



Managing patients taking tumour necrosis factor inhibitors

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Summary

Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or juvenile chronic arthritis that is unresponsive to standard disease-modifying antirheumatic drugs can now be treated with tumour necrosis factor inhibitors. These biological drugs all antagonise the actions of tumour necrosis factor, a key cytokine central to the inflammatory cascade. Their adverse effects can be severe and include sepsis, reactivation of pulmonary tuberculosis, blood dyscrasias, demyelinating syndromes, lymphoproliferative disease and precipitation of cardiac failure. Careful monitoring of patients is important.

Key words: adalimumab, etanercept, infliximab, rheumatology.

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Introduction

In recent years the treatment of inflammatory joint diseases has undergone a dramatic change with the advent of biological drugs. Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile chronic arthritis are potential candidates for this new therapy. Biological drugs are usually prescribed if the patient's condition has been resistant to treatment with standard disease-modifying antirheumatic drugs or if the patient has been unable to tolerate them.¹ In clinical trials biological drugs have been superior to disease-modifying antirheumatic drugs in achieving disease remission and retarding bony destruction. The most common biological drugs

used today belong to the class known as tumour necrosis factor (TNF) inhibitors. This class includes infliximab, adalimumab and etanercept. As these drugs are being used more frequently, it is important to be familiar with the principles of managing patients during treatment in the community.

Mechanism of action

Tumour necrosis factor is a critical pro-inflammatory cytokine in the cascade of inflammatory joint diseases.² It mediates many of the inflammatory processes in rheumatoid arthritis including immune-cell activation and proliferation, apoptosis and regulation of leucocyte movement. TNF inhibitors act to neutralise the actions of this cytokine by binding to TNF or its receptor. Infliximab and adalimumab are recombinant monoclonal antibodies while etanercept is a soluble TNF-receptor fusion protein.

In randomised double-blind placebo-controlled trials TNF inhibitors have significantly improved the clinical and radiological outcomes for patients whose rheumatoid arthritis has been poorly controlled by standard disease-modifying antirheumatic drugs. The majority of trials involved combination therapy with methotrexate.

Administration of TNF inhibitors

Infliximab is given by intravenous infusion while adalimumab and etanercept are self-administered as subcutaneous injections (Table 1). For rheumatoid arthritis infliximab is commenced at 3 mg/kg of body weight at 0, 2 and 6 weeks, then every 8 weeks. (In patients with an incomplete response, the maintenance dose may be gradually increased to a maximum of 10 mg/kg.) The dose of adalimumab is 40 mg fortnightly, while etanercept is given at 25 mg twice weekly or 50 mg once a week.

Table 1

Dose schedule for TNF inhibitors

Drug	Presentation	Route of administration	Dose in rheumatoid arthritis
Infliximab	Powder for reconstitution	Intravenous infusion	3 mg/kg repeated after 2 weeks and 6 weeks, then every 8 weeks
Adalimumab	Pre-filled syringe	Subcutaneous injection	40 mg repeated every 2 weeks
Etanercept	Powder for reconstitution	Subcutaneous injection	25 mg twice a week, or 50 mg once a week

TNF tumour necrosis factor

Indications

TNF inhibitors are indicated for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile chronic arthritis, however they are not subsidised by the Pharmaceutical Benefits Scheme for all these indications. The prescription of TNF inhibitors by a rheumatologist or clinical immunologist for adult inflammatory joint diseases must follow strict guidelines as set out in the Schedule of Pharmaceutical Benefits. These guidelines are under constant review and are updated to reflect results from new clinical trials. Psoriatic arthritis, for example, is an indication currently under review. As of June 2005 all TNF inhibitors are indicated for rheumatoid arthritis irrespective of the patient's rheumatoid factor status. In addition, infliximab and etanercept are indicated for ankylosing spondylitis. Only etanercept has been approved for juvenile chronic arthritis.

The efficacy of TNF inhibitors on the signs, symptoms, function, quality of life and retardation of radiological progression in patients with rheumatoid arthritis has been shown in a variety of roles. These include monotherapy, combination with methotrexate and in patients who have not previously been treated or have failed to respond to disease-modifying drugs. Combining a TNF inhibitor, especially infliximab, with methotrexate increases efficacy.

As there have been no direct head-to-head trials, no single TNF inhibitor can be said to be more effective than another. The choice of drug therefore depends on the patient's preference and the prescriber's experience with the particular TNF inhibitor. This includes considering the contraindications (see Box 1).

Before treatment

As part of the pre-treatment assessment, patients should have a chest X-ray to exclude latent pulmonary tuberculosis and congestive cardiac failure. The full blood count, liver function tests, hepatitis B and C serology, inflammatory markers

Box 1

Contraindications to TNF inhibitors¹¹

Previous untreated tuberculosis
Recurrent chest infections/bronchiectasis
Septic arthritis within 12 months
Infected prosthesis
Indwelling urinary catheter
Multiple sclerosis/demyelinating illness
Malignancy within 10 years (apart from fully resected basal cell carcinoma more than five years before)
Pregnancy and lactation
Congestive heart failure
Chronic cutaneous ulceration (but not pyoderma gangrenosum)

(CRP, ESR), and anti-nuclear and anti-double-stranded DNA autoantibodies should be checked before therapy. The presence of latent pulmonary tuberculosis warrants eradication therapy, usually for nine months, before starting a TNF inhibitor. This is best managed by a physician experienced in tuberculosis care.

Adverse effects

Given that TNF inhibitors are relatively new drugs, their long-term safety is still being established. From their mechanism of action it is predicted that there will be an increase in the incidence of infection and possibly secondary malignancy.

The pharmacovigilance database of the Australian Rheumatology Association contains many case reports of toxicities related to TNF inhibitors. These include severe injection-site reactions, infection (particularly mycobacterial and opportunistic organisms), lymphoproliferative disorders, lupus-like autoimmune disease, demyelinating disease, haematological abnormalities including aplastic anaemia, and precipitation of cardiac failure. These findings are important as infection (particularly pulmonary infection), cardiovascular disease and osteoporosis are the three conditions that cause the greatest morbidity and mortality in rheumatoid arthritis.³

Injection-site reactions

In patients receiving adalimumab and etanercept, injection-site reactions present as mild erythema, itching, pain or swelling, usually lasting a few days. It is important that patients mix etanercept correctly before injecting it. During infusion of infliximab some patients complain of headache and nausea. An immediate hypersensitivity response suggested by the development of rash, urticaria or anaphylaxis is rare. Patients rarely cease therapy because of injection-site reactions.

Infection

Many infections can occur. These include serious bacterial infections, tuberculosis, atypical mycobacterial infection, aspergillosis, histoplasmosis, listeriosis, *Pneumocystis jiroveci* pneumonia and cryptococcal infections. Infections may be more common in patients over 65 years of age than in younger patients.⁴

Latent viral infections may be reactivated. These include herpes simplex virus (including genital herpes), herpes zoster virus and cytomegalovirus.

Reactivation of tuberculosis has been reported in association with all TNF inhibitors. This usually occurs within the first 2–5 months of commencing treatment. The majority of cases present as extra-pulmonary and disseminated tuberculosis. A recent study has shown that screening for previous pulmonary tuberculosis with chest X-ray and Mantoux testing followed by appropriate treatment before starting TNF inhibitors, significantly reduces the incidence of tuberculosis.⁵

Lymphoproliferative disease

Cases of lymphoma have been reported in patients taking TNF inhibitors. The incidence of lymphoma and leukaemia is already increased in patients with rheumatoid arthritis, particularly those with high disease activity. Epidemiological studies differ on whether there is an additional risk of lymphoproliferative disorders among patients with rheumatoid arthritis who are treated with TNF inhibitors.^{6,7} There is no indication that patients with rheumatoid arthritis taking TNF inhibitors are at increased risk of other tumours.

Blood dyscrasias

Medically significant thrombocytopenia and leucopaenia have been reported with TNF inhibitors. However, pancytopenia including aplastic anaemia rarely occurs. These abnormalities are generally reversible upon cessation of the drug.

Lupus-like autoimmune responses

Positive antinuclear antibodies develop in over 50% of patients with rheumatoid arthritis during treatment with infliximab and 13% develop antibodies to double-stranded DNA.⁸ With etanercept, 11% of patients develop a new antinuclear antibody and 2% develop double-stranded DNA antibodies.⁹ Despite the high rate of autoantibodies, clinical manifestations of drug-induced systemic lupus erythematosus are rare.

Demyelinating syndromes

Exacerbations of previously quiescent multiple sclerosis and the onset of other demyelinating diseases (such as optic neuritis) have been reported in patients taking TNF inhibitors. Symptoms included paraesthesia, visual disturbance and confusion.

Cardiac failure

Patients with heart failure have elevated concentrations of TNF. Trials of etanercept and infliximab in heart failure were stopped early because there was no evidence that TNF inhibitors were of benefit. In the case of infliximab, mortality increased.¹⁰ TNF inhibitors are therefore contraindicated in patients with heart failure (New York Heart Association class III and IV).

Pregnancy and lactation

There are no clinical data for pregnant or lactating women being treated with TNF inhibitors. Animal studies were inconclusive with regard to the embryofetal toxicity so their use during pregnancy is not recommended. Women of childbearing age should be advised to use effective contraception during therapy.

Practice points (Box 2)

Before starting a patient on TNF inhibitors, immunisations should be brought up to date. Live vaccines should not be given to people receiving TNF inhibitors. There is no contraindication to yearly influenza and five-yearly pneumococcal vaccination. Varicella vaccination should be considered for individuals who

are seronegative. Routine screening for latent tuberculosis is mandatory before treatment. It is also important to remain clinically vigilant for reactivated tuberculosis, as a delayed diagnosis may lead to increased morbidity. Patients are reassessed after 8–12 weeks of treatment to see if they qualify for continuation of the drug. Routine clinical examination for signs of cardiac failure and pulmonary sepsis should be performed at each visit. Measurement of the full blood count at baseline and at regular intervals (initially monthly then three-monthly thereafter) is needed to monitor for blood dyscrasias. This may differ if patients are on other therapy such as methotrexate or leflunomide.

Cold application, simple analgesic drugs such as paracetamol, and antihistamines are adequate for treating minor injection-site reactions in patients administering adalimumab and etanercept. Rotation of injection sites is also a useful strategy to prevent skin irritation. Slowing the rate of infusion may ameliorate the infusion-related adverse reactions to infliximab.

The development of systemic or localised infection warrants cessation or postponement of TNF inhibitor therapy. Treatment can be continued after the infection has resolved. For patients exposed to chickenpox or shingles during therapy their serological status should be obtained. Those with a negative serology will require treatment with zoster immunoglobulin to prevent disseminated infection. For patients undergoing major surgery, it is prudent to interrupt TNF inhibitor treatment until the risk of postoperative infection has declined. Minor surgery such as dental procedures does not require cessation of therapy. When patients develop serious complications during treatment, the TNF inhibitors are to be stopped. Specialist advice should be sought immediately.

Box 2

Practice points

- Update immunisations, including yearly influenza vaccines
 - avoid live vaccines during treatment
- Clinical examination for signs of cardiac failure and pulmonary sepsis
- Monthly complete blood count, renal and liver function tests if on methotrexate, C-reactive protein and erythrocyte sedimentation rate
- Monitor for drug toxicities
- Withhold treatment if:
 - hypersensitivity
 - active sepsis
 - malignancy
 - pregnancy or lactation
 - worsening congestive cardiac failure
 - surgery

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

3. Tumour necrosis factor inhibitors can reactivate tuberculosis.
4. Influenza vaccination is contraindicated during treatment with tumour necrosis factor inhibitors.

Book review

Pocket guide to lung function tests: explanations without equations. 2nd edition. Hancox B, Whyte K.

Sydney: McGraw-Hill; 2006. 176 pages. Price \$34.95

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This little book first appeared in 2001 with a reprint in 2003. The appearance of a second edition shows that it has found a market. Although not specifically spelt out, it appears that the second edition has been 'revised throughout' with the addition of chapters 12 and 13 dealing with the preoperative assessment for thoracic surgery and fitness for flying. The basic approach in the interpretation of tests is of pattern recognition rather than requiring much knowledge of pure respiratory physiology and I have no quarrel with that. Most of us read an ECG without much knowledge of cardiac electrophysiology.

In nine chapters covering the commonly used tests, from spirometry to cardiopulmonary exercise tests, the authors present a commonsense approach in a compact yet highly readable text laced with clear diagrams and clinical examples. Things become a little more esoteric and perhaps premature

in chapter 10 (exhaled nitric oxide) and some 'non-routine tests' are discussed in chapter 11.

With so much useful information packed into a small book (the pages are 18 x 11.5 cm) it is hard to be critical, but a few minor things caught my eye. There is inconsistency in the use of the symbols so beloved by respiratory physiologists (for example VD in the glossary and V_D in the text). Despite stating that the book uses mmHg rather than kPa units, chapter 13 uses kPa. Mixed spirometric patterns would be better introduced in chapter 1 rather than chapter 4. A pitfall not mentioned with oximetry is the dependence on adequate circulation. The delay in elevation in carbon dioxide tension in ventilation/perfusion mismatching has less to do with solubility and more to do with the complexity of the carbon dioxide-oxygen-haemoglobin relationships in hypoxia, and even multi-breath nitrogen clearance will only be linear if plotted semi-logarithmically.

The book can be read slowly in 90 minutes and this would be time well spent by candidates for postgraduate exams, advanced trainees in general and thoracic medicine, respiratory scientists and nurses. There are good references for further study and an excellent index. Whether it will be carried around in many pockets is another matter, but it is a compact reference which deserves a wide readership.