MINI-SYMPOSIUM: SURGICAL RHEUMATOLOGY

(v) Biological therapy in the management of inflammatory arthritis with particular reference to orthopaedic surgery

Deborah Hazlewood*, John Winfield

Department of Rheumatology, The Royal Hallamshire Hospital, Glossop Rd, Sheffield S10 2JF, UK

KEYWORDS
Inflammatory arthritis; Biological therapy; Orthopaedic surgery

Summary
Research over the past 20 years has identified that tumour necrosis factor-α is one of the key cytokines in the pathogenesis of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. This has led to targeted disease modifying therapies, the “biological agents” which have revolutionised modern rheumatology practice. This article outlines the currently available biological therapies, their indications, modes of action, benefits and potential side effects together with the current advice on their use at times of general and orthopaedic surgery.

© 2007 Published by Elsevier Ltd.

Introduction
Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine, a type of cell messenger, which has a key role in perpetuating the inflammatory response in various rheumatic disorders, particularly rheumatoid arthritis, psoriatic arthropathy and the spondylo arthropathies. TNF-α is also pivotal in maintaining host resistance by mediating an acute and chronic inflammatory response against infection and in promoting tissue healing. Thus blocking the actions of TNF-α with specific antagonists suppresses the body’s inflammatory response, thereby improving the symptoms and signs of an inflammatory arthropathy but, at the same time, may interfere with host resistance and healing. This led to TNF-α being identified as an attractive therapeutic target in rheumatological management whilst recognising the potential complications of its inhibition. TNF-α blocking drugs, commonly called “biological therapies” have been shown to be very effective in the control of refractory inflammatory arthritis, particularly rheumatoid arthritis (RA).

Clinical assessment of rheumatoid disease activity
Rheumatoid disease activity is assessed by the Disease Activity Score using 28 target joint sites (the DAS 28). This is a computerised score of the number of swollen, tender joints out of 28 combined with the patient’s own global assessment of their disease activity on a visual analogue scale of 100 mm combined with an ESR. Patients with a DAS...
score of greater than 5.1 are judged to have active rheumatoid disease. Those with a DAS 28 score of less than 1.2 are judged to be in a relative remission. Serial DAS measurements over time, typically one month apart, will identify those patients with persistent inflammatory joint disease, and will assess the patient’s response to initial therapy. Patients with a low disease activity score, i.e. less than 5.1, are deemed to have insufficient activity of their joint disease to justify going onto anti-TNF therapy, and hence will fail to meet the BSR and NICE criteria. However, low DAS scores are not synonymous with cure of rheumatoid synovitis, only a relative remission of active disease.

Current non 'biological' therapeutic approaches

Disease modifying anti-rheumatic drugs (DMARDs) such as Methotrexate—now the 'gold standard' therapy—leflunomide or sulphasalazine used either singly or in combination(s) remain the cornerstone of treatment for inflammatory arthritis, but they rarely induce complete and sustained remission. Thus rheumatic patients usually continue to suffer joint pain and stiffness with signs of ongoing joint inflammation and variable radiographic cumulative joint damage.

It is now generally agreed that rheumatoid disease can be diagnosed in patients with symptoms of less than three months duration and that patients should be referred early for specialist advice. Patients waiting for more than one year between symptom onset and specialist referral have a greater risk (73% compared with 34% of patients seen within one year) of developing erosive damage prior to treatment being initiated. DMARDs are now increasingly used very early in an attempt to suppress joint inflammation and reduce joint damage, but it has proved difficult to accurately predict which patients with very early inflammatory synovitis, i.e. < for less than six weeks, will go on to develop progressive joint damage, but any patient with persistent synovitis with an inflammatory response, i.e. a raised ESR and/or CRP, are most at risk. There is also evidence that rheumatoid arthritis may be more responsive to both DMARD and anti-TNF- therapy early in the course of the disease, possibly as short as 3–4 months from onset. This may lead to better suppression of the disease and an improved functional outcome.

The inflammatory response and the mechanism of action of the biological therapies

In the inflammatory cascade activated T cells release a range of cytokines including interleukin 2, interferon gamma, lymphocytotoxin, interleukin 3 and TNF- . Monocytes and fibroblasts are also capable of producing TNF-. In turn, via TNF- receptors on the cell surface TNF- stimulates macrophages which produce more TNF- and interleukin 1 and 6. The cumulative effect of these various cytokines is to produce an acute phase response characterised by fever, leucocytosis and a raised C reactive protein. TNF- is also powerfully chemotactic for neutrophils, can release prostaglandin E2 and promotes phagocy- tosis. It also promotes the release of the matrix metalloproteinases, MMP1 and 3 and leukotrienes from chondrocytes, osteoclasts and fibroblasts which have been shown to be responsible for the erosion of cartilage and bone in inflammatory arthritis. Both TNF- and TNF- receptors possess important cellular regulatory functions which include activation of immune cells and regulation of apoptosis, the programmed cell death of immune cells. Hence, targeting TNF- or the TNF- receptor, to potentially block the effect of TNF- , is theoretically an attractive therapeutic target and this has proved to be the case in clinical practice.

Currently three TNF- antagonists are now widely available in rheumatology practice in the UK. They work by either neutralising TNF- by binding directly with it or by blocking the TNF- receptor.

Infliximab and Adalimumab are specifically designed monoclonal antibodies engineered to bind with high affinity to both the soluble and transmembrane forms of TNF- preventing its action with the receptor. Infliximab is a chimeric (25% mouse, 75% human) monoclonal TNF- antibody produced by a recombinant cell line cultured by continuous perfusion. Adalimumab is a fully humanised monoclonal antibody with a 100% human peptide sequence and structure produced by recombinant DNA technology in a mammalian cell expression system. The third agent, Etanercept, is a fusion protein made up of two recombinant p75 soluble receptors fused to the Fc fragment of human IgG 1. It is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system and works by binding directly to the TNF- molecule thus preventing TNF from binding to or activating the TNF- receptor. All are expensive e.g. Infliximab costs £7500 for drug costs alone per year, and Etanercept and Adalimumab £9295. As they are not curative, treatment is ongoing year on year with cumulative costs.

They are administered by intravenous infusion (Infliximab) or by subcutaneous injection (Etanercept and Adalimumab). The biological agents should only be used with specialist advice from rheumatologists and administration supervised by specialist nurses with particular knowledge and expertise in the use of these drugs. Patients can be taught how to administer the subcutaneous injection themselves at home although patients requiring intravenous infusions of Infliximab are currently admitted as day cases to hospital.

For the one third of rheumatic patients who may be unresponsive to anti-TNF- drugs rituximab, a monoclonal antibody which depletes B cells, may be an alternative approach.

The biological agents are usually co-administered with methotrexate even though the previous response to methotrexate may have been incomplete. There are two reasons for this, firstly methotrexate is continued to prevent the gradual rejection of the monoclonal antibody through the body’s immune response against the biological agent, notably in the use of Infliximab which contains a mouse antigen and secondly the co-administration of methotrexate has been shown to be more beneficial than the biological agent alone in suppressing joint inflammation and reducing erosive damage.

Current drug treatment for newly diagnosed RA still includes a DMARD such as methotrexate. Patients with a
poor response to such therapy are either changed to an alternative DMARD, or are commenced on a combination of DMARD therapies. There are some patients who respond sub-optimally to all the currently available DMARD therapies, and some patients are intolerant of DMARD therapy and are forced to withdraw from treatment. The British Society for Rheumatology (BSR) guidance states that all patients should have a formal assessment of treatment response or lack of it to justify continuing on therapy or changing drugs. It is at this stage that the anti-TNF therapies are now being considered when there has been an incomplete response to DMARD therapy. The current BSR and NICE guidance on the use of biological therapies states that patients with rheumatoid arthritis should have tried at least two DMARDs, one of which should be methotrexate, at maximum dosage for six months, and have also demonstrated a sub-optimal response, i.e. persistent joint inflammation, before biological agents are considered. At present in the UK the use of the biological agents before DMARD therapy is not felt to be justified in those patients who might respond equally well to much cheaper DMARD therapy but there is now good evidence that the biological agents are more effective than standard DMARD therapy. Trials assessing the addition of anti TNF therapy to methotrexate have shown evidence of a substantial additional response by combining the biological therapies with methotrexate, even in patients who have been previously been poorly responsive to methotrexate. Similar clinical responses have been documented with all three biological agents.

**Funding issues**

In the UK application for appropriate funding for these drugs has to be made through the patients’ Primary Care Trust using the clinical guidance provided by the BSR and the National Institute of Clinical Excellence (NICE). The current NICE guidance in the UK has been criticised for limiting patients’ access to biological therapy due to the huge cost implications for Primary Care Trusts.

There are no reliable predictors of future responsiveness to DMARD therapies but there is increasing evidence suggesting that early aggressive DMARD treatment markedly improves outcome. However if patients fail to respond to DMARD therapies, over months or possibly years whilst they are trialling these drugs, either singly or in combination, their disease will be progressing and irreversible joint damage will occur. As clinical experience builds, it is likely that biological agents will be increasingly used at an earlier stage in the management of inflammatory arthritis, possibly at onset of disease, in an attempt to induce a complete remission at the earliest possible opportunity preventing morbidity and progressive joint damage. The cost/benefit of early aggressive DMARD and/or biological therapy awaits detailed financial analysis.

**Selection of patients suitable for anti TNF therapy**

It is now possible to identify patients with inflammatory joint disease for whom biological therapy is appropriate but it is not suitable for all of them as there are certain contraindications. Thus it is important that they are carefully screened for suitability before treatment. In particular the biological agents should not be prescribed for patients who have active viral or bacterial infections. Serious infections including fatalities have been reported whilst on anti-TNF therapy. Of particular relevance are pneumonia, pyelonephritis, septic arthritis and septicemia. Therefore patients with a history of recurrent chest, urinary or joint infections may be unsuitable for biological therapy. It should be remembered that before the TNF-α era the incidence rate of infection in the rheumatoid population was nearly twice as high as in matched non-rheumatoid controls, due to rheumatoid disease itself which alters immunological function, decreases mobility and causes skin sepsis and also due to the use of immuno-suppressive drugs, particularly steroids. In the early placebo controlled trials evaluating the three anti-TNF agents the rate of infection did not exceed the rate in the placebo group but, as the early studies had strict inclusion criteria and were relatively short studies, infection was not thought to be a specific risk. Indeed two post-marketing studies from Sweden and the UK suggested that the risk of developing serious infections was not increased in patients receiving TNF-α therapy for rheumatic diseases with around five infection events per 100 patient years for all three anti-TNF drugs. Since then numerous case reports or small series of patients with serious infections, including tuberculosis (TB) and opportunistic infections, have been reported worldwide. TB was the most frequently reported granulomatous infection and has been reported with the use of all three anti-TNF-α blockers, particularly relevant for Infliximab. Latent TB can be reactivated and present in a disseminated, miliary form or develop at extra pulmonary sites with most cases occurring in patients with a known past history of tuberculosis. A pre-treatment chest X-ray looking specifically for TB is mandatory. Skin testing for the presence of TB with the tuberculin reaction or Heaf test may be unreliable. The Elispot test has shown promise in identifying patients with a latent TB infection. When the presence of TB is uncertain advice from respiratory or infectious diseases physicians is advisable and anti-tuberculous therapy may be necessary prior to commencing anti-TNF therapy if there is a high index of suspicion. Other invasive opportunistic infections also occur with the three TNF-α blocking drugs including pneumocystis carinii pneumonia, disseminated histoplasmosis, listeriosis and aspergillosis.

Even after these have been excluded prior to commencing anti-TNF-α treatment, patients must be regularly monitored during treatment for the possible emergence of infection and should carry an “infection alert card” and be advised to report any symptoms suggestive of infection. Patients are also advised to report to their clinical nurse specialist if they have been started on antibiotics by their general practitioner for incidental infections during the course of treatment to assess the severity of the infection, its duration, the response to antibiotic treatment and the possible need for temporary withdrawal from anti-TNF-α therapy.

Further specific contra-indications to biological therapy include moderate to severe heart failure (New York Heart Association grade 3 or 4), patients with a history of demyelinating disease, women who are pregnant or breast...
feeding and patients who have had a current or past history of malignancy except for certain cases of skin malignancy. This is relevant because patients with rheumatoid arthritis have an increased risk of developing a malignancy over time, particularly lymphoma. So far the theoretical increased risk of developing solid tumours in rheumatoid patients taking anti-TNF therapy, due to the therapy itself, has not been realised but ongoing surveillance is necessary.

**Other indications for anti TNF therapy**

Anti-TNF drugs have been shown to be effective in the management of poorly controlled psoriatic arthritis and ankylosing spondylitis. The use of anti-TNF drugs has provided a new line of treatment opportunity for patients with both these conditions based on the early work in rheumatoid arthritis.25-29

**Issues for orthopaedic management**

The increasing use of the biological agents has implications for the orthopaedic surgeon as there has been much debate about the risks associated with their use around the time of surgery. The main concern is the risk of peri/post operative infection if patients remain on anti-TNF therapy during the surgical period due to the immunosuppressive nature of their mode of action, but also the concomitant risk of losing control of inflammatory joint disease and inducing a ‘flare’ if therapy is stopped, particularly in patients with severe disease.

It has been estimated that 25% of patients with RA will require surgery within 20 years of the disease onset, a figure which may be declining.30 Hopefully the majority will now be patients whose overall disease is controlled on their current therapy, but who already have irreversible joint damage requiring joint replacement. These cases require careful assessment. Rheumatoid disease commonly causes atrophy of the skin and subcutaneous tissue over time, exacerbated by steroid therapy. Careful handling of the patient’s limbs and tissues before, during and after a surgical procedure to minimise soft tissue bruising and shearing stresses across the skin and meticulous skin closure at surgery are imperative. Even so it is common to observe small sections of a surgical wound breaking down after major orthopaedic surgery in rheumatoid patients. Fortunately most of these will heal without any further complications.

The most important complication in elective orthopaedic surgery is surgical site infection (SSI).31,32 Patients with RA are already at increased risk of infection which has been demonstrated in several high quality randomised trials and there is a further increased risk of infection with the biological agents.19 The calculated odds ratio for infection from pooled high quality randomised trials of patients on biological therapy between 1998 and 2004 revealed a figure greater than 1.5 for sepsis. Infections were found to be more likely to occur in the presence of increased age, extra-articular features of rheumatoid arthritis, leukaemia, and other co-morbidities. Strong predictors for the development of serious systemic infection were previous orthopaedic surgery and high cumulative steroid dose.19,20 Several studies assessing the infection risk peri-operatively in RA have identified various poor prognostic factors. These include the type of surgery especially foot operations, previous SSIs, co-morbidities particularly diabetes mellitus and pulmonary disease, active RA and steroid use.4

There is no convincing evidence that disease modifying agents such as methotrexate, sulphasalazine, hydroxychloroquine, leflunomide and Myocrisin increase this risk,13 but many surgeons still express concern about their effect on initial wound healing, subsequent wound dehiscence and the risk of surgical wound infection. There is little objective evidence of a relationship between anti TNF agents and infection risk at the time of orthopaedic surgery, but preliminary reports have suggested higher rates of infection in these patients.34,35 However several small studies have since failed to identify an increased incidence of SSIs.36

Wendling et al. reported a retrospective study of 50 surgical procedures in 30 rheumatoid patients. In 18 cases TNF was stopped prior to surgery, the remainder had surgery between their two sequential anti TNF injections. Minor post operative complications were recorded in 6%, principally delays in wound healing of 1–2 weeks, and a moderate, short lasting rheumatoid disease flare was reported in 12% of those who had their anti TNF drugs withdrawn. The study did not demonstrate an increased frequency of adverse events related to uninterrupted use of anti TNF, but did raise an important consideration about planning surgery between anti-TNF-α treatments.36

Bibbo et al. analysed the risk of healing/infectious complications in a small number of rheumatoid patients undergoing elective foot and ankle surgery.37 All patients continued their anti-rheumatic medications, with 16 patients on non TNF disease modifying treatments and 15 on anti TNF therapies. The study demonstrated no difference in complication rates for both groups including an analysis of sepsis rates. Giles et al. however reported adverse findings. Their study identified 91 patients from the Johns Hopkins Arthritis Centre who had undergone orthopaedic surgery,38 who had an increased risk of infection, with an odds ratio of 5.3, for patients receiving anti TNF therapy. Unfortunately due to patient record ambiguities there was some uncertainty regarding the timing of their last preoperative administration of anti TNF, which may have affected interpretation of data.

Den Broeder et al. performed a large retrospective study to assess the effect of withholding vs maintaining anti TNF therapy on the incidence of SSI, and secondarily looked at the effect of discontinuation of anti TNF therapy on other complications.32 A total of 1219 procedures were performed on 768 patients. Factors which led to an increased risk of SSI included foot, ankle or elbow surgery, but a history of previous SSI was by far the strongest predictor of future sepsis. Continued peri-operative use of biological agents was not a strong factor associated with the risk of SSI. However wound dehiscence and bleeding occurred significantly more frequently in patients who continued on anti-TNF-α therapy. Limitations of this study included the overall low infection rates. A study with much larger numbers to assess such risks is required. There was also a lack of data on rheumatoid disease activity which could affect the risk and incidence of sepsis.
In Sheffield it has been our practice not to stop or reduce any of the conventional DMARD therapies over the operative period. We have not observed any particular orthopaedic complications by continuing DMARDs. We have found that withdrawing disease modifying drugs over the operative period usually results in a flare of rheumatic disease activity which can take weeks or months to re-stabilise, during which time the patient is trying to mobilise and rehabilitate following their operation. Withdrawing anti-TNF-α treatments pose a similar issue.

In a small retrospective study in Sheffield reported at the meeting of the European Rheumatoid Arthritis Surgical Society in Zurich in 2006 we reviewed 49 of our rheumatoid arthritis patients on biological therapies who underwent various major and minor orthopaedic operations under different orthopaedic surgeons and some non-orthopaedic surgery (13 total knee replacements and four total hip replacements). In all patients the biological agents were withdrawn for two weeks prior to surgery and recommenced once the sutures had been removed and the wound had healed. No peri-operative infections or wound complications were identified but patients experienced flare ups of their rheumatoid arthritis on temporary withdrawal of their anti-TNF therapy. This was also seen in patients undergoing other orthopaedic operations such as metacarpophalangeal joint replacements, soft tissue corrections, forefoot arthroplasties, ankle and wrist fusions and a cervical decompression.

Eleven patients underwent non-orthopaedic operations including mastectomy, coronary artery bypass surgery, cochlear implant and dental extractions. They also had flares of their rheumatoid disease activity but no problems with wound infections or systemic sepsis on withdrawal of anti-TNF-α therapy. Rheumatoid disease control was re-established when patients were re-started on their biological agent in 46 of the 49 patients who had surgery but the remaining three patients required a switch to an alternative anti-TNF agent. Notably several patients experienced delayed wound healing despite being off anti TNF therapies, leading to significant delays in recommencing anti-TNF-α treatment and hence suffered marked prolonged flares of their disease. A confounding difficulty was regular examination of the wound for healing in patients with a plaster cast for a joint fusion. In this study we also reviewed 14 patients with rheumatoid arthritis who had undergone mini-arthroscopy of the knee under local anaesthesia. In these patients the anti-TNF drugs were not stopped before, during or after the procedures. No complications were identified apart from one case of minor knee swelling post-operatively but no infection was identified.

Should biological therapy be continued or withdrawn at the time of surgery?

Due to the lack of firm evidence current guidelines vary. Our current policy in Sheffield, supported by knowledge of the half life of the various biological agents used, is to withdraw the biological agent two weeks prior to the planned date of surgery to ensure a “washout period” and then to only restart the biological therapy two weeks after sutures have been removed and the wound has been shown to be fully healed. This view is supported by the manufacturers of the biological agents.

The Dutch guideline recommends cessation of anti TNF treatments four drug half-life times prior to an operation, which varies for the different treatments (Infliximab 39 days, Etanercept 12 days, Adalimumab 56 days).32,37 Most centres in the UK consider that it is prudent to stop anti-TNF-α treatments prior to surgery and a common timescale is cessation 2 weeks prior to surgery with reintroduction when wound healing is complete.

Summary

The available data do not give any clear evidence based recommendations regarding the continued use or discontinuation of anti TNF therapies peri-operatively. Higher patient numbers on anti-TNF-α therapy are required in controlled trials to assess the risks of continuing on anti-TNF-α therapy at the time of surgery. Given the lack of available data current guidance errs on the side of caution and recommends the withdrawal of the biological agents over the operative period. The length of time needed for withdrawal either side of surgery is still not clear but current practice in the UK is to withdraw the biologicals two weeks prior to a procedure and restarting when the wound has healed, accepting a loss of rheumatoid disease control which can be prolonged, particularly in the presence of delayed wound healing.

Practice points:

- Early diagnosis, early referral and aggressive suppressive DMARD therapy is necessary for most patients with inflammatory arthritis to minimise joint damage and maintain function.
- Disease modifying drugs, notably Methotrexate, still remain the cornerstone of suppressive treatment for the majority.
- Patients with an incomplete response to DMARDs including Methotrexate should be considered for anti-TNF-α therapy using the BSR and NICE Guidance.
- Biological therapy carries an increased risk of infections during treatment, including activation of latent TB and opportunistic infection and there are specific contra-indications to anti-TNF-α therapy.
- Currently biological therapy should be temporarily withdrawn over the operative period to obviate sepsis but flares of inflammatory joint disease active are common on withdrawal.

Research directions:

- Controlled trials of patients undergoing orthopaedic operations who continue or discontinue their anti-TNF-α therapy over the surgical period should be carried out to compare and document whether there is an increased risk of sepsis over the surgical period if the drug is continued and/or whether disease flares can be avoided by continuing on therapy. Such a study should include an analysis of other risk factors for sepsis.
- Earlier use of anti-TNF-α therapies in the course of an inflammatory arthritis may result in excellent remissions possibly reducing the future requirement for orthopaedic intervention.
References


