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# Anti-tumour Necrosis Factor Alpha (anti-TNF-alpha)

## Introduction

Biological agents targeting inflammatory cytokines such as tumour necrosis factor alpha (TNF-alpha) have been licensed for a variety of inflammatory conditions, particularly rheumatoid arthritis (RA). They are expensive drugs with a potential for serious toxicity. Selection of patients is therefore an important issue. The cytokine inhibitors affecting TNF-alpha currently available are adalimumab, etanercept and infliximab.

## Mode of action

TNF-alpha is an inflammatory cytokine or pro-inflammatory mediator which, when present in excessive concentrations, is responsible for the destructive inflammatory processes that occur in, for example, articular cartilage and bone in RA. Agents that inhibit the action of TNF-alpha might thus be expected to modify the inflammatory disease process.

- Adalimumab is an anti-TNF-alpha recombinant human IgG1 monoclonal antibody.<sup>[1]</sup>
- Etanercept is recombinant human TNF receptor fusion protein (consisting of p75 TNF-alpha receptor and human IgG) which inhibits the binding of TNF to its cell surface receptor.<sup>[2]</sup>
- Infliximab is a chimeric anti-TNF-alpha monoclonal antibody.<sup>[3]</sup>

## Indications

It is hoped that the high cost of disease-modifying drugs will prove to be balanced by savings from the benefits of treatment (reduced need for surgery, reduced need for other treatments, reduced care needs and improved longevity and quality of life). Such benefits have not yet been confirmed and the use of these drugs is careful and highly selective. They should be used according to appropriate guidelines and only with specialised supervision.

### Rheumatoid arthritis

Guidance for RA is available from:

- The National Institute for Health and Care Excellence (NICE).<sup>[4]</sup>
- The British Society for Rheumatology and the British Health Professionals in Rheumatology (joint guidelines).<sup>[5]</sup>
  - Rituximab plus methotrexate or abatacept plus methotrexate are the first-line option for severe active RA in patients who have had an inadequate response to, or have an intolerance of, other disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor. However, if either of these combinations fails, adalimumab, etanercept and infliximab can be offered as treatment options - each in combination with methotrexate.
  - As second-line options, adalimumab and etanercept can be used as monotherapy if methotrexate is contra-indicated or withdrawn because of an adverse event.
  - Treatment should be monitored using the Disease Activity Score-28 (DAS28) calculator and discontinued after six months if there is inadequate response to treatment.<sup>[6]</sup>
  - One study found a reduction in the incidence of cardiovascular disease in patients with RA taking TNF-alpha antagonists.<sup>[7]</sup>

### Juvenile arthritis

Etanercept is recommended by NICE for [juvenile idiopathic arthritis](#) in children aged 4 to 17 years with at least five joints affected and whose condition has not responded adequately to methotrexate (or who have been unable to tolerate methotrexate).<sup>[8]</sup>

### Psoriatic arthritis

NICE guidance was issued in August 2010 for [psoriatic arthritis](#).<sup>[9]</sup> This states that:

- Etanercept, infliximab and adalimumab can be used for adults with active and progressive psoriatic arthritis, providing the following criteria are met:
  - The patient has peripheral arthritis with three or more tender joints and three or more swollen joints.
  - The arthritis has not been helped by adequate courses of at least two standard DMARDs, either administered individually or together.
- Treatment should be started with the cheapest drug (this will vary depending on drug administration costs, the dose and product price per dose).
- Treatment should be discontinued if the arthritis does not respond adequately at 12 weeks, using the Psoriatic Arthritis Response Criteria (PsARC).<sup>[10]</sup> However, if the patient's psoriasis does start to improve, they should be referred to a dermatologist.

## Psoriasis

Etanercept is used for severe psoriasis refractory to at least two other systemic treatments and photochemotherapy. NICE guidance was issued in 2006. It recommends that etanercept be offered to adults with severe plaque psoriasis when:

- Other systemic treatments and photochemotherapy have not worked (usually ciclosporin and methotrexate).
- There is intolerance of other standard treatments.
- There are contra-indications to other standard treatments.

Etanercept should be withdrawn if the response is not adequate after 12 weeks.<sup>[2]</sup>

## Ankylosing spondylitis (AS)

NICE guidance is in progress on the use of adalimumab, etanercept and infliximab for AS.<sup>[11]</sup>

Etanercept and infliximab are currently licensed for use in severe AS not responding to conventional treatment.

Guidance from the British Society for Rheumatology is available with dosage regimens, guidance on diagnosis and selection for treatment as well as evidence for the treatment rationale.<sup>[12]</sup> There are measurable benefits with spinal disease from using either drug alone but not from combining with other drugs. It takes about six to nine weeks to show benefit. A systematic review and economic evaluation of all three drugs showed equal and significant clinical effectiveness (12-24 weeks of treatment).<sup>[13]</sup> Longer trials were called for to assess cost-effectiveness in AS.

## Crohn's disease

Infliximab and adalimumab have been shown to have benefits in severe active Crohn's disease.

NICE guidance recommends their use in adults with Crohn's disease who meet the following criteria:<sup>[14]</sup>

- The Crohn's disease should be severe and active. This is defined as disease in which there is very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent loose stools (3-4 or more) per day. There may be new fistulas or extraintestinal signs of the disease. This normally corresponds to one of the following:
  - A Crohn's Disease Activity (CDA) index score of 300 or more.<sup>[15]</sup>
  - A Harvey-Bradshaw score of 8-9 or above.<sup>[16]</sup>
- The Crohn's disease is refractory to other drugs (azathioprine, steroids, methotrexate, etc), patients have been intolerant of these drugs or there are contra-indications to conventional therapy.
- Patients for whom surgery is inappropriate.

Anti-TNF-alpha drugs should only be prescribed by clinicians familiar with their use and with the management of patients with Crohn's disease. NICE also recommends that:

- Treatment should be started with the cheapest drug (this will vary depending on drug administration costs, the dose and product price per dose).
- Treatment should be continued for 12 months or until treatment fails, whichever is the shorter.
- The risks and benefits of stopping treatment should be discussed with the patient and restarting treatment should be offered as an option if symptoms recur.
- Infliximab can be used for patients with active fistulising Crohn's disease who have not responded to conventional treatment. It can also be used in patients aged 6-17 years with severe active Crohn's disease who have not responded to conventional therapy. Treatment needs to be reviewed every 12 months.

## AS associated with inflammatory bowel disease (IBD)

5-10% of cases of AS are associated with IBD and an even greater number of patients with AS have subclinical IBD. There is some evidence of benefit in these patients.<sup>[17]</sup>

## Drug initiation

NICE guidance is available. This highlights that these drugs are for use usually when other drugs have proved inadequate. It also highlights that they are for initiation and monitoring by specialists and according to guidelines such as those of the British Society for Rheumatology (if not part of a clinical study). This means that GPs are unlikely to have much experience or knowledge of these drugs.

Adalimumab is licensed for:

- Moderate-to-severe RA when other DMARDs such as methotrexate have not been effective. It should be given **in combination** with methotrexate or **alone** if methotrexate cannot be tolerated or there are contra-indications.
- Crohn's disease. It is sometimes used on an unlicensed basis in fistulating Crohn's disease in patients unable to tolerate infliximab.<sup>[18]</sup>
- Psoriatic arthritis.<sup>[9]</sup>

Etanercept is licensed for:

- RA, specifically active RA - either alone or in combination with methotrexate.
- Psoriatic arthritis.
- AS.

Infliximab is licensed for:

- Highly active RA in combination with methotrexate when response to other DMARDs is inadequate.
- Psoriasis.
- Psoriatic arthritis.
- Crohn's disease.<sup>[19]</sup>
- Ulcerative colitis. This is an unlicensed indication but studies have shown some benefit both for:
  - Serious flare-ups of ulcerative colitis not responding to standard treatment.<sup>[20]</sup>
  - AS associated with IBD.<sup>[19]</sup>

## Dosage and administration

The trials have been done according to manufacturers' dosage schedules and can vary according to age and indication.

- Adalimumab is generally given by weekly (or alternate weeks) subcutaneous injection.
- Etanercept is generally given by once-weekly or twice-weekly subcutaneous injection.
- Infliximab is given by intravenous infusion at 6- to 8-weekly intervals.

## Cautions and contra-indications

### Cautions

These include:

- Hepatic and renal impairment.
- Mild heart failure (discontinue if symptoms worsen on treatment).
- Infections.
- Possible demyelinating disease.
- Primary vaccination with live attenuated vaccines, which should be avoided.<sup>[21]</sup>

### Contra-indications

These include:

- Women who are pregnant or breast-feeding.
- Septic arthritis within 12 months.
- Congestive cardiac failure New York Heart Association (NYHA) grade 4 for infliximab.
- Demyelinating disease.

## Common side-effects and complications

These drugs have all been associated with infections (sometimes severe and including tuberculosis and septicaemia). Nausea, hypersensitivity reactions, worsening heart failure and various blood disorders (anaemia, leukopenia, lymphoma, aplastic anaemia, thrombocytopenia and pancytopenia) have all been reported.<sup>[3]</sup> Of concern are cases of hepatosplenic T-cell lymphoma reported in adolescent and young adult patients with Crohn's disease treated with infliximab. This rare type of T-cell lymphoma is usually fatal. All these T-cell lymphomas have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.<sup>[3]</sup>

## Monitoring

- Monitoring of the disease and for drug side-effects should be under close specialised supervision.
- In RA, monitoring should continue on a six-monthly basis using the DAS28 calculator. Treatment should be discontinued if adequate response is not maintained.
- In juvenile arthritis, etanercept should be tried for six months before stopping and continued for up to two years although, again, disease activity and individual response should be taken into consideration.
- In Crohn's disease, treatment should be continued for 12 months or until treatment fails, whichever is the shorter. Loss of response to anti-TNF-alpha drugs is becoming an increasing clinical problem; the reason for this unknown.
- In psoriatic arthritis, treatment should be stopped after 12 weeks if there is no adequate response, unless the patient's psoriasis start to improve.

### Specialised supervision

These drugs are recommended only for initiation and supervision by suitably qualified specialists. This is appropriate, given the conditions being treated and the experience required to monitor these expensive drugs with specific indications and potentially serious adverse reactions. Important considerations before treatment (such as excluding tuberculosis infection and assessing the risk of reactivating a latent infection), awareness of the range of adverse effects and monitoring of the therapeutic benefits are all important aspects of the specialised supervision.

## Practice tips

GPs are unlikely to have knowledge or experience of these drugs because they will have been initiated and monitored in specialised centres. It is desirable in such circumstances for communication between specialist and GP to detail what drug is being used, the dosage and regimen being used and adverse effects of which to be aware.<sup>[22]</sup>

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