Title:
Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (03/54)

Details of appraisal group

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Dundar Y  Research Fellow, Clinical effectiveness
Haycox A  Senior Research Fellow, Health economics
Hill R  Research Fellow, Clinical effectiveness
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Walley T  Professor, Clinical pharmacology

A. Full title of research question

To assess the clinical and cost effectiveness of adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (AS).

B. Clarification of research question and scope

The systematic review will examine the comparative clinical and cost-effectiveness of adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis.

Clinical comparisons

Comparisons will be made between:
- Adalimumab and conventional management versus conventional management
- Etanercept and conventional management versus conventional management
- Infliximab and conventional management versus conventional management
- Comparisons between, adalimumab, etanercept and infliximab, where data are available

Conventional management currently includes non steroidal anti-inflammatory drugs (NSAIDs), physiotherapy, disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids, see background section for more detail.
If evidence allows, clinical effects in subgroups of patients will be explored. The consecutive use of TNF-alpha inhibitors will also be considered if data permits.

**Economic evaluation**
The evaluation of economic evidence will include quality assessment of published cost minimisation, cost effectiveness, cost utility and cost benefit analyses. Economic models included in the industry submissions will be critiqued as appropriate.

If appropriate data are available, an economic model will be developed that extends beyond the end of data collection period of any published trial to estimate the cost effectiveness of adalimumab, etanercept or infliximab for the treatment of ankylosing spondylitis.

Estimates will also be prepared of the likely budget impact that would arise for the NHS in England and Wales. These will take account of available information on current and anticipated patient numbers and service configuration for the treatment of this condition.

C. **Report Methods**

**Search strategy**
The following databases will be searched for relevant published literature for the period up to 31 January 2006.

- CENTRAL (Cochrane Central Register of Controlled Trials)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)

Research groups working on ankylosing spondylitis which are identified through searches of the information sources will be contacted for information about ongoing trials.

Bibliographies of reviews, retrieved articles and submissions to the National Institute for Health and Clinical Excellence (NICE) will be searched for further studies.

Handsearching of recent issues of journals with AS-related content that might not yet have been indexed in electronic databases and Internet resources will be examined for information on clinical trials and cost data. In addition, handsearching of recent AS conference abstracts will be conducted electronically, where this facility is available.

Full details of the search strategies used and process of selection of evidence sources will be recorded.
### Inclusion criteria

**Clinical effectiveness:**
- Primarily: Randomised Controlled Trials (RCTs)
- Secondly: In the absence of RCT data, non-RCTs (such as non-randomised Phase I trials) will be reported

**Economic evaluation:**
- Full economic evaluations that consider both costs and consequences (cost-effectiveness, cost-utility, cost-minimisation and cost-benefit analyses)

### Study design

**Patient population**
- Etanercept and Infliximab - Adults with active ankylosing spondylitis (AS) whose disease has responded inadequately to conventional therapy.
- Adalimumab - Adults with active AS

### Interventions
- Adalimumab, etanercept, and infliximab plus conventional management

### Comparators
- Conventional management without TNF-alpha inhibitors. Such as NSAIDs, physiotherapy, DMARDs and corticosteroids, see background section for more detail.

### Outcomes

**Clinical:**
- Pain and other symptoms (e.g. Bath Ankylosing Spondylitis Disease Activity Index - BASDAI)
- Functional capacity (e.g. Bath AS Functional Index - BASFI)
- Disease activity (e.g. BASDAI)
- Adverse effects of treatment
- Disease progression (e.g. BASDAI)
- Health related quality of life (e.g. SF-36 or ASQoL)

**Economic:**
- Incremental cost per life year gained – if relevant
- Incremental cost per quality adjusted life year gained

### Quality assessment strategy

All included studies will be assessed for methodological quality. The quality of clinical effectiveness will be assessed using criteria based on CRD Report No. 4.[1]

Cost effectiveness studies will be quality assessed using criteria updated from the checklist developed by Drummond and Jefferson.[2]

Two reviewers will independently evaluate the quality of the included studies and discuss disagreements. A third reviewer will be consulted, if necessary, to achieve consensus.
Data extraction strategy
Data from sources included in our search will be extracted as detailed below and will include information listed in Appendix II.

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, authors (and sponsors) of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed.

Methods of analysis/synthesis

a. Methods of analysis for clinical studies
Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed. Results from non randomised studies will be presented narratively. If evidence allows, meta-analyses will be conducted using Mantel-Haenszel method and fixed-effect model and will only include data from RCTs. Where quantitative heterogeneity is indicated, analysis using a random-effects model will be conducted for comparison with results of fixed-effect analysis.

For binary outcomes, where sufficient data are available, relative treatment effects will be presented in the form of relative risks (RR) or odds ratios (OR). For continuous outcomes, mean differences will be calculated provided skewness is not too great. For time to event outcomes, log hazard ratios (log HR) will be presented. Data will be pooled only if this makes sense clinically and statistically.

Studies that (1) provide only unplanned, interim findings (2) are continuing to recruit patients will be considered for inclusion in the review but will not be included in meta-analysis.

b. Methods of analysis for economic studies
Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions to NICE, will be collated and presented as appropriate.
Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

a. **Cost data**
The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with the interventions. If evidence indicates that a societal perspective is required to credibly value all important costs and outcomes, this will be explored and presented in the sensitivity analysis.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate costs will be discounted at 6.0% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions. Sensitivity analyses will be performed to explore the effects of varying the discounting rate to 3.5%.

b. **Assessment of benefits**
A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. We anticipate that the main measures of benefit will be improved quality of life, although it may be appropriate to augment these with AS-specific measures of clinical benefit.

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions. Sensitivity analyses will be performed to explore the effects of varying the discounting rate to 3.5%.

c. **Modelling**
We will undertake a review of any industry submitted model(s). This will include a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis. In addition, we will provide an assessment of the models’ strengths and weaknesses and discuss the implications of using different assumptions in the model. We will explore reasons for any major discrepancies between the results obtained from assessment review model and the industry model.

Our ability to construct an economic model will depend on the data available. A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost effectiveness analysis or cost minimisation analysis will be undertaken.

d. **Sensitivity Analysis**
If appropriate, sensitivity analysis will be applied to our model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision-making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

If evidence indicates that a societal perspective is required to value credibly all important costs and outcomes, this will be explored and presented.
D. Handling the company submission(s)

The Assessment Group intends to use the industry dossier:

- as a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost-effectiveness, cost utility studies and cost benefit analysis)
- to undertake an analysis of any industry models, including the strengths and weaknesses and the implications of different assumptions. The detail to which this can be undertaken will depend on the number and size of company dossiers submitted. Clarification of particular aspects of the model may be sought from the drug manufacturer.

Any ‘commercial in confidence’ or ‘academic in confidence’ data taken from the submission(s) or other sources will be underlined and highlighted in our report.

E. Project Management

a. Timetable/milestones:

<table>
<thead>
<tr>
<th>Submission</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft protocol to NICE</td>
<td>13 October 2005</td>
</tr>
<tr>
<td>Finalised protocol to NICE</td>
<td>27 October 2005</td>
</tr>
<tr>
<td>Consultee submissions received from NICE</td>
<td>31 January 2006</td>
</tr>
<tr>
<td>Progress report to NCCHTA</td>
<td>7 February 2006</td>
</tr>
<tr>
<td>Complete, near final draft report to referees and NICE Technical Lead</td>
<td>(Early – Mid April 2006)</td>
</tr>
<tr>
<td>Final assessment report to NICE and NCCHTA</td>
<td>11 May 2006</td>
</tr>
</tbody>
</table>

b. Review Advisory Panel

The Group will recruit an Advisory Panel of experts to support the development of the review. Panel members may advise on specific sections of the review: clinical, healthcare policy, health economics, statistics and review methodology. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking.

c. External Referees

The Technology Assessment Report will be subject to external peer review by at least two clinical experts and one methodological expert. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. External expert referees will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All referees are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external referees’ signed copies to NCCHTA. Comments from the referees and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

d. Competing Interests

No competing interests exist for members of the Assessment Group. Any competing interests relating to the external reviewers will be declared in the final report.
F. Appendices

I. Details of data extraction

a. Clinical effectiveness data to be extracted will include, but not be limited to:

Study Details
- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Methodological details of study
- Details of trial intervention
- Concomitant therapies
- Details of funding

Participants
- Age
- Sex
- Functional capacity
- Disease status
- Co-morbidity
- Number recruited or accrued

Results (data for all outcomes specified will be extracted as available)
- Disease related symptom improvement rates
- Treatment related adverse events
- Withdrawal due to adverse events
- Withdrawal due to inefficacy
- Quality of life
b. **Cost effectiveness** data extraction will include, but not be limited to:

*Study characteristics*
- Type of evaluation and synthesis
- Intervention
- Study population
- Time period of study
- Country of origin
- Author affiliations

*Economic model*
- Type of model
- Perspective
- Model assumptions

*Cost data and cost data sources*
- Cost items
- Cost data sources
- Discount rate
- Currency, and currency year

*Outcome data and data sources*
- Health outcomes
- Outcome data sources
- Discount rate

*Cost effectiveness*
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions
II Details of quality assessment

a. **RCTs of clinical effectiveness** will be assessed using the following criteria, based on CRD Report No. 4.[1]

- Was the method used to assign participants to the treatment groups really random? *(Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)*
- Was the allocation of treatment concealed? *(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)*
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention to treat analysis included?

Items will be graded in terms of **yes** (item adequately addressed), **no** (item not adequately addressed), **partially** (item partially addressed), **unclear** or not enough information, **NA** not applicable or **NS** not stated.
b. Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond and Jefferson.[2]

**Study design:**
- The research question is stated
- The economic importance of the research question is stated
- The viewpoint(s) of the analysis are clearly stated and justified
- The rationale for choosing the alternative programmes or interventions compared is stated
- The alternatives being compared are clearly described
- The form of economic evaluation used is stated
- The choice of form of economic evaluation is justified in relation to the questions addressed.

**Data collection:**
- The source(s) of effectiveness estimates used are stated
- Details of the design and results of effectiveness study are given (if based on a single study)
- Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
- The primary outcome measure(s) for the economic evaluation are clearly stated
- Methods to value health states and other benefits are stated
- Details of the subjects from whom valuations were obtained are given
- Productivity changes (if included) are reported separately
- The relevance of productivity changes to the study question is discussed
- Quantities of resources are reported separately from their unit costs
- Methods for the estimation of quantities and unit costs are described
- Currency and price data are recorded
- Details of currency of price adjustments for inflation or currency conversion are given
- Details of any model used are given
- The choice of model used and the key parameters on which it is based are justified.

**Analysis and interpretation of results:**
- Time horizon of costs and benefits is stated
- The discount rate(s) is stated
- The choice of rate(s) is justified
- An explanation is given if costs or benefits are not discounted
- Details of statistical tests and confidence intervals are given for stochastic data
- The approach to sensitivity analysis is given
- The choice of variables for sensitivity analysis is justified
- The ranges over which the variables are varied are stated
- Relevant alternatives are compared
- Incremental analysis is reported
- Major outcomes are presented in a disaggregated as well as aggregated form
- The answer to the study question is given
- Conclusions follow from the data reported
- Conclusions are accompanied by the appropriate caveats

All items will be graded as either √ yes (item adequately addressed), × no (item not adequately addressed), ? unclear or not enough information, NA not appropriate or NS not stated.
III. Background

Ankylosing spondylitis (AS) is a chronic inflammatory condition which mainly affects the spine and sacroiliac joints, causing pain and stiffness in and around the spine. Over time chronic spinal inflammation (spondylitis) can lead to fusion of the spinal vertebrae (ankylosis), which is debilitating and irreversible. Osteoperosis (loss of bone density) leading to vertebral fractures[3] is another late but serious spinal complication of AS. However, the disease is not only limited to the spine, many AS patients also suffer from inflammation of peripheral joints (particularly of the hip and knee), as well as periodic eye inflammation (uveitis).

According to the British Society for Rheumatology (BSR) guidelines for ankylosing spondylitis[4] the age of onset is usually in the patients’ thirties, and continues to progress throughout the patients’ lifetime. Owing to its early onset, the disease has a significant effect on employment, with approximately one third of AS patients withdrawing from the labour market prematurely owing to ill health.[4]

Genetic tests indicate that AS may be inherited, with many patients presenting with the HLA-B27 gene (approx 90% of patients).[5] However, the HLA-B27 gene only increases the risk of developing AS, as the vast majority of individuals carrying the gene never develop AS (in the USA 7% of the population carry the gene, but only 1% actually exhibit AS).[5] The prevalence of the HLA-B27 gene varies between different ethnicities, as does the prevalence of AS. In Caucasians, the prevalence of AS ranges from 0.05—0.23% of adults, with three to four times more men presenting with the disease than women.[4]

Although not fully understood, cellular immune responses are thought to be involved in the pathology of AS. Release of TNF-alpha (among other cytokines) by activated T-cells and macrophages promote inflammatory processes including further release of cytokines; ingress and activation of immune cells and release of potentially damaging enzymes. TNF-alpha not only has a role in inflammation but has also been implicated in osteoporosis.

The diagnosis of ankylosing spondylitis is based on the modified New York criteria, which measures the patient’s symptoms using both radiological and clinical criteria.[6] However, early clinical symptoms of ankylosing spondylitis can be very deceptive, as stiffness and pain in the lower back can be seen in many other conditions, which may be confounded by a low awareness of AS among non-rheumatologists.[7] Hence, often many years can pass before a diagnosis of AS is confirmed. Furthermore, the radiological requirement by the modified New York criteria for radiographic sacroilitis grade II bilaterally or grade III or IV unilaterally, which may not appear for up to several years after first symptoms, could further delay the diagnosis of AS.[7] It has been suggested that the delay between onset of first chronic symptoms and diagnosis of AS may be in the region of 8 years or more.[8]

Currently there is no gold-standard therapy for ankylosing spondylitis. Conventional management of AS involves regular physiotherapy and non steroidal anti-inflammatory drugs (NSAIDs). NSAIDs offer a quick palliation of symptoms for the majority of patients, although their long term benefits on disease progression is unclear. Disease modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine, and methotrexate are also used, together with systemic or intra-articular corticosteroids, for the relief of extreme symptoms of pain and stiffness.

Response to treatment is typically measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The Assessment in Ankylosing Spondylitis Working Group (ASAS) has recommended that response to therapy be assessed by a 50% reduction or fall of two or more units in BASDAI, and the spinal pain Visual Analogue Scale (VAS) to reduce by two or more units. This assessment is carried out between 6 – 12 weeks post commencement of therapy, and subsequently reviewed quarterly. Other measures that may be used for assessing response include the Bath Ankylosing Spondylitis Functional Index (BASFI), and expert opinion.
Withdrawal or change of therapy is considered if the BASDAI does not fall by two or more units or decrease by 50%, and/or if the spinal pain VAS does not decrease by two or more units, within three months of commencement therapy or if the initial response is not maintained. Treatment is also ceased or changed if serious adverse events occur.

The technologies

The three agents considered in the scope (adalimumab, etanercept and infliximab) are all ‘biologicals’ targeting the action of TNF-alpha with the aim of reducing inflammatory effects.

Adalimumab (*Humira*) is a recombinant monoclonal antibody which binds to TNF-alpha and blocks its interaction with the TNF receptor, thereby preventing the downstream activation of pro-inflammatory cytokines. It is not currently licensed for AS, although studies have been conducted in patients with active AS. The anticipated dose is 40mg twice weekly by subcutaneous injection.[9]

Etanercept (*Enbrel*) is a recombinant dimeric fusion protein that competitively antagonises the action of TNF-alpha upon its receptor. It is licensed for the treatment of active ankylosing spondylitis in adults who have had an inadequate response to conventional therapy. The recommended dose is 25mg twice weekly by subcutaneous injection.[10]

Infliximab (*Remicade*) is a chimeric monoclonal antibody, which as with adalimumab, binds to TNF-alpha and prevents its receptor mediated inflammatory response. It is licensed for the treatment of active ankylosing spondylitis in adults with severe axial symptoms who have not responded adequately to conventional therapy. The recommended dose is 5mg/kg by intravenous injection at nought, two and six weeks, followed by a maintenance dose of 5mg/kg every six to eight weeks.[10]

Adalimumab, etanercept, and infliximab have been associated with several side-effects, notably infections which can be severe, including upper respiratory, tuberculosis and septicaemia. Other side-effects include nausea, abdominal pain, worsening heart failure, hypersensitivity reactions, fever, headache, depression, lupus erythematosus-like syndrome, pruritus, injection-site reactions, and blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia).[10]

Economics

With the introduction of TNF-alpha inhibitors the cost of AS therapy is likely to increase greatly, owing to the high costs of this technology. In view of the relatively early onset of the disease the costs of treating AS over a patient’s lifetime could be extremely large. However, the potential benefits of this type of therapy in terms of improving a patient’s quality of life and functional capacity may be highly significant, owing to the fact that AS is a life limiting disease which primarily affects patients of working age. Hence, the question is whether the benefits offered by this new technology justify the increased costs associated with it.
IV References


5. MedicineNet.com, What causes AS.


