Review Article

Biologic treatments in rheumatoid arthritis and juvenile idiopathic arthritis

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Abstract

A number of biological approaches to the management of inflammtory arthropathies have been explored. These include the development of IL-1 receptor antagonists and TNF antagonists. Four biological agents are currently marketed in Europe. Most studies have revolved around Rheumatoid Arthritis, but an increasing number of studies are now completed or ongoing in the other inflammatory joint diseases. These studies are reviewed in this article with a view to guiding practice and usage in the Maltese Islands.

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis in the UK with 0.5 – 1% of the population being affected. RA accounts for significant morbidity and mortality and its medical costs in the UK account for nearly 8% of Health Service and related expenditure (Clinical management of RA and OA www.rheumatology.org.uk. The overall annual inclusive cost of RA in the UK is between £0.8 and £1.3 billion with the majority of costs being generated by a small proportion of patients with severe disease.[1]

The aetiology of RA is unknown but it has a complex, multifactorial pathogenesis with a fluctuating clinical course and an unpredictable prognosis. Approximately 15-30% of patients are unable to work within 1-2 years of onset of RA.

Keywords

Arthritis, advances, treatment

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The goals of therapy are to relieve symptoms, including fatigue, pain, swelling and stiffness as well as the prevention of joint destruction, loss of joint function, deformity and disability. The gold standard is increasingly becoming the achievement of clinical remission although there is little evidence that conventional disease modifying agents even if started early or in combination can achieve this goal. This has fuelled much of the research into new paradigms such as the biologic therapies.

The importance of anti-Tumour Necrosis Factor (anti-TNF) strategies in rheumatic diseases requires little introduction to rheumatologists. Tumour Necrosis Factor (TNF) and Interleukin-1 (IL-1) are two of the most important cytokine mediators of the inflammatory response in a variety of conditions. Produced primarily by activated macrophages, monocytes and endothelial cells, the effector functions of these two cytokines are similar and include a variety of powerful local and systemic effects.

Release of TNF leads to activation of vascular endothelium, including expression of adhesion molecules and upregulation of class II major histocompatibility (MHC) molecules. These events orchestrate the recruitment of further inflammatory cells (neutophils, lymphocytes and monocytes) and increase production of immunoglobulins and complement proteins. As a major cytokine in the inflammatory pathway, TNF stimulates the release of other pro-inflammatory cytokines, including interleukins (IL) -1, -6, and -8.

TNF and IL-1 also function synergistically to produce the rampant inflammatory cascade accompanying gram-negative sepsis, RA, and a variety of other inflammatory conditions.[1]

Three anti-TNF modalities are available for clinical use in the UK although only the first two have been formally appraised and approved by the National Institute of Clincal Excellence (NICE):

1. ETANERCEPT – a soluble 100% human peptide sequence made *in vitro* using recombinant DNA technology. Etanercept is a fusion protein made up of two recombinant p75 soluble receptors fused with the Fc fragment from the human IgG1. It binds TNF-α and TNF-β.
2. INFLIXIMAB – A chimeric monoclonal IgG1 antibody with human (75%) constant and murine (25%) variable regions which bind soluble TNF-α in the plasma as well as cell membrane-bound TNF-α.
3. ADALIMUMAB – A recombinant fully humanised monoclonal antibody containing only human peptide

sequences. It binds soluble TNF-α by blocking its interaction with p55 and p75 cell surface TNF receptors forming relatively large, stable trimer complexes that are rapidly and efficiently cleared from the body.[2]

One recombinant IL-1 Receptor antagonist (IL-1ra) is licensed: Anakinra.

Il-1ra is a naturally occurring competitive inhibitor of IL-1 that shares approximately 40% sequence homology with IL-1. Il-1ra binds to the Il-1 receptor. There are multiple isoforms of this enzyme, each released by activated macrophages, monocytes, neutrophils and hepatocytes. Il-1ra isoforms function naturally as local anti-inflammatory mediators, and plasma levels are increased in patients with RA and Systemic Lupus Erythematosus. [3, 4]

Recent animal model studies have examined the role of IL-1ra in vivo.[5, 6] These studies show that low concentrations of IL-1ra are sufficient to control massive inflammatory responses. However, much higher concentrations of IL-1ra are required to suppress the IL-1 initiated inflammatory cascade completely. Exogenous IL-1ra molecules are therefore potentially very useful in systemic inflammatory disease such as RA and systemic vasculitis.

Contraindications / Precautions / Monitoring

TNF-alpha blockers are not recommended in women who are pregnant or breast-feeding. They are contraindicated in active infection and in patients at high risk of infection, including chronic leg ulcers, tuberculosis, septic arthritis or continuing chronic sepsis of a prosthetic joint. They are contraindicated in patients with a history of multiple sclerosis, in patients with malignancy or pre-malignancy excluding basal cell carcinoma and malignancies diagnosed and treated more than 10 years previously. In patients with a past history of TB, it is prudent to give prophylactic treatment prior to commencing anti-TNF treatment. Biologic agents are contraindicated in patients with moderate to severe heart failure but can be administered with caution to patients with mild heart failure (NYHA Class 1-2). Live vaccines should not be administered concurrently to patients receiving biologic therapies.

No particular blood monitoring is required. However, all patients should be assessed to establish their response to treatment using objective response criteria such as the ones recommended by the BSR. All patients have their details recorded in a central Biologics register. Patients are followed up and advised to immediately report possible treatment-associated side-effects, including infection.

Rheumatoid Arthritis

1. **Infliximab**

Three placebo controlled Randomised Controlled Trials (RCT) have evaluated the use of infliximab in RA.[7, 9] The first RCT (101 people) compared 1, 3, or 10 mg/kg infliximab with or without methotrexate (MTX) versus placebo. It found a greater improvement with 3 or 10mg/kg infliximab versus placebo (ACR20 improvement: 60% in people taking 3 or 10mg/kg infliximab vs 15% in people taking placebo).[7] (See Table 1 for an explanation of ACR assessment criteria).

Table 1: *American College of Rheumtology (ACR) Response Criteria.*[25]

- Improvement in swollen joint count
- Improvement in tender joint count
- Improvement in at least three of the following measures:
  - Patient global assessment of disease activity
  - Physician global assessment of disease activity
  - Patient assessment of pain
  - Acute-phase reactant
  - Disability

The definition of response (ACR20, 50, 70) requires a 20%, 50% or 70% improvement in both tender and swollen joint count and a 20% improvement in three of the five remaining ACR core set measures. Using these criteria, REMISSION is defined as:

- Morning stiffness absent or not exceeding 15 minutes
- No fatigue
- No joint pain by history
- No joint tenderness
- No joint or tendon sheath swelling
- No elevation of ESR

The landmark ATTRACT study was a large multicentre RCT (428 people with active disease not responsive to MTX) comparing five groups over 12 months: placebo versus infliximab at 10mg/kg, given every 8 weeks.[8] All continued to receive MTX. AT 54 weeks ACR20 criteria were reached by 59% who received infliximab/MTX and by 20% of the MTX/placebo group. ACR50 was attained by 39% of the people receiving infliximab and by 5% in the placebo group($P < 0.001$; CI not provided). Longer term results at 54 weeks found that all infliximab groups improved versus placebo in terms of ACR20, ACR50, and ACR70 criteria (all results $P<0.05$; CI not provided).

The important unblinded extension of the ATTRACT study was also recently reported.[9] This lasted 102 weeks and 216 patients were studied. The mean radiological progression was quite low (but not as low as with Etanercept) with the total Sharp score increasing by a mean of 1.14. At 102 weeks 48% of patients had achieved an ACR 20 and 20% achieved an ACR 70. No data was available regarding remission.

In the RCTs, common adverse reactions were upper respiratory infections, headache, diarrhoea, and abdominal pain. Reactions during or immediately after the injection (headache, nausea, urticaria) were also observed in the

Table 2: *Description of ADALIMUMAB pivotal trials and study populations*

	ARMADA	DE019	STAR	DE011
Description	Efficacy and saftey in MTX-resistant RA in patients with > 1 other DMARD failure	Radiographic progression and physical function in MTX resistant RA	Safety and efficacy in RA with standard rheumatologic care (SOC	Efficacy and saftey in DMARD resistant RA
Treatments	Humira + MTX **vs.** Placebo + MTX	Huminra+ MTX **vs.** Placebo + MTX	Humira + SOC **vs.** Placebo + SOC	Humira monotherapy **vs.** Placebo
Study Duration	24 weeks	52 weeks	24 weeks	26 weeks
Patients	271	619	636	544
RA duration	12.7 years	11 years	9.3 years	10.8 years
Mean HAQ	1.5	1.44	1.37	1.86
Mean CRP (mg/1)	26	16	15	50
# failed DMARD	3	3	2.1	3.8

placebo groups, but were more frequent with infliximab. Antibodies to double stranded DNA were found in about 16% of people taking infliximab.

The rates of serious adverse effects in both groups were not significantly different, but there was insufficient power to detect clinically important differences. Worldwide, over 150 cases of reactivation of TB have been documented, and people should be screened for previous TB before treatment.

2. **Etanercept**

Two 6-month placebo controlled RCTs and two RCT that compared etanercept versus MTX have been published.[10 – 13] One RCT (234 people who had failed to respond to other disease modifying antirheumatic drugs) compared two doses of etanercept (10 and 25mg both given twice weekly) versus placebo.[10] Improvement by at least 50% (ACR50 criteria) was found in 40% of people with high dose etanercept, in 24% with low dose etanercept, and in 5% with placebo (10mg vs placebo; P < 0.001; 25mg vs placebo; P < 0.001; 25mg vs 10mg; P = 0.032; CI not provided). The RCT also found that etanercept improved functional status (measured by disability index; P , 0.05) and quality of life (measured by general health status; P < 0.05).

The second RCT (89 people with inadequate response to MTX) compared etanercept (25 mg/wk) versus placebo.[11] People were allowed to continue MTX. More people achieved ACR20 criteria with etanercept than with placebo (71% with etanercept vs 27% with placebo; P < 0.001; CI not provided). A 12-month RCT (632 people with early rheumatoid arthritis) compared MTX versus two doses of etanercept (10 and 25mg both given twice weekly).[12] It found significantly more people achieved ACR20, ACR50, and ACR70 responses with etanercept (25 mg) versus MTX at 6 months. By 12 months there was no significant difference in ACR response rate (72% with etanercept vs 65% with MTX; P = 0.16; CI not provided). The higher dose etanercept was significantly better than the lower dose in terms of ACR20, ACR50, and ACR70 response at 12 months (P < 0.03 for all comparisons).

The pivotal study for Etanercept is the TEMPO study.[13] This was a 52 week randomised, double-blind, clinical efficacy, safety and radiographic study in patients who were refractory to DMARDs other than methotrexate. 682 patients were enrolled. Three radiographic analyses were performed and in all cases there was a significant reduction in progression in the Etanercept + MTX arm (total Sharp score, change in erosions, change in joint space narrowing :- 0.54, -0.3, +0.23 respectively). 80% of patients showed no progression (radiological deterioration) at 12 months in the etanercept arm. Markers of disease activity at 52 weeks (ACR20, ACR50, ACR70) were reached in 85%, 69% and 43% respectively and 37% of patients were found to be in clinical remission. One double blind RCT (424 people with rheumatoid arthritis for < 3 years) found no significant difference between entanercept (25mg sc twice weekly) versus oral MTX (rapidly escalating to 20 mg/wk) for health related quality of life at 52 weeks (SF-36 physical scale, mean improvement 10.7 points with etanercept vs 9.6 points with MTX, P = 0.84; SF-36 mental scale, mean improvement 3.6 points with etanercept vs 4.1 points with MTX, P = 0.39; health related quality of life, mean improvement 0.73 points with etanercept vs 0.76 points with MTX, P = 0.46).[14]

The common adverse effect was mild injection site reaction (42-49% in the treated group vs 7-13% in the placebo group). One report of placebo-controlled trials (249 people on etanercept vs 152 people on placebo) found that injection site reactions were significantly more

common for etanercept versus placebo. (7.73 events/ patient years with etanercept vs 0.62 events/patient years with placebo, P < 0.001.[15] Other adverse effects included upper respiratory symptoms or infections, headache, and diarrhoea. Autoantibodies to double stranded DNA developed in 5-9% of the treated group. Less than 1% of people developed malignancies or infections in the 6-month trials. Reactivation of demyelinating disease has been described.

3. **Adalimumab**

As it is identical to full-length human immunoglobulin (IgG1), adalimumab shares the properties of a natural human IgG including a terminal half-life of about two weeks. In contrast, infliximab is cleared after about 8-9.5 days while etanercept is cleared after 70 hours.[16]

The efficacy and safety of adalimumab is supported by evaluations in over 2400 patients with RA and more than 5000 patient-years of exposure across 23 trials in Europe and the USA. Four of these trials (Table 2) assessed the efficacy of adalimumab both as monotherapy as well as in combination with MTX.

4. **Anakinra**

Approaches to the inhibition of IL-1 in RA have trailed the development of anti-TNF strategies. Recombinant human IL-1ra has been studied both as monotherapy and in combination with disease-modifying agents in RA. Daily subcutaneous injections resulted in up to 35% improvement in a number of clinical parameters, and patients receiving the highest doses of IL-1ra had radiographic improvement in bony erosions compared to placebo.[17] Combination therapy of IL-1ra with MTX results in approximately 40% of patients receiving ACR 20 responses.[18.]

Juvenile Idiopathic Arthritis

There is currently no evidence to support treatment with biologic agents beyond 2 years and continuation of therapy is therefore dependent upon ongoing monitoring of disease activity and clinical effectiveness in the individual cases. NICE appraised the evidence for etanercept in Juvenile Idiopathic Arthritis (JIA) in March 2002 and recommended its use for children aged 4 to 17 years with active polyarticular JIA whose condition has not responded adequately to, or who have proved intolerant of MTX. NICE further recommends that initiation of etanercept therapy should only be undertaken by a consultant who regularly sees children with JIA. In addition, the prescribing centre should have a nurse specialist or a trained nurse who is able to teach children and parents injection techniques.

Infection

The risk of serious and sometimes fatal infection is well documented during anti-TNF therapy.[19-24] In a number of deaths administration of methylprednisolone in close temporal proximity to the initiation of anti-TNF therapy or the presence of severe organ compromise was postulated as a cause presumably due to increased (? excessive) immunosuppression. However, all the fatalities occurred in patients above the age of 60 years so an age-related factor may also have been operative and may well be an independent risk factor for infection.[20]

The UK Position regarding TNF-Alpha blocking agents in Arthritis

Etanercept and Infliximab were reviewed under the NICE guidance of March 2002 regarding their use in RA and JIA. These agents have been recommended for use in patients who have continuing clinically active RA that has not responded to at least two disease-modifying anti-rheumatic drugs, including MTX (unless contraindicated).

TNF-alpha blocking agents are commenced under the direction of a consultant rheumatologist. Effectiveness of the medications is assessed using the guidelines established by the British Society of Rheumatology which set out the criteria for eligibility, define response to treatment and define lack of response and criteria for cessation of therapy. All clinicians prescribing TNF-α blocking agents should register the patient with the Biologics register established by the BSR and recommended by NICE.

Conclusions

TNF inhibitors have provided a major advance in our therapeutic options for treating RA. Understanding why some patients do not respond to these therapies remains a challenge and provides opportunities for a better understanding of the pathogenetic mechanisms operative in RA. Important questions that remain regarding these therapies include the likelihood of opportunistic or unusual infections in the context of their chronic administration.

Finally, the costs of these potent therapies needs to be evaluated in terms of their long-term benefit, the predicted reduction in joint replacements, and their potential to provide improved quality of life.

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