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 licensed in the UK are adalimumab, certolizumab pegol, etanercept, golimumab, 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.[1]
- Certolizumab pegol is an anti-TNF-alpha recombinant humanised Fab fragment conjugated to polyethylene glycol.[2]
- 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.[3]
- Golimumab is a human IgG1k anti-TNF-alpha monoclonal antibody.[4]
- Infliximab is a chimeric anti-TNF-alpha monoclonal antibody.[5]

Indications

Anti-TNF-alpha drugs are effective treatments, but - even with the availability of cheaper biosimilars [6] - expensive. Healthcare systems therefore generally restrict their use to specific patient subgroups; they are usually a second- or third-line treatment.

Rheumatoid arthritis

The National Institute for Health and Care Excellence (NICE) states that adalimumab, etanercept, certolizumab pegol, golimumab and infliximab (all with methotrexate) are recommended as options for treating severe active rheumatoid arthritis, if the disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs). [7]

NICE additionally recommend adalimumab, etanercept, and infliximab (all with methotrexate) for moderate rheumatoid arthritis, if intensive therapy with 2 or more DMARDs has failed to achieve sufficient disease control. [7]

In both cases, treatment should only be continued if there is an adequate clinical response at 6 months.

Juvenile arthritis

Adalimumab and etanercept are recommended by NICE for juvenile idiopathic arthritis (JIA) in children aged 2 years or older with polyarticular JIA, whose condition has not responded adequately to 1 or more DMARD (or, for etanercept, methotrexate specifically). [8]

Adalimumab and etanercept are also options for treating enthesitis-related JIA when conventional therapy has been ineffective. [8]

Psoriatic arthritis

NICE guidance was issued in August 2010 for psoriatic arthritis. [9] 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).[10] However, if the patient's psoriasis does start to improve, they should be referred to a dermatologist.

Psoriasis

Etanercept,[11] infliximab,[12] and adalimumab[13] are all recommended by NICE as treatment for severe plaque psoriasis when standard systemic therapies have not worked, or there is an intolerance of, or contraindication to, these treatments.

Ankylosing spondylitis (AS)

NICE guidance recommends adalimumab, certolizumab pegol, etanercept, golimumab and infliximab as options for the treatment of severe ankylosing spondylitis, where there has been inadequate response, or intolerance to, NSAIDs.[14]

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthritis where NSAIDs are ineffective or not tolerated.[14]

Inflammatory bowel disease

Biologics are increasingly used to treat inflammatory bowel disease.

For Crohn's disease, NICE recommends the use of infliximab or adalimumab[15] :

- In adults with severe active Crohn's disease, which is non-responsive to conventional therapy (immunosuppressants and/or corticosteroids), or when these are contraindicated or not tolerated.

In addition, infliximab is recommended:

- For people with active fistulating Crohn's disease that has not responded to conventional therapy (antibiotics, drainage and immunosuppressive treatments), or when these are contraindicated or not tolerated.
- For people aged 6-17 with severe active Crohn's disease that has not responded to conventional therapy (corticosteroids, immunomodulators and primary nutrition therapy), or when these are contraindicated or not tolerated.

For ulcerative colitis, NICE recommends:[16]

- Infliximab, adalimumab, and golimumab for adults with moderately to severely active ulcerative colitis, where conventional therapy including corticosteroids and mercaptopurine or azathioprine has been ineffective, contraindicated, or not tolerated.
- Infliximab for treating severely active ulcerative colitis in children and young people aged 6-17, where conventional therapy has been ineffective, contraindicated, or not tolerated.

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.[17]

Hidradenitis suppurativa

Adalimumab is recommended by NICE as a treatment for moderate to severe hidradenitis suppurativa in adults, where their disease has not responded to conventional systemic therapy.[18]

Uveitis

Adalimumab is recommended by NICE as an option for treating non-infectious posterior uveitis in adults for whom there is inadequate response to corticosteroids, but only if: there is active disease; there has been inadequate response or intolerance to immunosuppressants; there is systemic disease, both eyes are affected, or one eye is affected but the second eye has poor visual acuity; and that there is worsening vision with a high risk of blindness.[19]

Drug initiation

As detailed above, TNF-alpha inhibitors are usually second- or third-line agents for moderate or severe disease. They should only be initiated and prescribed by secondary or tertiary specialist care.

Pre-treatment investigations may differ depending on local protocols and the condition in question, but generally include:[20]

- Baseline bloods: full blood count, urea and electrolytes, and liver function tests.
- Screening for tuberculosis (tuberculin skin test, interferon-gamma release assay - one or both if appropriate - and a chest X-ray).
- Serological screening for Hepatitis B and C.
- Screening for HIV, in people at higher risk of HIV infection.

Dosage and administration

Always refer to the BNF for up-to-date dosing and administration instructions.

In general:

- Adalimumab is generally given by weekly (or alternate weeks) subcutaneous injection.
- Certolizumab pegol is given as a loading dose every two weeks for 3 doses, then maintenance every two or four weeks, by subcutaneous injection.
- Etanercept is generally given by once-weekly or twice-weekly subcutaneous injection.

- Golimumab is either given with an initial loading regime, twice over two weeks, then given every four weeks, or given monthly from the outset, by 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.
- Infections, particularly tuberculosis and hepatitis B and C; hence, screening for these conditions is part of the pre-treatment workup. Biologic treatment can often still proceed, but after these infections are adequately treated.[20]
- Possible demyelinating disease.
- Primary vaccination with live attenuated vaccines, which should be avoided.[21] Ideally, these should be given before starting TNF-alpha inhibitor treatment, but many patients will already be on other immunosuppressant therapy that precludes them from having these.
- Heart failure. NYHA III or IV heart failure was previously a contra-indication to TNF-alpha inhibitors, but more recent data suggests they may be used with caution.[20]
- Significant interstitial lung disease; TNF-alpha inhibitors may be associated with worsening of interstitial lung disease, though the evidence is not clear.
- Pregnancy; limited data suggest that TNF-alpha inhibitors do not seem to cause serious problems in pregnancy. Their use may be considered on a case-by-case basis; untreated inflammatory/autoimmune disease may be more detrimental to pregnancy than their continued use.[22]
- Breastfeeding; there are very limited data. Amounts of TNF-alpha inhibitors entering breast milk seem to be low, and differ from agent to agent; certolizumab, for example, seems to be undetectable in breast milk.[23]

Contra-indications

These include:

- Serious active infections (those requiring IV antibiotics or hospitalisation).[20] Initiation, or ongoing use, of TNF-alpha inhibitors should wait until the infection has been treated and resolved.
- Malignancy; TNF-alpha inhibitors may possibly promote cancer progression.[24]
- 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.[5]

There has been significant concern about the possibility of cancers induced by anti-TNF biologics, with case reports and early studies drawing links with solid organ malignancies and lymphomas. However, more recent data is more reassuring, and, at present, there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease that is attributable to TNF-alpha inhibitors.[20]

Monitoring

- Monitoring of the disease and for drug side-effects should be under close specialised supervision. Patients should be able to contact their specialist team directly with queries and issues relating to the treatment.
- For rheumatological conditions, patients receiving TNF-alpha inhibitors should be reviewed at least every 6 months by a rheumatologist, though high-risk patients may need to be reviewed more frequently.[20]

- In inflammatory bowel disease, all patients should be reviewed by an IBD clinician within 2-4 weeks of completing loading doses of TNF-alpha inhibitors. At a minimum, patients with IBD receiving biologics should have their treatment reviewed annually.
- In dermatology, patients are usually followed up at 3 months after initiation of TNF-alpha inhibitors, at 6 months, and then every 6 months after that.[25]
- Therapeutic drug monitoring (measurement of TNF-alpha inhibitor levels) has an established role in inflammatory bowel disease, but is not routinely recommended in rheumatological conditions.[26]

Practice tips

GPs are unlikely to have much 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.[27]

Ensure that TNF-alpha inhibitors are entered into primary care records as 'hospital issued' medication for patients who are receiving them; this also assists with achieving appropriate recall of patients for vaccinations (such as influenza, Covid-19, and pneumococcal vaccines in patients who would not otherwise be eligible).

- Hepatic and renal impairment.
-

Further reading

- Hyrich KL, Watson KD, Lunt M, et al; Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. Rheumatology (Oxford). 2011 Jan;50(1):117-23. Epub 2010 Jul 29.
- Reenaers C, Louis E, Belaiche J; Current directions of biologic therapies in inflammatory bowel disease. Therap Adv Gastroenterol. 2010 Mar;3(2):99-106.

Last updated by: Dr Doug McKechnie, MRCGP 23/08/2023	
Peer reviewed by: Dr Toni Hazell 23/08/2023	**Next review date:** 21/08/2028

View this article online at: patient.info/doctor/anti-tumour-necrosis-factor-alpha-anti-tnf-alpha

Discuss Anti-tumour necrosis factor alpha (Anti-TNF-alpha) and find more trusted resources at Patient.