Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation

C McLeod,[1] A Bagust,[2] A Boland,[1] P Dagenais,[3] R Dickson,[1*] Y Dundar,[1] RA Hill,[1] A Jones,[4] R Mujica Mota[2] and T Walley[1]

[1] Liverpool Reviews and Implementation Group, UK
[2] University of Liverpool Management School, UK
[3] Agency for Health Services and Technology Assessment (AETMIS), Montréal, Canada
[4] Cochrane Cystic Fibrosis and Genetic Disorders Group/Centre for Medical Statistics and Health Evaluation, University of Liverpool, UK

* Corresponding author

Executive summary

Health Technology Assessment 2007; Vol. 11: No. 28

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

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

Ankylosing spondylitis (AS) is a chronic inflammatory condition (a member of the spondyloarthropathies) affecting the spine, sacroiliac joints and peripheral joints, causing pain, stiffness and disability. Diagnosis is problematic and current UK incidence and prevalence data are uncertain. Currently, there is no standard or effective therapy for AS. Conventional management is composed of physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). None of these agents has been shown to alter the progression of the disease, but they may offer palliation of pain and symptoms. Adalimumab, etanercept and infliximab target the activation of tumour necrosis factor-α (TNF-α) and its subsequent activation of downstream inflammatory processes, and as such have the potential to offer symptom palliation as well as altering disease progression.

Objectives

The objectives of this review were to assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of AS. The following comparisons are made:

- adalimumab and conventional management versus conventional management
- etanercept and conventional management versus conventional management
- infliximab and conventional management versus conventional management
- between adalimumab, etanercept and infliximab, where data are available.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Evidence on clinical effects and cost-effectiveness of anti-TNF-α therapy was identified using a comprehensive search strategy (for the period up to November 2005) of bibliographic databases (including the Cochrane Library, EMBASE and MEDLINE) as well as handsearching activities. Unpublished evidence such as conference abstracts was considered for inclusion in the assessment.

The assessment of health economics evidence included a review of published economic evaluations and a critique of company submissions to the National Institute for Health and Clinical Excellence.

Inclusion criteria

The assessment was restricted to adults diagnosed with active AS. Randomised controlled trials (RCTs) comparing an anti-TNF-α agent (adalimumab, etanercept or infliximab) with conventional management or another anti-TNF-α agent were considered for inclusion.

Clinical outcomes had to include at least either a response to treatment based on Assessment in Ankylosing Spondylitis (ASAS) criteria, disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)], function [Bath Ankylosing Spondylitis Functional Index (BASFI)] or their component measurements. Studies reporting quality of life or adverse events were also eligible for inclusion.

Full economic evaluations that compared two or more options for treatment and considered both costs and consequences were eligible for inclusion in the economic literature review.

Results

Clinical findings

Nine placebo controlled RCTs were included in the review of clinical effects. These included two studies of adalimumab, five of etanercept and two of infliximab in comparison with placebo (along with conventional management). No RCTs directly comparing anti-TNF-α agents were identified.

Data from the nine RCTs were included for at least one outcome in the meta-analysis. Meta- ▶

analyses were conducted for data on ASAS (20, 50 and 70% improvement), mean change in BASDAI and mean change in BASFI at 12 weeks following initiation of anti-TNF-α therapy or placebo preparation for all three drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab only. Each meta-analysis of anti-TNF-α therapy, as a group or as individual anti-TNF-α agents, demonstrated statistically significant advantages over placebo.

At 12 weeks ASAS 50% responses were 3.6-fold more likely to be achieved with anti-TNF-α treatment than with placebo [relative risk 3.58, 95% confidence interval (CI) 2.72 to 4.71].

Compared with baseline, disease activity scores were reduced by close to 2 BASDAI points at 12 weeks (random-effects weighted mean difference –1.89, 95% CI –2.23 to –1.55). Functional scores (BASFI) were reduced at 12 weeks (weighted mean difference –1.46, 95% CI –1.69 to –1.24).

Meta-analyses for each anti-TNF-α drug were also conducted. Statistical indirect comparisons, based on available anti-TNF-α versus placebo comparisons, were unable to distinguish a statistically significant difference between individual anti-TNF-α agents.

Economic evaluation

Six full economic evaluations (two peer-reviewed published papers, four abstracts) were included in the review. The conclusions among economic evaluations were mixed, although the balance of evidence indicated that over short time-frames anti-TNF-α therapies were unlikely to be considered cost-effective.

The limitations of the clinical outcome data impose restrictions on the economic assessment of cost-effectiveness. The only period for which direct unbiased RCT evidence was available was in the short term. The current assessment tools are limited and at present BASDAI and BASFI are the best tools available, although not designed for, or ideal for, use in economic evaluations.

The review of the three submitted models identified a number of inherent flaws and errors. Once the serious errors had been corrected, the incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of £30,000. However, once the Schering-Plough model had been corrected, the ICER for infliximab was in the range of £40,000–50,000 per quality-adjusted life-year (QALY).

The short-term (12-month) model developed by the assessment group confirmed the large front-loading of costs with a result that none of the three anti-TNF-α agents appears cost-effective at the current acceptable threshold, with infliximab yielding much poorer economic results (£57,000–120,000 per QALY).

The assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-α agents in the long term. It is acknowledged that this model is far more speculative than the first since trends and parameter values must be projected far beyond the available evidence, with consequent loss of precision. Sensitivity analyses reveal wide variations in estimates of cost over the long term; however, the analyses challenge the assumptions made in the company submissions that costs will decrease over time.

It is not possible to make a definitive assessment of economic performance in the face of the wide-ranging uncertainties; however, three clear conclusions can be drawn:

- Assuming clinical equivalence, the higher costs associated with infliximab (even if given less frequently) make it a much less favourable option than either adalimumab or etanercept.
- It is unlikely that extending the period of continuous treatment over decades will automatically improve cost-effectiveness.
- Without proven criteria by which to identify those patients most likely to benefit, the sequential trial and error approach to finding an effective agent for a patient will lead to less attractive economic results than those provided in the current single treatment model.

Implications for the NHS

In terms of budget impact, uncertainties in the basic epidemiology of AS and the eligibility of patients to be offered anti-TNF-α agents lead to an extremely wide range of potential additional costs to the NHS. However, the present analyses indicate that the approval of anti-TNF-α agents for the general treatment of active AS is likely to lead to considerable financial consequences as well as large additional service demands. ▶

Conclusions

The review of clinical data related to the three drugs (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term (12–24 weeks) the three treatments demonstrate clinical and statistical effectiveness in relation to assessment of ASAS, BASDAI and BASFI. Indirect comparisons of treatments were limited and were not able to determine a significant difference in effectiveness between the three agents.

The short-term economic assessment indicates that none of the three anti-TNF-α agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least favourable option. Analyses carried out by the assessment group over the longer term challenge the assumptions made in the company submissions that costs will decrease over time. Owing to these large and sustained costs, the impact on the NHS budget is likely to be considerable.

Recommendations for further research

There is an absence of evidence concerning a number of limiting factors related to patients suffering from AS, the disease itself and its treatment.

Patient factors

- What are the current incidence and prevalence rates for AS?
- What patient variables are appropriate to predict disease progression?
- If a patient does not respond to one anti-TNF-α agent will they respond to another?
- What criteria should be used in the decision to discontinue treatment?
- Should the same criteria be applied to patients restarting treatment after previous treatment failure?

Disease factors

- What is standard disease progression?
- Could alternative disease measurements be developed to inform economic modelling more adequately?

Treatment factors

- Is disease progression halted/slowed in patients treated with anti-TNF-α agents?
- Do patients require treatment with anti-TNF-α agents continuously?
- Can anti-TNF-α treatment be titrated down or withdrawn over time?
- Can anti-TNF-α treatments be of use to manage disease flares rather than continuously?
- Is there dose creep that requires drug dosages to increase over time?
- What are the issues related to sequencing of treatments?
  - Which treatment should be considered first line?
  - If one treatment fails should a second/third be tried?
  - If one treatment works initially and then fails should a second/third be tried?
  - If the second/third treatment fails should the first be tried again?
- What role does conventional treatment (NSAIDs) play when an anti-TNF-α agent is prescribed?

In order to obtain robust estimates of the longer term clinical effectiveness and cost-effectiveness of anti-TNF-α agents for AS, clinical trials that aim to address these limiting factors need to be conducted.

Publication

McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(28).

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies 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 research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work 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 03/54/01. The protocol was agreed in October 2005. The assessment report began editorial review in August 2006 and was accepted for publication in February 2007. 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 or the Department of Health.

ISSN 1366-5278

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.