

Adalimumab

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Rheumatoid arthritis (RA) is one of the commonest autoimmune diseases. Management includes NSAIDs, COX-II inhibitors, DMARDs (disease modifying anti-rheumatic drugs) and biological therapies including TNF (tumour necrosis factor)- α -blockers.
- Adalimumab is the first anti-TNF- α -antibody that is entirely humanised. In theory, antibody formation is less likely than with other TNF- α -blockers and there should be few allergic reactions.
- Adalimumab can be used with or without concomitant methotrexate (MTX). The 40mg dose is given by sub-cutaneous injection.
- Administration is weekly if used as monotherapy; if used with MTX then adalimumab should be given fortnightly.
- Only one Phase II trial has been fully published. The Phase III trials are still in abstract form.
- Efficacy data to date suggests that adalimumab, whether given as monotherapy or in combination with MTX, is as efficacious as infliximab or etanercept. There are no head-to-head trials comparing them.
- NICE guidance is available on the use of etanercept and infliximab in patients with RA (No. 36).

Introduction

Adalimumab is the first anti-TNF (tumour necrosis factor) antibody that is entirely human in origin. In theory patients should be able to tolerate the drug for longer, antibody formation will be less likely (there is a risk of developing antibodies against the murine component of the infliximab monoclonal antibody) and there will be few allergic reactions. Adalimumab was licensed in September 2003 for the treatment of rheumatoid arthritis (RA) in adults.

Evidence

There is only one fully published trial involving adalimumab – the **ARMADA trial**¹. This was a 24-week, randomised, double-blind, placebo-controlled, phase II trial comparing three sub-cutaneous doses of adalimumab (20mg, 40mg and 80mg) to placebo in 271 patients stabilised on methotrexate (MTX). Adalimumab was given on alternate weeks.

Analysis was on an intention-to-treat basis and the study was powered to detect a 35% difference in the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) response rates between placebo and adalimumab (all doses). The primary efficacy endpoint, ACR 20, was achieved in significantly more patients receiving adalimumab than those receiving placebo. (47.8% in 20mg group; 67.2% in 40mg group; 65.8% in 80mg group, 14.5% placebo group; $p < 0.001$ vs. placebo).

There were a number of secondary endpoints. The ACR 50 was achieved in 31.9% (20mg), 55.2%* (40mg), 42.5%* (80mg) and 8.1% (placebo) * $p < 0.001$. The ACR 70 was achieved in 10.1%, 26.9%*, 19.2% and 4.8% respectively, * $p < 0.001$.

Brand Name, (Manufacturer): Humira™ (Abbott Laboratories)

BNF Therapeutic Class: 10.1.3

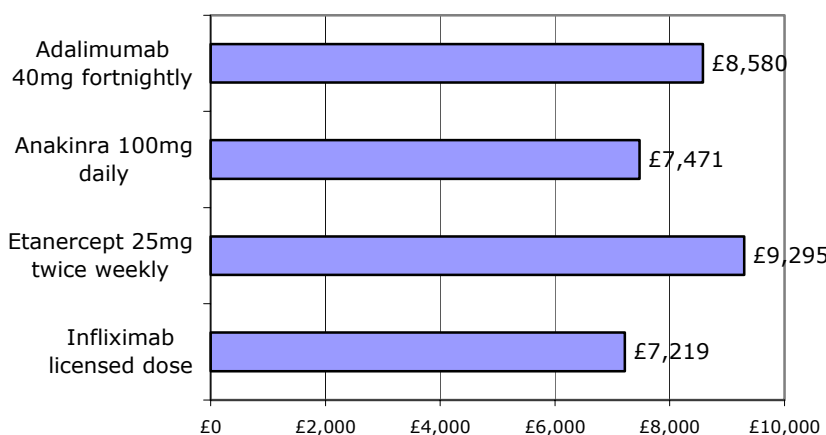
Licensed Indications: Treatment of RA in Adults

Dosage and Administration: Weekly (monotherapy); fortnightly (if given with methotrexate).

Marketed: September 2003

Cost Comparisons: Cost for one years treatment. Infliximab dose = 3mg/kg week 0, 2 & 6, then every 8 weeks as necessary.

N.B. Doses shown for general comparison and do not imply therapeutic equivalence



(Adalimumab)

All of the ACR core set of disease activity measures were significantly improved in the adalimumab groups compared to placebo.

Onset of response was seen after one week of treatment. The sample size was too small to allow for meaningful comparisons between the adalimumab groups.

The following trials have only been published in abstract form. It is not possible to fully evaluate them from the abstracts.

544 patients were enrolled into a 26 week placebo-controlled **Phase III trial**². During the trial period no DMARDs were administered. Patients received either 20mg or 40mg adalimumab every other week (e.o.w.), weekly or placebo.

Significantly more patients taking adalimumab achieved ACR 20, 50 and 70 responses compared to placebo ($p < 0.05$). 40mg weekly was significantly better than 40mg e.o.w. ($p < 0.05$) with respect to ACR 50 response and to both 20mg doses with respect to ACR 20 and 50 responses.

The **STAR trial**³ was a 24 week randomised, placebo-controlled study involving 636 patients. Safety was the primary endpoint with efficacy being the secondary endpoint. Adalimumab, 40mg fortnightly was given in combination with standard RA therapy.

Overall, patients treated with adalimumab had a higher ACR20 response rate (51.9% vs. 34.6%, $p < 0.001$). Adverse events occurred in 86.5% of adalimumab-treated patients compared to 82.7% given placebo. This was not significantly different.

Safety

The main side effect of adalimumab is injection site reactions. Other adverse reactions are similar to those seen with the other TNF- α -blockers, such as respiratory tract infections, auto-antibody formation, headache and rash. The STAR trial did not show that adding adalimumab to existing therapy increased the incidence of adverse or serious adverse effects.

Place in Therapy

Adalimumab has not been compared in head-to-head trials with infliximab or etanercept, nor is this likely to happen.

Administration of adalimumab is favourable when compared to the administration of etanercept and anakinra. Etanercept is given twice weekly by subcutaneous (sc) injection, with or without MTX. Anakinra is given by daily sc injection with MTX. Adalimumab can be given fortnightly or weekly, with or without MTX. Adalimumab is administered as a sc injection, rather than an infusion, which is how infliximab is administered. Infliximab is given at 0, 2 and 6 weeks and then every 8 weeks thereafter, concomitantly with MTX.

There is NICE guidance available on the use of infliximab and etanercept (No. 36) and guidance on anakinra is expected in January 2004.

For full London New Drugs Group document

See www.druginfozone.nhs.uk (password protected)

Key Papers

1. Weinblatt ME et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. The ARMADA Trial. *Arth Rheum* 2003; 48(1):35-45.
2. van de Putte L.B.A. et al. Efficacy and safety of adalimumab (D2E7), the first fully human anti-TNF-alpha monoclonal antibody, in patients with rheumatoid arthritis who failed previous DMARD therapy: 6-month results from a phase III study. *European League Against Rheumatism (EULAR), Stockholm, Sweden.*(Abstract) : 2002 <http://www.eular.org/index.cfm?famePage=/eular2002.cfm>
3. Furst DE et al. Efficacy of adalimumab (D2E7), the first fully human anti-TNF-alpha monoclonal antibody, administered to rheumatoid arthritis patients in combination with other antirheumatic therapy in the STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) Trial. *European League Against Rheumatism (EULAR), Stockholm, Sweden.*(Abstract) : 2002 <http://www.eular.org/index.cfm?famePage=/eular2002.cfm>

Risk Management Issues:

Patients should be evaluated for active or latent TB infection before treatment is started. If latent infection is diagnosed, the patient should be treated appropriately. Patients should seek medical advice if signs or symptoms of TB manifest. Patients with other active infections should also not receive adalimumab.

Adalimumab must be protected from light and stored in a refrigerator.

Produced for the UK Medicines Information Pharmacists Group

By Alexandra Topol, Principal Pharmacist, London Medicines Information, Northwick Park Hospital, Watford Road, Harrow, Middlesex. HA1 3UJ. 020 8869 3551

The information contained in this document will be superseded in due course. Not to be used for commercial purposes. May be copied for use within the NHS.