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Anti-tumour necrosis factor therapy in seronegative spondyloarthritis

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Background

The seronegative spondyloarthritides are a group of chronic inflammatory disorders that include ankylosing spondylitis (AS), reactive arthritis and the axial forms of psoriatic and enteropathic arthritis. Standard therapy for AS to date has comprised non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, focused on reducing pain and maintaining mobility. There is however no substantial evidence that 'as required' NSAIDs alter the radiological or clinical progression of the disease and the risks associated with long-term therapy are legion.

Interest has therefore turned to the use of the so-called 'biologics', particularly the tumour necrosis factor (TNF)-α blocking agents which have a proven record in rheumatoid arthritis (RA) (see accompanying article on biologic therapy in RA). Open-label and randomised controlled trials (RCTs) have demonstrated the efficacy of these agents in spondyloarthropathy, prompting both the Assessment in Ankylosing Spondylitis (ASAS) Working Group and the British Society of Rheumatology (BSR) to produce guidelines for their use.

This review summarises the clinical features of AS, current methods of its diagnosis and assessment, focusing on the role of TNF-α blockade in treatment of AS. Although benefit from anti-TNF therapy has also been shown for psoriatic arthritis, the bulk of clinical research and guidelines have focused on AS.

Clinical features, diagnosis and activity assessment

The prevalence of AS is up to 1.1%.[1] Onset of symptoms typically occurs in the third decade, with men affected 3–4 times more frequently than women, both morbidity and mortality are increased, and the socioeconomic costs are substantial. Susceptibility to AS has a major genetic component, with HLA-B27 the biggest single contributor,[2] with over 90% of AS patients HLA-B27 positive. AS primarily affects the axial skeleton. Peripheral arthropathy (frequently asymmetrical), enthesitis (inflammation at the site of tendon or ligament attachment to bone) and anterior uveitis are common. Fibrotic lung disease, aortic incompetence and amyloidosis are less frequent.

Diagnosis

The diagnosis of AS is made according to the modified New York criteria and relies upon one radiological criterion and at least one clinical criterion.[3]

Table 1. New York radiological scoring method for sacroiliac joints.

Grade		
0	No abnormalities	
1	Suspicious changes:	no specific abnormalities
2	Minimal sacroiliitis:	loss of definition of the joint, some sclerosis, minimal erosions, some joint space narrowing
3	Moderate sacroiliitis:	definite sclerosis on both sides of the joint, blurring and indistinct margins, erosive changes, loss of joint space
4	Ankylosis	

Radiological criteria

The New York radiological scoring method for the sacroiliac joints is shown in Table 1. Radiological diagnostic criteria are grade 2 bilaterally or grade 3 or 4 unilaterally.

Clinical criteria

The main clinical criteria are:

- low back pain and stiffness of more than three months' duration, improving with exercise but not with rest
- limitation of lumbar spine mobility in both sagittal and frontal planes
- limitation of chest expansion relative to normal age- and sex-matched values.

For AS, in addition to the above, symptoms that should raise the clinical suspicion of a seronegative spondyloarthropathy include:

- morning stiffness of the lumbar or dorsal spine
- alternating buttock pain
- 'sausage' digits (diffuse swelling of a digit)
- asymmetrical inflammatory arthritis
- plantar fasciitis

Key Points

Over 50% of ankylosing spondylitis patients treated with anti-tumour necrosis factor show a 50% improvement

Infliximab, etanercept (and probably adalimumab) are equally effective

Stable responses are maintained for two years

If treatment is discontinued, almost all patients relapse

Retreatment is probably as effective as initial treatment

Pre-test screening for tuberculosis is essential

The overall risk to benefit ratio is favourable

KEY WORDS: ankylosing spondylitis, therapy, TNF

- iritis
- history of psoriasis or inflammatory bowel disease and/or
- family history.

Assessment of disease activity

Two clinical activity measures have been commonly used in clinical trials of AS.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

This is a validated index using visual analogue scores to grade patients' fatigue, pain and both duration and degree of early morning stiffness. The ASAS working group recommends a 50% reduction in the BASDAI score as a definition of response to treatment.[4]

Composite Assessment in Ankylosing Spondylitis grade

This measure was used in earlier clinical trials and is derived from visual analogue scores of pain, inflammation, well-being and function. Improvement in three of these modalities by 20%, 50% or 70% without deterioration in the fourth constitutes an ASAS 20, 50 or 70 response, respectively.

Current clinical trials reveal comparability between the BASDAI 50% reduction and ASAS 50 response.

In addition to these clinical scoring measurements, a significant proportion of the open-label trials included C-reactive protein (CRP) (as an objective measure) and expert opinion in their definition of active disease.

Tumour necrosis factor-α and spondyloarthropathy

TNF-α mRNA has been identified in inflamed sacroiliac joints in AS patients and in both tissue and joint fluid of those with psoriatic arthropathy.[5] TNF-α, which is largely macrophage-derived, stimulates the release of interleukin (IL)-1, IL-6, IL-8 and arachidonic acid metabolites, thereby recruiting and co-ordinating monocyte, neutrophil, B and T cell function. It is also responsible for a number of mechanisms of joint destruction. Three TNF-α blocking agents have now been approved for use in RA (see accompanying article on biologic therapy in RA):

- infliximab, a chimeric immunoglobulin (Ig) G1 antibody
- etanercept, a recombinant TNF receptor IgG1 fusion protein, and
- adalimumab, a fully humanised monoclonal antibody.

Clinical trials

All published open-label and RCTs have shown infliximab and etanercept to be highly effective compared with placebo in the treatment of active AS. Adalimumab is currently under evaluation in a large multicentre, randomised, placebo-controlled trial. The largest RCTs[6–9] are summarised in Table 2). In the study by Braun *et al*,[6] 53% of patients (*vs* 9% of controls) reached a BASDAI 50% reduction within 12 weeks of receiving infliximab. In the study of Davis *et al*,[8] etanercept generated an ASAS 20 in 59% of patients (*vs* 9% of controls).[6,7] The number needed to treat to achieve clinical response for TNF-α blockade in AS is therefore under two. Infliximab and etanercept appear comparably effective and, unlike the equivalent data in RA, there is no clear benefit from combining TNF-α blockade with methotrexate. The response to TNF-α blockade is rapid (usually evident at 6–12 weeks) and stable maintained responses have been seen up to two years. Almost all patients relapse if TNF-α blockade is discontinued, but reintroducing therapy appears as effective as initial treatment (Dr M Rudwaleit, Berlin; personal communication). It is likely that persistent suppression of disease activity will prevent ankylosis, but there are currently no long-term data to support this.

Practical considerations

The National Institute for Clinical Excellence (NICE) has not formally declared eligibility criteria for prescribing TNF-α blockade in AS; its use therefore faces great financial constraints. Despite this, the ASAS working group and the

Table 2. Key randomised controlled clinical trials in ankylosing spondylitis.

Agent	Ref	No of patients	Primary response criteria	Result: active *vs* placebo
Infliximab	6	70 AS	BASDAI 50% reduction	53% *vs* 9% at 12 weeks
Infliximab	7	40 SpA	Pt assess DA and pain Phys assess ESR, CRP	*p* highly significant
Etanercept	9	40 AS	20% improvement in 3 criteria	80% *vs* 30% at 4 months
Etanercept	8	277 AS	ASAS 20	59% *vs* 28% at 12 weeks
Etanercept	11	30 AS	BASDAI 50% reduction	57% *vs* 6% at 6 weeks

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DA = disease activity; ESR = erythrocyte sedimentation rate; Phys = physician; Pt = patient; SpA = spondyloarthritis.

BSR have produced their own anti-TNF guidelines.[4,10] The most recent BSR guidelines for TNF blockade in AS comprise:

- confirmation of diagnosis of AS (as outlined above)
- clinical evidence of active inflammatory disease (based on the BASDAI)
- failure of conventional treatment, cited as two or more NSAIDs each taken sequentially at a maximum tolerated/recommended dosage for four weeks.

Guidelines for psoriatic spinal disease are identical to the original BSR document on AS.

Patients with shorter disease duration and/or elevation in CRP are more likely to respond to treatment. In those with clinically active disease but a normal CRP, magnetic resonance imaging-positivity may play a useful role in predicting a positive response.[11,12]

Exclusion and drug withdrawal criteria are the same as those for RA and include:

- pregnancy/breast feeding
- active significant infection
- septic arthritis of a native or prosthetic joint within the last 12 months
- New York Heart Association grade 3 or 4 congestive cardiac failure, and/or
- clear history of demyelinating disease.

Adverse events

Treatment should be withdrawn in the event of a severe adverse event (including infection) or lack of response as determined by the BASDAI and other appropriate visual analogue scores.

Tuberculosis. The major concern with TNF-α blockade is the increased risk of developing serious infection, most notably mycobacterium tuberculosis (TB). The incidence of active TB is increased in patients receiving anti-TNF-α therapy and their pattern of disease differs from immunocompetent individuals. The majority of TNF-α blocked patients who contract TB develop extrapulmonary manifestations (57% *vs* 18% in normal cohorts) and almost a quarter suffer disseminated disease. Disseminated TB has occurred with all three types of TNF-α blockade.[13] All patients being considered for TNF therapy should therefore undergo TB screening, with a full history, clinical examination, chest X-ray ± Heaf test. For patients with evidence of latent TB infection, it is our practice to begin a nine-month course of isoniazid therapy a month before initiating TNF-α therapy,[14] although formal guidelines from the British Thoracic Society are still awaited.

Conclusions

Anti-TNF therapy has been conclusively shown to be highly effective therapy for AS, a disease for which previous treatments have been largely ineffective. Robust clinical evidence both in open-label trials and RCTs demonstrates that anti-TNF agents generate a rapid and sustained improvement in pain, mobility and function. It is likely that such impressive suppression of disease activity will also reduce the structural and osteoporotic sequelae of long-term inflammatory disease. However TNF-α blockade is not without cost or risk. Although widely used in continental Europe, it is currently limited in the UK due to restricted funding pending a formal NICE declaration. The infection risk related to therapy is reduced by screening for TB and maintaining a high index of clinical suspicion for opportunistic infection. On the basis of current evidence, the benefits of anti-TNF therapy in seronegative spondylarthritis greatly outweigh this risk.

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Beyond methotrexate: biologic therapy in rheumatoid arthritis

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A sea change has occurred in the management of rheumatoid arthritis (RA) over the last decade with the introduction of 'biologic' disease-modifying drugs. Derived from biologic sources (eg proteins, protein fragments), these medications target specific molecules in the inflammatory cascade (eg tumour necrosis factor (TNF-α), interleukins (IL)). Colloquially known as 'biologics,' they have become an integral part of RA management, altering the natural history of this condition. Three anti-TNF-α agents (infliximab, adalimumab and etanercept) and an IL-1 receptor antagonist (anakinra) are the biologics currently licensed in the UK for RA (Fig 1). Infliximab and etanercept have National Institute for Clinical Excellence (NICE) approval, adalimumab is awaiting review, whilst anakinra does not have approval.[1] This article concentrates on anti-TNF-α drugs as they are the most widely used biologic agents.

Rationale

Understanding of the pathophysiology of RA has grown enormously in recent years, yet the aetiology remains elusive.[2] Activation of CD4+ T lymphocytes by an unidentified antigen appears to lead to stimulation of monocytes, macrophages, plasma cells, dendritic cells and fibroblasts. The synovial lining of joints becomes inflamed due to an imbalance in favour of pro-inflammatory cytokines (chiefly TNF-α and IL-1), leading not only to the symptoms and signs of synovitis but also to articular cartilage and bony destruction. Because of their pivotal role in the inflammatory cascade, TNF-α and IL-1 were attractive initial targets for therapeutic intervention. Appraisal of all the potential target cytokines in RA is beyond the scope of

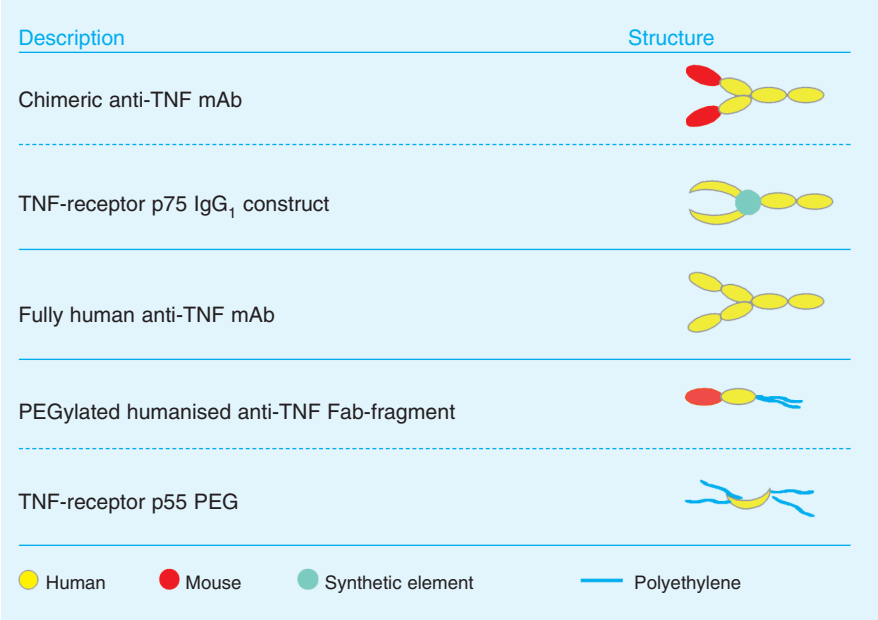

Fig 1. Molecular structure of biologic agents: infliximab (a chimeric anti-tumour necrosis factor (TNF) antibody), adalimumab (a humanised anti-TNF antibody), and etanercept (a TNF receptor construct) (Ig = immunoglobulin; mAb = monoclonal antibody; PEG = polyethylene glycol). Adapted from Abbott Immunology Slide Kit, 2003.