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## Beyond methotrexate: biologic therapy in rheumatoid arthritis

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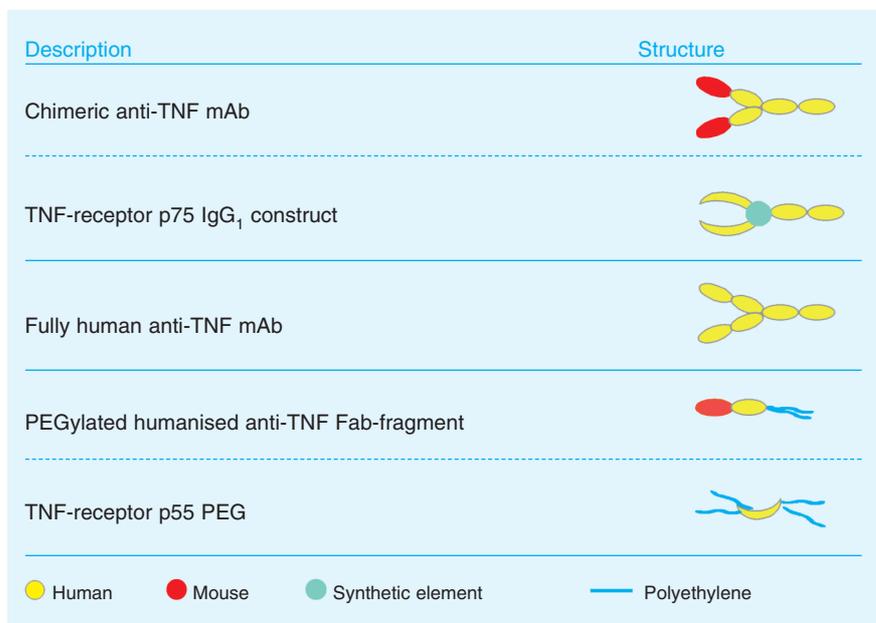
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A sea change has occurred in the management of rheumatoid arthritis (RA) over the last decade with the introduction of 'biologic' disease-modifying drugs. Derived from biologic sources (eg proteins, protein fragments), these medications target specific molecules in the inflammatory cascade (eg tumour necrosis factor (TNF- $\alpha$ ), 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- $\alpha$  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.<sup>1</sup> This article concentrates on anti-TNF- $\alpha$  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.<sup>2</sup> 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- $\alpha$  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- $\alpha$  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.

this article (for a useful review of the inflammatory cytokine pathway in RA see Ref 3).

In addition to cytokine targeting, there is increasing interest in B lymphocyte immunomodulation as these cells may mediate inflammation in RA via rheumatoid factors (principally immunoglobulin (Ig) M to the Fc portion of IgG), resulting in complement fixation and cell damage. An area of research now arousing considerable interest is targeting B cells by biologic agents.<sup>4</sup>

### Evidence of efficacy

Rheumatologists are chiefly concerned with four aspects of patient management:

- reduction in signs and symptoms of disease
- preservation of function
- reduction of radiological progression, and
- improvement in quality of life (QoL).

Improvement in all these areas with biologic therapy has been demonstrated in multiple randomised controlled trials. Furthermore, the amelioration (particularly in symptoms, signs and QoL) can occur within the first few doses of treatment.

### Anti-tumour necrosis factor- $\alpha$ agents

#### *Infliximab*

Infliximab (Remicade, Schering-Plough) is a chimeric (part mouse/part human) monoclonal antibody to TNF- $\alpha$ , directed against both soluble and membrane bound TNF- $\alpha$ . It is given as a 2-hour intravenous infusion in a dose of 3 mg/kg at weeks 0, 2 and 6, then eight-weekly. In the event of waning efficacy, the dose may be increased (up to 10 mg/kg) or the infusion frequency increased (6-weekly). Concurrent methotrexate (MTX) administration is mandatory to reduce the incidence of deactivating antibodies to the foreign (murine) component of the molecule.

In the Anti-Tumor Necrosis Factor

## Key Points

**Biologic agents are highly effective anti-rheumatic medications**

**Biologic agents improve the signs and symptoms and quality of life of patients with rheumatoid arthritis and retard the radiological progression of disease**

**Physicians should be vigilant for the potential side-effects of biologic agents**

**Treatment should commence early for optimal outcome**

**KEY WORDS:** adalimumab, anti-tumour necrosis factor- $\alpha$ , biologics, etanercept, infliximab, rheumatoid arthritis, side effects

Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, four regimens of infliximab were compared with placebo in 428 RA patients taking MTX over 54 weeks.<sup>5</sup> The actively treated subjects showed significant improvements in the American College for Rheumatology (ACR) responder indices (the most widely used response criteria in clinical trials for RA). Radiological progression of disease was also inhibited and QoL was improved in the actively treated patients for up to two years.<sup>6,7</sup> Interestingly, in a sub-analysis, radiological progression was shown to be reduced even in the absence of clinical response.

#### *Adalimumab*

Adalimumab, a fully human monoclonal anti-TNF- $\alpha$  antibody, in patients taking concomitant methotrexate (ARMADA), has an action similar to infliximab. It is given as a 40 mg subcutaneous injection every second week. In the ARMADA trial (271 patients on MTX), there was significant improvement in ACR responses and QoL measures in patients treated with additional adalimumab over 24 weeks compared with placebo.<sup>8</sup> Another trial (619 patients) over 52 weeks showed improvement in radiographic, clinical and functional outcomes in the adalimumab treated group compared with placebo.<sup>9</sup>

#### *Etanercept*

The third anti-TNF- $\alpha$  agent is etanercept, a soluble TNF receptor fusion protein (Enbrel, Wyeth Pharmaceuticals). It comprises two soluble TNF- $\alpha$  receptors linked

to human IgG1. Etanercept binds both soluble TNF- $\alpha$  and TNF- $\beta$  but not membrane-bound TNF. It is given as a 25 mg subcutaneous injection twice weekly.

In a study in 234 patients with active RA, significant improvements were found in ACR responses and QoL in the active groups compared with placebo.<sup>10</sup> In a trial directly comparing etanercept with MTX in 632 patients response rates were more rapid in the etanercept group, although responses converged at 12 months. Progression of the mean joint erosion score was less in the etanercept group.<sup>11</sup> The combination of etanercept and MTX is more effective than either agent alone, including improvement in disability measures.<sup>12</sup>

### Other agents

#### *Anakinra*

Anakinra, a recombinant IL receptor antagonist (Kineret, Amgen), binds to the IL-1 receptor. Although it is efficacious in RA when administered both alone and in combination with MTX,<sup>13,14</sup> Anakinra has not been approved by NICE for use in RA.

#### *Newer agents*

The most promising newer agents include:

- rituximab, a chimeric antibody directed at the CD20 antigen on B lymphocytes
- anti-IL-6 monoclonal antibodies, and
- CTLA4-Ig, T lymphocyte co-stimulatory molecule blocker.

**Table 1. Properties of biologics licensed for rheumatoid arthritis in the UK.**

Biologic agent	Infliximab	Adalimumab	Etanercept	Anakinra
<b>Proprietary name</b>	Remicade	Humira	Enbrel	Kineret
<b>Construct</b>	Chimeric mAb to TNF- $\alpha$	Fully humanised mAb to TNF- $\alpha$	TNF- $\alpha$ receptor fusion protein	IL-1 receptor antagonist
<b>Mode of action</b>	Binds to soluble and membrane bound TNF- $\alpha$	Binds to soluble and membrane bound TNF- $\alpha$	Binds to soluble TNF- $\alpha$ and TNF- $\beta$	Binds to IL-1 receptor
<b>Half-life</b>	9 days	14 days	4 days	6 hours
<b>Dose</b>	3 mg/kg of body weight at 0, 2, 6 weeks then 8-weekly. For incomplete response, dosage interval may be shortened or dose increased to 10 mg/kg	40 mg every second week For incomplete response, dose may be given weekly	25 mg s/c twice weekly	100 mg s/c daily
<b>Administration</b>	iv	s/c	s/c	s/c
<b>Monitoring</b>	Regular review and vigilance for potential side effects especially serious infection	As for infliximab	As for infliximab	FBE at baseline, then monthly for 3 months, then 3-monthly
<b>Combination</b>	MTX	MTX, other DMARDs, or mono	MTX or monotherapy	MTX or monotherapy
<b>Other licensed indications</b>	Crohn's disease, ankylosing spondylitis and psoriatic arthritis		JIA, ankylosing spondylitis, psoriatic arthritis and psoriasis	

DMARD = disease-modifying antirheumatic drug; FBE = full blood examination; IL= interleukin; iv = intravenous; JIA = ; mAb = monoclonal antibody; MTX = methotrexate; s/c = subcutaneous; TNF = tumour necrosis factor.

This is reassuring as a significant proportion of patients do not respond to the currently licensed agents.

Table 1 lists the similarities and differences between different biological agents.

### Complications and side effects

Initial clinical trials of anti-TNF- $\alpha$  agents showed few serious adverse events but post-marketing surveillance revealed several important complications. Principal among these was reactivation of latent mycobacterium tuberculosis (TB) infection because TNF- $\alpha$  is required to maintain the integrity of the granuloma.<sup>15</sup> Reports of serious bacterial infections and other opportunistic infections continue, including histoplasmosis.

Other complications include exacerbation of heart failure, demyelinating disease and the development of lymphoproliferative disorders. The occurrence of lymphoma secondary to biologic therapy is controversial because there is a 2–6 fold

increased incidence of this disease with RA *per se*.<sup>16</sup>

Further side effects include injection site reactions, immune and autoimmune responses. The development of antinuclear antibodies (ANA) is seen quite frequently, although a systemic lupus erythematosus-like illness is rare. This resolves upon discontinuation of the medication and ANA development does not necessitate stopping therapy.

The exact relationship between several of these recognised complications and biologic therapy is unknown.

### Treatment paradigm

The previously well established treatment pyramid for RA has been deconstructed. In the traditional model, therapy focused on symptomatic treatment (usually with non-steroidal

**Table 2. Disease Activity Score 28 (DAS28).**

The DAS28 scoring system, developed in Europe, is used to assess the activity of RA.

Based on a total of 28 joints, the ESR and general health status on a 100 mm visual analogue scale, the following formula is used:

$$\text{DAS28} = 0.56 \times \sqrt{\text{tender joint count}} + 0.28 \times \sqrt{\text{swollen joint count}} + 0.7 \times \ln \text{ESR} + 0.014 \times \text{GH}$$

DAS28: <3.2 low disease activity  
3.2–5.1 moderate disease activity  
>5.1 high disease activity

A change of >1.2 is a significant change in disease activity

ESR = erythrocyte sedimentation rate; GH = general health; RA = rheumatoid arthritis.

anti-inflammatory drugs), gradually progressing through treatments of increasing potency. The prevailing evidence dictates early intervention with disease-modifying antirheumatic drugs (DMARDs) such as MTX, sulfasalazine, leflunomide and hydroxychloroquine.

Current practice, as outlined by NICE, is to commence biologic therapy once a patient has failed to respond to at least two DMARDs, including MTX which remains the current gold standard for the treatment of RA. Active disease eligible for treatment with anti-TNF- $\alpha$  agents is defined as a disease activity score (DAS28) (Table 2) over 5.1 measured at two time-points one month apart.

All anti-TNF- $\alpha$  agents can be given in combination with MTX; in the case of infliximab, this is required (as discussed above). This author's practice is to use the combination of MTX and biologic agent, wherever possible, to improve outcome and reduce the development of neutralising antibodies. In those unable to tolerate MTX or where it is contraindicated, etanercept or adalimumab are the biologics of first choice since they can be given as monotherapy.

If there is no response (failure of the DAS28 to improve by  $>1.2$ ) after three months of treatment, an alternative biologic agent may be tried as some patients respond differently to different anti-TNF- $\alpha$  agents.<sup>17</sup>

Biologics are contraindicated in patients with active infections, history of TB, heart failure, demyelinating illness, malignancy and in pregnancy.

### Pre-treatment and monitoring

During pre-biologic assessment, exclusion of TB infection is required by a combination of history and examination, chest X-ray and Heaf test. Immunisations (fluvax, pneumovax) should be given prior to treatment initiation and patients must not receive live vaccines once biologics have been started. No specific blood test or radiographic monitoring is required for anti-TNF- $\alpha$  therapy, but vigilance is required for any possible infection and other complications. As concurrent DMARD treatment is frequent, standard blood monitoring of this

should continue. All rheumatology patients in the UK treated with biologic agents must be enrolled on the British Society for Rheumatology biologics registry.

### Cost

Biologic agents are expensive (£10,000 per patient per annum) and must be continued indefinitely. This cost must be offset, however, by the enormous direct and indirect costs of RA.

### Summary

Biologics have revolutionised the treatment of RA due to their efficacy, speed of onset and tolerability. Increasing evidence suggests that early intervention is the key to combating RA. The future challenge is to find the best time to introduce biologics into the treatment paradigm in the hope of inducing disease remission — something unthinkable even a decade ago.

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### Self-Assessment Questionnaire (SAQ) Clinical Pharmacology CME

*Clinical Medicine* January/February 2005

The SAQ for Clinical Pharmacology was the first set of CME questionnaires in over six years to have been so flawed as to invalidate the entire exercise. Despite our question writing and selection process, followed by expert editing, many of the questions were incorrectly answered by between 40 and 86% of those undertaking them. It was therefore unjustifiable to use them as a valid assessment leading to the award of two External CPD credits.

As if this failing was not enough, unfortunately the heading of the box (on page 120 of the March/April issue) showing the answers for the Clinical Pharmacology SAQ published in January/February 2005, was incorrectly printed as 'Nutrition'.

We apologise unreservedly for this lapse of standard. Steps have been taken to ensure that this does not recur.

**Peter Watkins**  
Editor