

Biologic therapies in autoimmune diseases

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ABSTRACT – Over the past decade, the treatment of rheumatoid arthritis has been revolutionised by the development of therapies targeted at molecules involved in driving the inflammatory response. This review briefly summarises the established uses of biologic therapies in rheumatoid disease, and outlines other diseases in rheumatology and other fields where biologic agents are finding a role.

KEYWORDS: autoimmune diseases, biologic therapies, etanercept, infliximab, rheumatoid disease, rituximab

Biologic therapies

Biologic agents are molecules of biological origin, used therapeutically. Most of these agents are based on antibodies or receptor proteins, which may be biologically modified to attempt to make them less immunogenic in humans. The anti-tumour necrosis factor α (anti-TNF α) agent infliximab is an example of a chimaeric biological agent – mouse B-cells were used to raise a clone of anti-human TNF α antibodies, and the antigen binding site from that antibody was then incorporated into a human IgG1 antibody. This produces an agent that binds TNF α with high specificity, but is less immunogenic in humans than mouse antibody. Etanercept is also an agent which blocks the effects of anti-TNF α , but is a human TNF α receptor altered to be soluble rather than membrane bound, through changing the membrane-bound portion and intracellular domains for an IgG1 Fc domain (Fig 1).

This is a powerful approach to generating drugs which are highly specific for their site of action (a protein). This specificity can be achieved using the immune system's ability to generate molecules that bind with high affinity and specificity (the antibody response). Alternatively, a receptor can be used, which binds its own ligand with high specificity. These large biological molecules are much more specific than small-molecule 'conventional' drugs. However, with this advantage come costs – notably the expense of manufacturing these proteins; and the need for parenteral administration to prevent enzymatic degradation of the proteins.

Biologics in rheumatoid arthritis

Since the introduction of infliximab in the early 1990s, biologic therapies have revolutionised the treatment of inflammatory arthritis, and given relief to patients with severe pain and disability who have failed treatment with conventional disease-modifying drugs. There are now three agents licensed for treatment of rheumatoid arthritis that antagonise TNF α – infliximab, etanercept, and adalimumab – and other biologic agents which act at other sites in the immune response – anakinra (an interleukin-1 (IL-1) antagonist), and rituximab (an anti-CD20 antibody).

Tumour necrosis factor alpha is a trimeric protein which is upstream of many cytokines in the inflammatory response found in rheumatoid disease. It is mainly secreted by macrophages and has effects on a wide variety of cell types, including endothelial activation,

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Conference programme

■ Introduction – biological principles

Professor Hill Gaston

■ Current use and toxicity

Professor Robert Moots, University Hospital Aintree, Liverpool

■ The BSR Biologics Register: a model for the future

Professor Deborah Symmons, University of Manchester

■ Biological therapy in dermatology

Professor Jonathan Barker, St John's Institute of Dermatology, King's College London

■ Biological therapies in eye disease

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Professor Sir Ravinder Maini, Kennedy Institute of Rheumatology, Imperial College London

■ New biological targets in rheumatoid arthritis

Dr Ernest Choy, King's College Hospital, London

■ B cell depletion for autoimmune rheumatic disease

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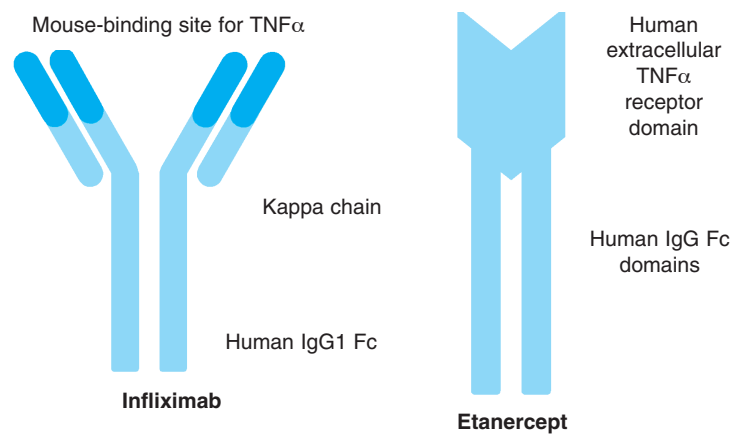


Fig 1. Structure of infliximab (a chimaeric antibody), and etanercept (a solubilised receptor).

synovial proliferation, metalloproteinase secretion, and generation of the acute phase response. It is found at high levels in the synovium in rheumatoid disease, and may be upstream of other inflammatory cytokines, including IL-6 and IL-1.

Inhibition of TNF α is an effective treatment for rheumatoid disease, and the three agents above all have convincing data demonstrating clinical efficacy using the American College of Rheumatology (ACR) 20, 50 and 70 response criteria (a standard method of evaluating rheumatoid arthritis activity, with the 20 response representing a 20% improvement, 50 a 50% improvement, and 70 a 70% improvement). The National Institute for Health and Clinical Excellence (NICE) has issued guidance about the use of these agents in the UK,¹ recommending their use be restricted to patients with active rheumatoid arthritis (RA) who have failed treatment with methotrexate and at least one other disease modifying anti-rheumatic drug (DMARD).

Infliximab was the first licensed anti-TNF α . It neutralises TNF α bioactivity in the circulation, and possibly at the cell surface. It has to be administered intravenously, and is recommended to be used in conjunction with methotrexate as they have a significant synergistic effect, probably by prolonging the response to infliximab. It has an allogeneic (mouse) portion (Fig 1), and can cause generation of anti-infliximab antibodies in humans. Methotrexate reduces the generation of these antibodies, as does giving larger doses of the infliximab (presumably an example of an immunomodulatory agent inducing tolerance to itself).

Etanercept is the most commonly used biologic in RA. It is given as subcutaneous injections. The NICE guidance does not at present recommend its use in combination with methotrexate, although the results from the TEMPO study² suggest that there is significant synergy in co-administration. It does have some different actions to infliximab and adalimumab – for example, it is less effective in treating Crohn's disease, and can be demonstrated to bind lymphotoxin alpha (TNF β) unlike the antibody-based treatments. It is not able to bind complement to membrane-bound TNF α and cause cell death, unlike the antibody-based anti-TNF α biologics.

Adalimumab is a fully humanised anti-TNF α antibody, which

may be less immunogenic than infliximab, and is administered fortnightly. Anakinra is an inhibitor of IL-1 which is little used in RA because it appears less effective than anti-TNF α agents.

Side effects of anti-TNF α

At the outset, it was clear that it would be important to gather data about these new, powerful and expensive drugs. The British Society for Rheumatology (BSR) set up a mechanism for collecting data and auditing the use of these drugs – the BSR Biologics Register. The NICE guidelines¹ included the recommendation that all patients starting on biologics be registered with this database (this is no longer the case for etanercept now that sufficient patients have been registered). As a result of this, there are ample data about side effects, and there is a comparison cohort to act as a control (important given the known increase in mortality, serious infections, and certain tumours in patients with RA).

It has been well publicised that blocking TNF α predisposes to tuberculosis (TB) infection, and there have been 11 cases of TB to date, with a high proportion (7/11) of extrapulmonary TB. There is, however, no significant rise in the proportion of patients developing serious infections compared with the control cohort.

Malignant disease is a contra-indication to treatment with anti-TNF α , and there has been to date no increase in malignant disease in this group. It has been recognised that there is an increase in lymphoma incidence in RA patients (perhaps related to the inflammatory burden of the disease), but no increase has been seen in anti-TNF α treated patients. However, the follow-up time for these data is still relatively short.

Induction of autoimmune disease has also been a concern for these agents. All three agents may induce anti-nuclear antibodies in up to one-third of patients, and anti-double stranded DNA antibodies may also be induced. However, drug-induced systemic lupus erythematosus (SLE) is unusual, and usually remits on discontinuation. Early concerns about demyelinating disease have not been reproduced in practice.

The registry cohort has shown an elevated standard mortality ratio, but without any significant difference between those on

biologics and those on conventional DMARDs alone. At present, therefore, there is no evidence for anti-TNF α agents causing or preventing death in patients with RA.

Disease-modifying activity of anti-TNF α

The aims for any treatment of RA are to suppress symptoms and to prevent (and ideally reverse) joint damage. A recent trial³ suggests that intensive treatment with conventional DMARD therapy can achieve comparable control of symptoms and signs, but that etanercept results in significantly less progression of joint damage. The TEMPO study² even produced results suggesting a reduction in joint damage (ie healing) in patients treated with etanercept and methotrexate. It seems likely therefore that anti-TNF α may be more efficacious at reducing deformity and long-term disability than conventional DMARD therapy.

Rituximab in RA and SLE

Ever since the description of rheumatoid factor in RA, it has been clear that the humoral arm of the immune response must have a role to play in RA pathology. The biologic agent rituximab is a chimaeric antibody which binds to the CD20 molecule present on the surface of B-cells. Given as an intravenous bolus, it results in the death of about 80% of all B-cells, and over 95% of circulating mature B-cells. B-cells may participate in RA pathogenesis in several ways, including by their action as antigen-presenting cells, generation of rheumatoid factors, and secretion of proinflammatory cytokines; and they are clearly central in developing SLE.

Rituximab is licensed for treatment of non-Hodgkin's lymphoma. It has been used to treat RA. It results in a fall in disease activity in most seropositive patients, with a corresponding fall in inflammatory markers, B-cell numbers, and rheumatoid factor. Falls in immunoglobulin levels are modest. Patients may go into remission and stay in remission for up to 4 years – the treatment therefore is given as a 'one off'. B-cell repopulation occurs after treatment, but patients may stay in remission despite this. Re-treatment can be given at relapse. The predominant side effect is a lower respiratory tract illness which may be infective, and is found in nearly a quarter of recipients.

In SLE, rituximab is given with cyclophosphamide, and results in a fall in the British Isles Lupus Assessment Group (BILAG) global score (a measure of lupus activity), and in a fall in the titres of ds-DNA antibodies. This allows steroids to be weaned. Again, the treatment caused a transient fall in the B-cell levels in almost all patients.

Other indications for biologic therapies

Infliximab is licensed for treatment of severe Crohn's disease in patients who have not responded to medical therapy. NICE have issued guidelines on this area, and recommend only one to three infusions in patients who would not be more suited to surgical intervention.

Key Points

Biologic therapies offer highly specific ways to target individual molecules and cells of the immune response

Use of biologic therapies is limited by their expensive manufacture, and need for parenteral administration

Cytokine blockade is effective and safe in rheumatoid arthritis, Crohn's disease, psoriasis, and other inflammatory conditions where TNF α is overexpressed

Biologic agents affecting the immune response at other sites are under investigation

Anti-TNF α drugs are known to be effective in treating ankylosing spondylitis (AS), a disease for which previously there had been very little potent treatment. Guidelines have been published for the use of anti-TNF in AS,⁴ and NICE are appraising the use of these agents at present.

Similarly, psoriatic arthropathy (PsA) and psoriasis have been demonstrated to respond to anti-TNF α treatment, and NICE are releasing their appraisal on use of etanercept in PsA and psoriasis in the near future. Dermatologists have also been using T-cell directed biologic therapies to treat psoriasis – alefacept (anti-CD2) and efalizumab (anti-LFA-1) – and have demonstrated significant improvement in the Psoriasis Area and Severity Index in patients with severe disease. Guidelines on this topic have been published, and they recommend establishing a national registry analogous to the BSR Biologics Register.⁵

Other rarer autoimmune diseases have high levels of TNF α as a pathological feature, and have been treated in small series with anti-TNF α drugs. Behcet's disease and sarcoidosis have been treated successfully using etanercept and infliximab, as have relapsing polychondritis and pyoderma gangrenosum. Similarly, rare diseases which are thought to be mediated by B-cells such as pemphigus vulgaris have been treated successfully with rituximab, as has acute transplant rejection.

Systemic sclerosis is a rare disease that causes fibrosis and vasculopathy in a wide range of organ systems. Transforming growth factor beta (TGF β) is over-expressed in patients with early systemic sclerosis, both in lesional and non-lesional skin. Anti-TGF β antibodies have been demonstrated to reduce fibrosis in animal models. A human anti-TGF β -1 antibody has been evaluated and shown to be safe in a pilot study, but the study was not powered to demonstrate efficacy.

Other candidates for future biologic therapies

There are other agents under development for treatment of autoimmune disease. Blockade of interleukin-6 has been proposed as a further candidate to treat inflammatory arthritis, and initial trials of a humanised anti-IL-6 receptor antibody were effective at reducing signs and symptoms of RA. IL-15 has also been proposed as an important pro-inflammatory cytokine, and trials have demonstrated some efficacy using a humanised anti-IL-15 antibody.

Abbreviations

ACR	=	American College of Rheumatology
AS	=	ankylosing spondylitis
BILAG	=	British Isles Lupus Assessment Group
BSR	=	British Society of Rheumatology
DMARD	=	disease modifying anti-rheumatic drug
Ds-DNA	=	double stranded DNA
IL-1	=	interleukin-1
IL-6	=	interleukin-6
IL-15	=	interleukin-15
NICE	=	National Institute for Health and Clinical Excellence
PsA	=	psoriatic arthritis
RA	=	rheumatoid arthritis
SLE	=	systemic lupus erythematosus
TGFb	=	transforming growth factor beta
TNFa	=	tumour necrosis factor alpha
TNFb	=	tumour necrosis factor beta

Contact mediated interactions between cells are also clearly a fundamental part of the inflammatory response. The interaction between antigen presenting cells and T lymphocytes is believed to be central in the abnormal immune response in RA and other inflammatory conditions, as well as in generating the normal immune response. This interaction relies on T cell stimulation by a specific (antigen-dependent) signal (a peptide presented on a major histocompatibility complex molecule), and a non-specific co-stimulatory signal provided by another molecule on the antigen presenting cell. Without this co-stimulation, the T-cell becomes anergic or maybe apoptose. An attempt to block this co-stimulatory signal has been made using a form of the co-stimulatory molecule chimaerised to IgG – abatacept. A phase 2 trial showed a significant improvement in ACR 20, 50 and 70 criteria in combination with methotrexate when compared with methotrexate and placebo, and was well tolerated.⁶

Other candidates for immune modulation include molecules involved in lymphocyte trafficking with the aim of preventing lymphocyte entry into the joints, although attempts to block chemokines have been difficult due to the degree of redundancy in the lymphocyte migration at this stage. Attempts continue, however, to find and block a putative lymphocyte homing molecule for joints.

Conclusions

In summary, these are exciting times for those involved in caring for patients with autoimmune diseases, as new agents become available and more is found out about where they should fit into management. Much research remains to be done, but the seeds of laboratory research are bearing fruit in the form of therapeutic effect in these challenging diseases. Biological therapies

now have an established place in therapy, and are providing important clues about pathogenesis and disease mechanisms.

Acknowledgement

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