

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

Y-F Chen,¹ P Jobanputra,² P Barton,³ S Jowett,³
S Bryan,³ W Clark,¹ A Fry-Smith¹ and A Burls^{1*}

¹ West Midlands Health Technology Assessment Collaboration (WMHTAC),
Department of Public Health and Epidemiology, University of
Birmingham, UK

² Department of Rheumatology, Selly Oak Hospital, University Hospitals
Birmingham NHS Trust, Birmingham, UK

³ Health Economics Facility, Health Services Management Centre, University
of Birmingham, UK

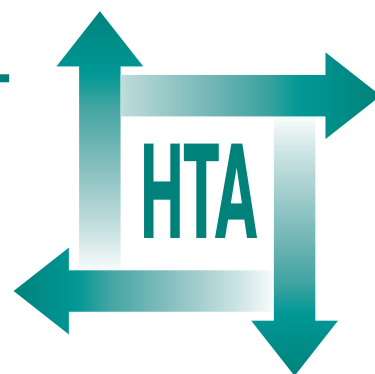
* Corresponding author



Executive summary

Health Technology Assessment 2006; Vol. 10: No. 42

**Health Technology Assessment
NHS R&D HTA Programme**





INAHTA

How to obtain copies of this and other HTA Programme reports.

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (<http://www.hta.ac.uk>). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

- fax (with **credit card** or **official purchase order**)
- post (with **credit card** or **official purchase order** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card

The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order

You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.



Executive summary

Background

Rheumatoid arthritis (RA) is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Description of technology

Drugs that inhibit joint destruction are known as disease-modifying antirheumatic drugs (DMARDs). There are around eight DMARDs, which are not biologics, in common use in the UK. These drugs are not always effective, may lose effectiveness with time or may cause adverse effects. Alternative DMARDs are therefore needed and tumour necrosis factor (TNF) inhibitors are one class of new agents that has been developed.

Tumour necrosis factor- α (TNF- α) is a cytokine that plays an important role in joint inflammation. TNF inhibitors have been designed to inhibit its actions. Three are currently licensed for use in the UK:

- *adalimumab*: given by subcutaneous injections (40 mg) every other week, but the dose may be increased to weekly if the disease is poorly controlled
- *etanercept*: given by a once-weekly subcutaneous injection (50 mg) or twice weekly (25 mg each)
- *infliximab*: given by intravenous infusion (3 mg kg⁻¹) at 0, 2 and 6 weeks and at 8-weekly intervals thereafter. It is only licensed for use concomitantly with methotrexate.

Current recommendations and service provision

National Institute for Health and Clinical Excellence (NICE) 2002 guidance for the use of TNF inhibitors recommended that:

- etanercept and infliximab be used in patients with clinically active disease that has not responded adequately to at least two DMARDs including methotrexate (unless contraindicated)
- details of patients and their treatment should be recorded in a registry.

There is variable implementation of the guidance, with limited access to these agents in some areas. Where used, these drugs have tended to be used after people have failed two or more DMARDs (as recommended), but they are also being used sequentially, after patients fail on a TNF inhibitor (not recommended). There are currently around 10,000 patients (about 2% of the RA population) on these drugs in the UK, with an estimated annual cost to the NHS of around £100 million. These figures are rising.

Since 2002 more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. In addition, all three agents have been licensed for use in early disease.

Objective to the report

This report reviews the clinical and cost-effectiveness of adalimumab, etanercept and infliximab when used in the treatment of RA in adults.

Methods

Systematic reviews of the literature on effectiveness and cost-effectiveness were undertaken. A wide range of databases was searched and information sought from researchers and industry. Industry submissions to NICE were reviewed. Meta-analyses of effectiveness data were undertaken for each agent.

The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model, was further developed and used to produce an incremental cost-effectiveness analysis.

Results

Number and quality of studies

Twenty-nine randomised controlled trials (RCTs), most of high quality, were included: nine on adalimumab, 11 on etanercept and nine on infliximab. There were 14 economic



evaluations: three from industry submissions, one from the British Society for Rheumatology and ten from published literature.

Direction of evidence and size of treatment effect

Direct comparison with standard treatments

The only head-to-head comparisons were against methotrexate. For patients with short disease duration (≤ 3 years) who were naïve to methotrexate:

- adalimumab was marginally less and etanercept was marginally more effective than methotrexate in reducing symptoms of RA; etanercept was better tolerated than methotrexate
- both adalimumab and etanercept were more effective than methotrexate in slowing radiographic joint damage.

Etanercept was also marginally more effective and better tolerated than methotrexate in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate.

TNF inhibitors versus placebo

All the three agents, either alone (where so licensed) or in combination with ongoing DMARDs, were effective in reducing the symptoms and signs of RA in patients with established disease. At the licensed dose the numbers needed to treat (95% CI) required to produce an American College for Rheumatology (ACR) response compared with placebo were: ACR20: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0); ACR50: adalimumab 4.2 (3.7 to 5.0), etanercept 3.1 (2.7 to 3.6), infliximab 5.0 (3.8 to 6.7); ACR70: adalimumab 7.7 (5.9 to 11.1), etanercept 7.7 (6.3, to 10.0), infliximab 11.1 (7.7 to 20.0).

Combination (TNF inhibitor plus methotrexate) versus methotrexate

In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. Infliximab combined with methotrexate had an increased risk of serious infections (relative risk 2.74, 95% CI 1.12 to 6.70; number needed to harm 25, 95% CI 16.7 to 100).

Existing economic evaluations

All ten published economic evaluations met standard criteria for quality, but the incremental cost-effectiveness ratios (ICERs) ranged from being within established thresholds to being very high

because of varying assumptions and parameters. All three sponsors submitted economic models. All made assumptions favourable to their product (e.g. assuming that 'responders' can be separated from 'non-responders' and choosing the most favourable trial data for effectiveness).

Cost-effectiveness

BRAM incorporates improvements in quality of life and mortality, but assumes no effect of TNF inhibitors on joint replacement. For use in accordance with current NICE guidance as the third DMARD in a sequence of DMARDs, the base-case ICER was around £30,000 per quality-adjusted life-year (QALY) in early RA and £50,000 per QALY in late RA. Sensitivity analyses showed that the results were sensitive to the estimates of Health Assessment Questionnaire (HAQ) progression while on TNF inhibitors and the effectiveness of DMARDs, but not to changes in mortality ratios per unit HAQ.

TNF inhibitors are most cost-effective when used last. The ICER for etanercept used last is £24,000 per QALY, substantially lower than for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). First line use as monotherapy generates ICERs around £50,000 per QALY for adalimumab and etanercept. Using the combination of methotrexate and a TNF inhibitor as first line treatment generates much higher ICERs, as it precludes subsequent use of methotrexate, which is cheap. The ICERs for sequential use are of the same order as using the TNF inhibitor alone.

Conclusions

Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function and slowing radiographic changes in joints. When used alone, adalimumab is marginally less effective and etanercept is marginally more effective than methotrexate, in methotrexate-naïve patients. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in early RA, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well-established effectiveness of MTX alone. In addition, an increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab or infliximab. ►

Results of published economic evaluations vary: some analyses suggest that the use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, whereas others report very high ICERs. Although most are of high quality, none of them uses all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. The societal perspective generates more favourable ICERs. All economic evaluations submitted by the manufacturers report ICERs that fall within the currently accepted thresholds of cost-effectiveness. However, in the authors' opinion, these models make assumptions and use data that favour the TNF inhibitor being evaluated, the appropriateness of which can be questioned.

The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (£24,000 per QALY) being significantly lower than the ICER for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). Other things being equal, etanercept would be, therefore, the TNF inhibitor of choice based on this evidence. However, the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance, which gives ICERs around £30,000 per QALY using early RA effectiveness data. Using data for late RA, however, gives an ICER of around £50,000 per QALY for etanercept, with higher figures for adalimumab and infliximab.

First-line use gives ICERs around £50,000 per QALY for adalimumab and etanercept as monotherapies with much higher figures for combinations with methotrexate.

Sequential use of TNF inhibitors was modelled, with the TNF inhibitors starting as third line therapy and using the 'late RA' values for the TNF inhibitors. The results are similar to those using the given TNF inhibitor as the sole TNF inhibitor in third place, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept.

Recommendations for further research

Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs, and sequential use in patients who have failed a previous TNF inhibitor, are needed. Longer term studies of the quality of life in patients with RA and the impact of DMARDs on this are needed, as are longer studies that directly assess effects on joint replacement, other morbidity and mortality.

Publication

Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al.* A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess* 2006;**10**(42).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/26/01. The protocol was agreed in January 2005. The assessment report began editorial review in March 2006 and was accepted for publication in May 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Aileen Clarke, Dr Peter Davidson, Dr Chris Hyde,
Dr John Powell, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2006

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.