Infliximab: a new treatment for rheumatoid arthritis

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Infliximab, a chimeric mouse human monoclonal antibody, is an anti-TNF treatment for rheumatoid arthritis. In the past there was a sizeable group of people who had exhausted disease-modifying antirheumatic drugs (DMARDs) and were left largely untreated. This has been revolutionized by treatments such as infliximab which have been shown to be effective for patients in whom standard DMARDs have failed.

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases and one of the most common causes of treatable disability in the western world. Its prevalence is estimated at around 1%, with an incidence of 0.04%. Disease onset is insidious with gradual spread from small joints leading to the involvement of the majority of synovial joints over the first few years. Although RA is not immediately life-threatening it is a chronic disease which, when there is active inflammation, leads to significant disability, shortened life expectancy and important economic consequences. The direct and indirect costs have been estimated for the UK at £1.3 billion per annum (McIntosh, 1996).

Conventionally two major classes of drugs are used for the management of this disorder. First are the non-steroidal anti-inflammatory drugs which block cyclo-oxygenase and thus inhibit inflammatory prostaglandins. These are effective early in RA in reducing joint swelling and pain. However, as they have no effect on cytokine production, they do not influence the underlying basis of the disease (and thus do not influence spread of disease) and have no effect on cartilage or bone destruction. The absence of effect on cytokines is consistent with the observed lack of effect on the acute phase proteins, C-reactive protein and fibrinogen (the latter measured by the erythrocyte sedimentation rate), which are elevated because of the action of proinflammatory cytokines on the liver.

By contrast, disease-modifying anti-rheumatic drugs (DMARDs) inhibit proinflammatory cytokines, thus retarding the cartilage and bone lesions characteristic of RA, and secondarily reduce the acute phase response. The observation that such damaging effects occur early in the disease has led to increased emphasis on the importance of early diagnosis of RA and prompt initiation of therapy with DMARDs. When DMARDs are well tolerated and given in optimal doses they are effective in reducing the disease progression by reducing the number of swollen joints and preventing spreading of disease. The current most popular approach for managing RA patients with these drugs is to use them sequentially, adding extra DMARDs to partially effective drugs in so-called combination therapy.

An advantageous consequence of the availability and effectiveness of new agents has been that existing DMARDs have been used more effectively. This has meant the dose escalating more rapidly and using higher total doses, with doses of 25 mg methotrexate now commonplace. Such protocols have produced a greater efficacy than previously had been observed, fortunately with little excess toxicity. There is no doubt that for many patients existing therapies can be very effective, although even with new approaches there remain a considerable number of patients who do not have their disease adequately controlled.

In the past there was no effective therapy for those who had exhausted existing DMARD treatment and they were condemned to a progressive catabolic state resulting in disability and premature death (reduced life expectancy of approximately 7 years). This has been revolutionized by the availability of a number of new agents which have been shown to be effective for patients in whom standard DMARDs have failed. So far the side-effect:benefit ratio of these drugs has been so favourable as to raise the question whether they should be first-line therapy in this disorder.

THE ROLE OF TISSUE NECROSIS FACTOR IN THE PATHOGENESIS OF RA

In RA there is a systemic immune response, with the major pathology localized within the joint

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lining: the synovium. The activation of lymphocytes within the synovium and the peripheral lymph nodes leads to the production of cytokines and immunoglobulins. It is uncertain why a mechanism which leads to a self-limiting response in unaffected people changes to sustaining a chronic response in patients with RA.

T lymphocytes are involved in the initiation of the immune response and tumour necrosis factor-alpha (TNFα) has a central role in the continuation of the pathological process. TNFα is a proinflammatory cytokine, produced largely by macrophages and monocytes, which stimulates lymphocytes to produce interleukin (IL)-6 and granulocyte-macrophage colony stimulating factor (GM-CSF). TNF has recently been shown to have a major effect on osteoclasts, largely through its effect on the RANK ligand (Receptor Activator of NF κ B). In addition, TNFα encourages migration of inflammatory cells from the vascular compartment by upregulating the expression of adhesion molecules on the endothelial cell. Elevated levels of TNFα and soluble TNF receptors have been demonstrated in RA in the blood and synovial fluid in patients with active RA, whereas they may be detected but usually at low levels in normal individuals. The actions of TNF are mediated through two receptors, P55 and P75, truncated versions of which are the respective soluble receptors. These soluble receptors increase in concentration with release of TNF and are thought to modulate the effects of TNFα.

TREATING RA BY BLOCKING TNF'S ACTIONS

The last 5 years have seen the development of molecules which antagonize TNF directly and indirectly. These include monoclonal antibodies to TNF and soluble TNF receptors coupled to immunoglobulin molecules. Infliximab is a chimeric mouse human monoclonal antibody and was the first anti-TNF treatment to be used in man. An initial pilot study (Elliott et al, 1994) was undertaken followed by a randomized controlled study of 73 patients who received an intravenous infusion of infliximab 1 or 10 mg/kg or placebo. The higher dose resulted in a 20% improvement in the composite American College of Rheumatology criteria for improvement in around 80% of patients, and a 50% improvement in the response criteria in nearly 60% of patients at week four.

A further study (Maini et al, 1998) assessed the effect of various doses of infliximab or placebo in combination with various doses of methotrexate. This study showed a rapid and sustained improvement in approximately 60% of patients receiving either 3 or 10 mg/kg infliximab. There was a prolongation of the beneficial effects in those groups receiving methotrexate.

The pivotal ATTRACT study (1999) evaluated infusions of infliximab 0, 3 or 10 mg/kg at either 4- or 8-weekly intervals in patients on a stable dose of methotrexate (median 15 mg). Around 50% of patients achieved 20% response by 6 months and there was no significant difference between the different doses. Importantly the results were confirmed by equal improvement at 54 and 108 weeks. The discontinuation rate as a result of toxicity was not greater in the active treatment group than for placebo, whereas the withdrawal rate because of lack of efficacy was considerably lower in patients receiving infliximab (8% overall) compared with placebo (25%).

These impressive results were felt to be largely caused by the inhibition of the inflammatory process by TNFα. However, there were doubts as to whether blocking TNF alone would be enough to completely block the effect of all proinflammatory cytokines on bone and cartilage. This perception was reinforced by animal work (Joosten et al, 1999) suggesting that IL-1β was more dominant than TNFα in its impact on bone. Therefore the radiological changes demonstrated in the ATTRACT study were awaited with great interest.

It should be re-emphasized that the patients in this trial had a long duration of disease and already a great deal of structural damage to their joints. The damage was assessed radiologically by a scoring method which is a composite measure of joint space narrowing and erosion score. The data showed that infliximab in combination with methotrexate significantly reduced the rate of progression of damage compared to methotrexate alone (Lipsky et al, 2000). In the majority of patients the erosions were completely arrested. However, it should be noted that there is insensitivity in this measure in that a large number of patients who had received methotrexate treatment alone also did not progress. Nevertheless it should be stressed that these results represent the best retardation of structural damage that has ever been demonstrated in patients with RA, and also this retardation occurred in a group of patients who had previously been thought to be untreatable as they had not responded to conventional DMARDs.

SAFETY AND TOLERABILITY OF INFLIXIMAB

The most immediate problems with infliximab treatment are infusion reactions which tend to occur during the first four infusions and are usually overcome with symptomatic measures, e.g. slowing the infusion or adding bronchodilators. Longer-term problems include occurrence of anti-

nuclear and anti-double stranded DNA antibodies, which may cause a lupus-like reaction to develop. This is fortunately rare and reversible (ATTRACT Study Group, 1999). Long-term worries include development of malignancy and lymphoma although at present there is no evidence from the extensive databases provided by companies to the Food and Drug Administration to suggest that either of these are increased over background levels in equivalent matched RA patients.

COST-EFFECTIVENESS WITH INFLIXIMAB IN RA

RA is associated with high direct and indirect costs in comparison to other chronic diseases. Indirect costs can reach $20 000 in patients with a health assessment questionnaire (HAQ) score (functional) over 2.6 (Kobelt et al, 1999). From projections by Kobelt et al (1999), a reduction in the HAQ score to 1.1–1.6 might reduce costs to about $11 500 and reducing it further to 0.5–1.1 might reduce costs to about $6000. Using these comparators the ATTRACT data can be analysed. The functional score was reduced from 1.8 to 1.4, which should result in a $8000 saving, combining direct and indirect costs (Yelin and Wanke, 1999).

Despite the high direct costs of these agents they may prove to be cost-effective, although current data are preliminary (Emery et al, 1999).

GUIDELINES AND LONG-TERM ISSUES OF TNF BLOCKING AGENTS

A number of proposals have been presented for the use of TNF. Initially it was felt sensible to restrict use of this drug until more data were available on the long-term safety and thus not to recommend anti-TNF therapy in patients who were responding to existing therapies. The initial recommendation was that appropriate patients would be those who had documented evidence of failure to respond to a full course of the most effective therapy and still had active RA, or patients who had suffered toxicity from all available DMARDs (Emery et al, 1999; Bingham and Emery, 2000).

The side-effects of the disease in patients with active disease are considerable. There is now good evidence that patients with active disease results in elevated functional disability score (HAQ), increased bony erosions, increased osteoporosis and therefore are virtually certain to outweigh any potential danger from the therapy. Increasing evidence of the safety of these drugs will alter the cost–benefit equation and therefore make their use more attractive to physicians. As this happens the limitations to treatment then become financial. Restrictions are bound to occur as there are very few areas of the country that have sufficient funds available for these new treatments.

As the evidence for the cost efficacy of these new treatments increases the issue of comparative importance of anti-TNF in RA *vs* therapy in other diseases arises. Importantly the pivotal data for the current TNF blocking agents were obtained from patients who had failed all other therapeutic options. The magnitude of the response was better than that of previously untreated patients treated with DMARDs. These therapies are therefore a major health advance (health gain) and it is likely than new money will have to be rapidly found to fund such significant new advances. **HM**

KEY POINTS

- Tumour necrosis factor (TNF) is a crucial cytokine in pathogenesis of rheumatoid arthritis (RA).
- In the past many patients had no effective therapy for RA.
- The first TNF blocking agents are licensed for treatment (150 000 patients treated worldwide), and are remarkably effective in patients with RA.
- The short-term toxicity appears to be no greater than existing disease-modifying antirheumatic drugs (DMARDs).
- Infliximab has been shown to be effective for patients unresponsive to existing DMARDs.
- Concerns about long-term toxicity have not been confirmed.
- Given the large number of patients who could potentially benefit strict guidelines have been produced for their use.
- In the medium term use is likely to be limited by financial rather than medical reasons.

Conflict of interest: The Leeds early arthritis clinic was a major contributor to the ATTRACT study and has undertaken studies with Etanercept.

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