatoid arthritis drugs. The commonly prescribed disease-modifying rheumatoid arthritis drugs and their side effects are listed in Table I.

Gold and penicillamine are older treatments of rheumatoid arthritis. They have an efficacy comparable to newer agents but have a slow onset of action and a high incidence of adverse events.

Antimalarials are less effective than gold and penicillamine but are also less toxic. Sulphasalazine and methotrexate are now established as the most widely prescribed second-line agents in clinical practice. They have a relatively rapid onset of action and a low incidence of serious adverse events. Azathioprine and cyclophosphamide are comparable in efficacy to gold.

Although steroids are undoubtedly effective in suppressing inflammation, their use is limited by their side effects, in particular osteoporosis. Steroids are not historically regarded as disease-modifying rheumatoid arthritis drugs, but a recent study has questioned that belief.

A recent report of an Arthritis and Rheumatism Council study showed that, in patients with early rheumatoid arthritis, two years of low-dose prednisolone reduced the rate of radiologically detected disease progression. Interestingly, the anti-inflammatory effect was lost in three-six months but the anti-erosive effect continued, suggesting the existence of different mechanisms for inflammation and bone erosion in rheumatoid arthritis. The issue of osteoporosis was addressed in this study and routine bone densitometry measurements were not made. This is of critical importance as bone mineral loss occurs rapidly at the beginning of steroid treatment.

Active synovitis can cause both local and systemic osteoporosis. The routine use of steroids in early rheumatoid arthritis is not practised by the authors and remains a controversial issue at present. If patients do receive steroid therapy, then a concurrent "bone sparing" agent such as a bisphosphonate should be considered.

Combination therapy

The combination of methotrexate, sulphasalazine and hydroxychloroquine has shown greater efficacy than dual or monotherapy but also a much greater tolerance with fewer adverse events. Combination therapy provides a sensible treatment strategy in patients not responding to monotherapy. It will have an important role in the future management of rheumatoid arthritis.

New Therapies

The majority of new therapies can be divided into those that target cytokines or those that target activated T cells. These therapies are based on the concept that if cytokines or T cells play a role in the disease process, then their inhibition will cause disease suppression.

Cytokines are soluble molecules that control cellular communications and mediate the inflammatory response. Cytokines are produced by a variety of cells including macrophages, fibroblasts, and lymphocytes. Some are pro-inflammatory (TNFα, IL1, IL6, IL8, IL12, and GM-CSF) and others anti-inflammatory (IL4, IL10 and TGFβ).

As more and more cytokines are being characterised, therapeutic agents to inhibit their actions are being developed. Some of the cytokines targeted in rheumatoid arthritis are shown in Fig.1. Macrophage- and fibroblast -derived cytokines have been found in abundance in inflamed joints but surprisingly T cell derived cytokines have been difficult to find.

We can neatly divide most future therapies into those that are directed against macrophage/fibroblast cytokines, T cells and their cytokines or cytokine products.

Table 1: Side effects of DMARDs

Gold	Rashes, mouth ulcers, diarrhoea, glomerulonephritis
Penicillamine	Rashes, taste loss, mouth ulcers, agranulocytosis, thrombocytopenia
Antimalarials	Headache, retinal damage, conrneal opacities, alopcia
Azathioprine	Nausea, diarrhoea, agranulocytosis, thrombocytopenia
Sulphasalazine	Nausea, vomiting, haematological abnormalities, azospermia, lupus-like syndrome
Methotrexate	Nausea, marrow suppression, hepatic fibrosis, pneumonitis, lung-fibrosis

Fig 1. Potential therapeutic targets in Rheumatoid arthritis

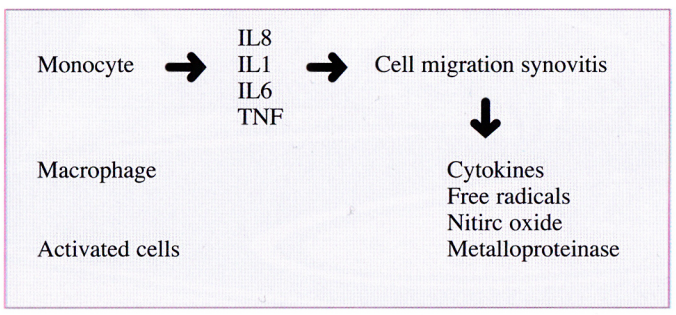

Fig 2. Four week trial of anti TNF treatment.

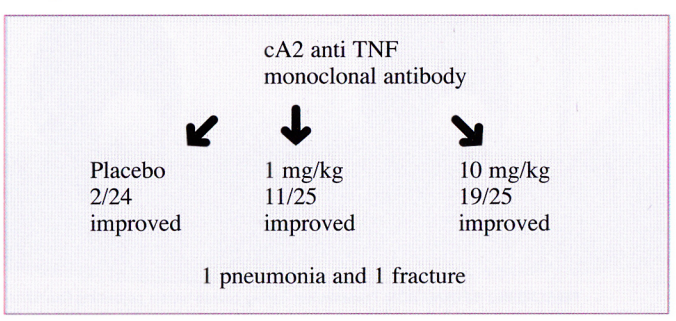

Table 2: Side effects of monoclonal antibody (MoA) therapy.

Fever, chills, anaphylaxis	Risk of infection
Nausea, diarrhoea	Carcinogenesis
Myalgia	Human anti-mouse antibodies
Hypertension, seizures	Anti-nuclear antibodies

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- Dr. Fahim Kahn

Agents directed against macrophage /fibroblast cytokines

Monoclonal antibodies (MoA)

Following the use of monoclonal antibodies in transplant medicine, their use is now being evaluated in the treatment of rheumatoid arthritis. Experience so far has mainly been with monoclonal antibodies targeted against TNFα, T cell epitopes and other receptor-ligand interactions. The important results to date are discussed below.

Anti-TNFα Monoclonal Antibodies: There is some evidence that TNFα is an important inflammatory mediator in rheumatoid arthritis. Following encouraging results regarding the safety profile and efficacy of the monoclonal chimeric anti-TNFα antibody cA2 in open trials, a four-week randomised double-blind placebo-controlled trial was undertaken. The results and major adverse events of this study are summarised in Fig.2.

It was concluded from this study that specific cytokine blockade can rapidly suppress inflammation for a short-time, but the mode of action was not clear and long-term adverse effects remain unknown.

Anti-IL6 Monoclonal Antibody: This treatment has shown a transitory improvement in some patients.

Somewhat surprisingly the IL6 levels actually increased in four patients with no increase in disease activity.

Overall it would seem that monoclonal antibodies offer a brief respite during active disease, although apart from anti-TNFα treatment, the results of clinical trials have been disappointing. The side effects experienced with those biologic agents are listed in Table 2.

Importantly, patients receiving monoclonal antibodies develop human anti-mouse antibodies that may cause resistance to future treatment and may even be pro-inflammatory. The need for randomised controlled trials and evaluation of long-term toxicity of monoclonal antibodies is critical if they are to be used in routine clinical practice. The effects of long-term cytokine suppression also need to be studied.

TNFα soluble receptor (TNFsR)

TNFα soluble receptor is a specific inhibitor of TNFα. Two recent studies published in abstract form have shown a modest improvement in rheumatoid arthritis patients treated with TNFsR infusions. One of the difficulties has been the extremely short circulating half-life of TNFsR and an immunoconjugate with a longer half-life is being developed for further studies.

IL1 receptor antagonist protein (IRAP)

IL1 is a major pro-inflammatory cytokine which is increased in rheumatoid arthritis along with its inhibitory receptor protein, IRAP. There is evidence that IRAP production relative to IL1B is

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