Antitumour necrosis factor α treatments for rheumatoid arthritis

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Drs Fu and Bertouch present their review of an important development in the management of rheumatoid arthritis.

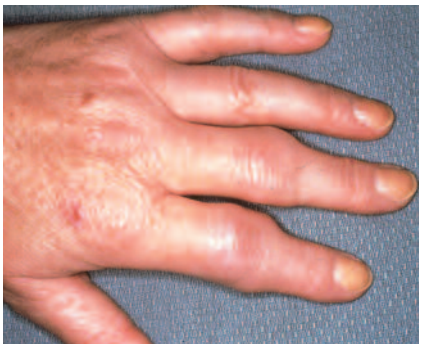

Figure. Acute rheumatoid arthritis.

Rheumatoid arthritis is a common progressive inflammatory disease that can result in erosive joint damage, functional disability, and increased mortality comparable to that of triple vessel coronary artery disease and stage IV non-Hodgkins lymphoma.[1] Epidemiological studies have shown that 30% of patients develop joint erosions within the first year and 70% within two years.[2] Despite the early introduction of disease-modifying antirheumatic drugs (DMARDs), often in combination rather than as monotherapy, many patients continue to have active disease and to show progressive joint damage.

Insight into the roles of proinflammatory cytokines such as tumour necrosis factor α (TNFα) and the availability of biological blocking therapies have revolutionised the management of rheumatoid arthritis in patients who have failed conventional treatment. Cytokines are a large family of proteins produced by activated macrophages and monocytes, and TNFα has been found in high levels in the synovium and fluid of joints affected by rheumatoid arthritis.[3] It upregulates other inflammatory mediators, induces matrix metalloproteinases that degrade cartilage, induces endothelial adhesion molecules that recruit cells into inflammatory sites, and stimulates the proliferation of synoviocytes and osteoclasts, ultimately leading to bone erosions.[3,4] The biological activity of TNFα is mediated through binding to two receptors, p55 and p75.

Agents and availability

There are three anti-TNFα agents available in Australia and indicated for treating severe active rheumatoid arthritis. These are:

- etanercept (Enbrel), which inactivates soluble TNFα
- infliximab (Remicade), which inactivates membrane-bound TNFα, leading to cell lysis, and soluble TNFα
- adalimumab (Humira), which inactivates membrane-bound and soluble TNFα.

Although the three TNFα agents are now all listed on the PBS, they cannot be prescribed by GPs – an application must be made in writing by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis. Patients need to satisfy predetermined criteria, including arthritis activity and demonstrated failure to achieve an adequate response to conventional DMARDs, given singly or in combination and in adequate dosage. PBS-subsidised treatment will be ceased after three months if there is failure to show a significant response as specified in the criteria (e.g. a 50% reduction in active joint count), and patients need to sign a declaration form agreeing to these conditions before commencing treatment.

Some key points for GPs with patients using these agents are given in the box on page 83.

Clinical efficacy

Etanercept

Etanercept has been compared with methotrexate in a two-year, double-blind, randomised, placebo-controlled trial of patients with early rheumatoid arthritis.[5] Both agents were effective DMARDs, but etanercept resulted in more rapid clinical improvement, with differences between the groups apparent at two weeks and sustained through two years. In addition, etanercept resulted in significantly less progression of joint erosions than methotrexate. In a study of patients with persistent rheumatoid arthritis, etanercept significantly improved clinical response and reduced erosion scores when added to methotrexate; furthermore, it allowed dose reduction or discontinuation of methotrexate and corticosteroids.[6]

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Anti-TNFα therapies: key points for GPs

- The three TNFα agents available in Australia cannot be prescribed by GPs – referral to a rheumatologist or clinical immunologist is required. The prescribing doctor will need to submit a detailed written application and may require information about the patient's history (e.g. use of past DMARDs and side effects) from the GP.
- Injection site reactions comprising erythema and/or pruritis, pain and local oedema are the most common adverse effects of anti-TNFα treatments given by self-administered subcutaneous injection.
- GPs should look out for opportunistic infections in patients using anti-TNFα therapies and encourage them to seek medical attention immediately for symptoms suggestive of infection (e.g. fever, rigor, night sweats, etc).
- Patients receiving anti-TNFα therapy should not receive live vaccines concurrently.
- Patients should be advised to seek medical attention for any symptom suggestive of tuberculosis. Anti-TNFα treatment should be stopped immediately if active tuberculosis is suspected.

Infliximab

Studies have shown infliximab therapy plus methotrexate to be significantly more effective than methotrexate alone in those patients with active rheumatoid arthritis.[7,8] The combination has also been shown to result in significantly less radiological damage and greater improvement in quality of life than methotrexate alone.[8] Responses are generally observed within a few weeks.

Adalimumab

In trials lasting up to six months, adalimumab has been effective both as monotherapy and in combination with methotrexate, with significant improvements in clinical parameters and radiological joint damage.[9] The onset of action is usually rapid, although the response may take longer in some patients.

Adverse effects and contraindications

The common adverse reactions reported in clinical trials are injection site reactions, headache, upper respiratory tract infections, cough, sinusitis and nasopharyngitis, nausea, diarrhoea, dizziness, fatigue and dermatitis. Contraindications are listed in the Table.

Injection or infusion-related reactions

In clinical trials, injection site reactions comprising erythema and/or pruritis, pain and local oedema were the most common adverse effect of etanercept and adalimumab. These reactions tended to occur one or two days after an injection in the first two months and subsequently decreased in frequency; generally they were self-limiting, lasting 2 or 3 days, and did not necessitate discontinuation of therapy.[5,6,10,11] Approximately 90% of injection site reactions to etanercept resolved without treatment, and the remainder were managed with oral or topical antihistamine or topical corticosteroids.[10]

Infusion-related reactions with infliximab have been reported in about 5% of patients, most commonly during the first infusion.[7] Most of these were reported to be mild, transient nausea and headache, and were usually controlled by slowing the infusion rate. Immediate hypersensitivity reactions, including fever, chills, urticaria and cardiopulmonary events, are rare,[4,7] and an infusion should be ceased immediately if these occur. Intravenous hydrocortisone and/or antihistamine may be needed to control symptoms.

Table. Contraindications to anti-TNFα therapies

- Previous tuberculosis, unless:
  - there is documented completion of a full course of modern antituberculosis therapy or the patient is undergoing isoniazid cover, and
  - the patient is fully aware of the risks and benefits
- Active infection (including chronically infected prosthesis)
- Septic arthritis within past 12 months
- Recurrent chest infections or bronchiectasis
- Indwelling urinary catheter
- Multiple sclerosis or a demyelinating illness (e.g. optic neuritis)
- Malignancy within the previous 10 years (five years for a fully resected basal cell carcinoma)
- Pregnancy and lactation
- Congestive cardiac failure
- Chronic cutaneous ulceration

Infections

Mild upper respiratory tract infections have been the most commonly reported type of infection, but in published trials the overall incidence and frequency of serious infections requiring hospitalisation or intravenous antibiotics did not differ from those in patients treated with placebo or methotrexate. GPs should encourage their patients to seek medical attention immediately if they develop symptoms suggestive of infection because septic work up needs to be performed and appropriate antibiotics given promptly to reduce morbidity. Anti-TNFα agents should be discontinued if a patient develops a life-threatening infection.

Mycobacterial infection

TNFα plays an important role in host defence against tuberculosis by inducing

macrophage apoptosis after mycobacterial infection.[12] Postmarketing surveillance has documented more than 100 cases of tuberculosis after treating approximately 200,000 patients worldwide with infliximab: 56% of patients had extrapulmonary tuberculosis, and approximately one-quarter had disseminated disease.[13] The median interval from the start of infliximab treatment to onset of tuberculosis was 12 weeks. The diagnosis was delayed in many cases because of the atypical presentation – development of tuberculosis in infliximab-treated patients is thought to represent reactivation of latent disease rather than newly acquired infection. The incidence is less with the other agents, which may reflect differences in binding to TNFα.

Every effort should be made by the treating physician to determine whether the patient has evidence of latent tuberculosis infection before initiating anti-TNFα therapy, and a baseline chest x-ray and Mantoux testing are essential for all patients. If there is evidence of prior tuberculosis exposure, a patient should be given prophylactic treatment to prevent reactivation of disease prior to anti-TNFα therapy: isoniazid, 300 mg twice daily for nine to 12 months, is the treatment of choice. Patients should be advised to seek medical attention if they have any symptom suggestive of tuberculosis while on treatment (e.g. persistent cough, weight loss, low grade fever), and GPs should be aware of this possibility. Anti-TNFα treatment should be stopped immediately if active tuberculosis is suspected.

Autoimmunity

The induction of positive antinuclear and anti-DNA antibodies has been described in patients with rheumatoid arthritis after anti-TNFα therapy. However, the frequency of clinical lupus related to these treatments is low,[14] and the symptoms of drug-induced lupus and serum antibody levels resolved with discontinuation of the offending agent in the majority of cases.

Demyelinating diseases

There have been rare case reports of demyelinating diseases with anti-TNFα agents. These have included new onset multiple sclerosis, exacerbation of pre-existing multiple sclerosis, myelitis, encephalopathy and optic neuritis.

Malignancies

Various types of new malignancies, including lymphoma, have been reported in patients with rheumatoid arthritis being treated with infliximab, etanercept or adalimumab in clinical trials. The observed rates and incidences were similar to those reported for the control populations of patients with rheumatoid arthritis.

Vaccination

Data regarding the safety and efficacy of vaccines administered in patients receiving anti-TNFα therapy are limited. The most commonly administered vaccines in adults are for pneumococcal disease and influenza. Patients on etanercept are able to mount an effective response to pneumococcal vaccine, but antibody titres are lower.[15] Ideally, pneumococcal or influenza vaccination of rheumatoid arthritis patients should be performed prior to starting anti-TNFα therapy because some patients on treatment may not mount an adequate response. Live vaccines should not be given concurrently.

Surgery

The safety of these medications in patients with rheumatoid arthritis undergoing surgical procedures has not been specifically studied. It is reasonable, however, to cease anti-TNFα agents during the perioperative period of any major surgery.

Cardiac failure

Congestive cardiac failure has been reported in patients receiving anti-TNFα therapy. Its presence should be regarded as a contraindication to the use of these agents.

Administration

Etanercept and adalimumab are given by subcutaneous injection (by self administration, if possible); adalimumab can be given less frequently than etanercept because it has a longer half-life. To satisfy PBS requirements, etanercept can be given without methotrexate, but adalimumab must be given in combination with methotrexate (oral or subcutaneous). Infliximab is given intravenously as a hospital day-treatment and in combination with methotrexate (either oral or subcutaneous) to reduce human anti-infliximab antibodies that can decrease efficacy.

Conclusion

The TNFα blocking agents represent an exciting development in the management of rheumatoid arthritis. They are expensive, and therefore should be reserved for patients whose disease is resistant to conventional DMARDs – in particular, methotrexate at doses up to 20 mg per week. Response to treatment should be assessed by validated response criteria at regular intervals. The majority of patients respond within the first weeks of treatment, and therefore treatment may be stopped at 12 weeks if the patient has not met response criteria. Side effects, including opportunistic infections, may occur, and hence careful monitoring of patients is required. These agents do not cure rheumatoid arthritis, and the disease usually flares after discontinuation of therapy. MT

A list of references is available on request to the editorial office.

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