Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation

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Scientific summary

Anti-TNFs for ankylosing spondylitis and nr-AxSpA

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Scientific summary

Background

Spondyloarthritis encompasses a heterogeneous group of inflammatory rheumatologic diseases. Spondyloarthritis can be categorised as having predominantly axial or peripheral involvement. In people with axial spondyloarthritis (axSpA), the predominant symptoms are back pain and stiffness developed before age 45 years. For axSpA patients to be classified as having ankylosing spondylitis (AS), imaging evidence of joint damage using radiography is required. Patients with non-radiographic axial spondyloarthritis (nr-AxSpA) may, or may not, have signs of sacroiliac joint inflammation on a magnetic resonance image. The use of magnetic resonance imaging allows for earlier detection of axSpA, as joint damage may not become evident on radiographs for many years. Progression of axSpA is difficult to predict.

Tumour necrosis factor (TNF)-α inhibitors (anti-TNFs) are typically used when the disease has not responded adequately to conventional therapy. Current National Institute for Health and Care Excellence (NICE) guidance recommends treatment with adalimumab, etanercept and golimumab in adults with active (severe) AS only if certain criteria are fulfilled, but it does not recommend infliximab for AS. Anti-TNFs for patients with nr-AxSpA have not previously been appraised by NICE.

Objectives

To determine the clinical effectiveness, safety and cost-effectiveness within the NHS of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, within their respective licensed indications, for the treatment of severe active AS or severe nr-AxSpA (but with objective signs of inflammation).

Methods

For the systematic review of clinical efficacy, randomised controlled trials (RCTs) were eligible, including any open-label extensions. Adverse events data were sought from existing reviews of anti-TNFs used in any disease and from other appropriately large studies. For studies of natural history, long-term effectiveness, adherence and sequential use, published analyses based on large and long-term data sets (registry data) were eligible. Eligible studies were of adults with either severe active AS or severe nr-AxSpA but with objective signs of inflammation. The treatments of interest were adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or any of their biosimilars. The relevant comparators were conventional management strategies (either with or without placebo) and alternative anti-TNFs. Key outcomes included multiple domain response criteria [such as Assessment in Ankylosing Spondylitis (ASAS) 40] and measures of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] and function [Bath Ankylosing Spondylitis Functional Index (BASFI)].

Fifteen databases were searched for relevant studies in July 2014. Clinical effectiveness data from RCTs were synthesised using Bayesian network meta-analysis methods. Sensitivity analyses were performed in which trials at risk of bias were excluded. Results from other studies were summarised narratively.

A systematic review of cost-effectiveness studies was undertaken to assess the relevance of existing data from the perspective of the NHS. Three databases were searched. Only full economic evaluations that compared two or more options and considered both costs and consequences were included. The

differences in the approaches and assumptions used across the studies were examined in order to explain any discrepancies in the findings and to identify key areas of uncertainty. A separate review of the manufacturer's submissions was also undertaken and the findings were compared with those found in the review of previously published studies.

The findings from the clinical effectiveness and cost-effectiveness reviews were used to inform the development of a de-novo decision model to assess the cost-effectiveness of the alternative anti-TNFs in accordance with their licences for the separate indications. We developed a generalised framework for evidence synthesis that pools evidence on the change in BASDAI by considering those studies that report this measure directly and also those that report the proportion of patients achieving a BASDAI 50 response (a $\geq$ 50% improvement in BASDAI score). We expressed BASDAI 50 as a function of the absolute change in BASDAI and we used this relationship in the extended synthesis. We also aimed to simultaneously synthesise information on BASFI (function) score, a measure that is used together with the BASDAI score to determine the long-term quality-adjusted life-year (QALY) and cost burden of the disease in the economic model. The decision model was a cohort model structured as a modified decision tree tracking response at 12 weeks and treatment failure at subsequent time points within the time horizon. These events determine changes in BASDAI and BASFI scores, which are further used to define costs and utilities. The model considers the independent effects on BASFI as a result of disease activity (BASDAI) and the extent and progression of radiographic disease (as measured by the modified Stoke Ankylosing Spondylitis Spinal Score). The model was developed in accordance with the NICE reference case. The model has a lifetime horizon (60 years) and considers costs from the perspective of the NHS and personal social services. Health effects were expressed in terms of QALYs.

Results

Clinical efficacy from randomised controlled trials

Twenty-eight eligible RCTs were identified, with 24 being suitable for data synthesis. All but seven of the trials were extended into open-label active treatment-only phases. Most RCTs were judged to have a low risk of bias overall.

For the AS population, the 10- to 16-week data showed consistent effects across the different anti-TNFs when compared with placebo: for ASAS 20 the pooled relative risks ranged from 1.80 (certolizumab pegol) to 2.45 (infliximab); for the ASAS 40 data the relative risks ranged from 2.53 (certolizumab pegol) to 3.42 (adalimumab) and for BASDAI 50 the relative risks ranged from 3.16 (adalimumab) to 4.86 (infliximab). Adalimumab, certolizumab pegol, etanercept and infliximab produced statistically significant and clinically important reductions in disease activity, with BASDAI reductions ranging from 1.46 units (certolizumab pegol) to 2.28 units (infliximab), and function, with BASFI reductions ranging from 1.1 units (certolizumab pegol) to 2.16 units (infliximab).

When analysed as a class, anti-TNFs were statistically significantly more likely than placebo to result in patients with AS achieving an ASAS 20 response (relative risk 2.21), an ASAS 40 response (relative risk 3.06), and a BASDAI 50 response (relative risk 3.37). They also produced statistically significant improvements (calculated using mean difference in change from baseline) in disease activity (BASDAI mean difference –1.66 units) and in function (BASFI mean difference –1.38 units). There was little evidence of statistical heterogeneity for the key outcomes (ASAS outcomes, BASFI, BASDAI and BASDAI 50) but substantial heterogeneity was seen for other outcomes. Results of the sensitivity analyses performed for the AS studies were very similar to the main analyses.

For the nr-AxSpA population, five RCTs were included. When anti-TNFs were considered as a class, statistically significant improvements were found for ASAS 20 (relative risk 1.65); ASAS 40 (relative risk 2.74); BASDAI 50 (relative risk 2.31); BASDAI (mean difference –1.32 units); and BASFI (mean difference

–0.99 units). For the disease activity, function and responder outcomes, these common class efficacy estimates were consistently slightly smaller for nr-AxSpA than for AS, most noticeably for BASFI and BASDAI 50. Statistical heterogeneity (when such estimates could be calculated) was apparent in the nr-AxSpA analyses.

Long-term efficacy

For AS, across all the anti-TNFs, after around 2 years and 5 years of treatment, roughly half of patients were still achieving a good level of response to therapy. However, the long-term studies produced less reliable data than the RCTs. Fewer studies were available of nr-AxSpA patients, although the results were broadly similar to those of the AS studies.

Evidence for an effect of anti-TNFs on radiographic disease progression was limited; the relatively short-term follow-up available to date and the insensitivity of radiography as an imaging tool precluded the drawing of firm conclusions regarding the role of anti-TNFs in preventing or delaying the progression of AS. There are some data to suggest an identifiable benefit from around 4 years, but results from ongoing long-term studies should help to clarify this issue.

Registry data demonstrate that around 60% of patients with AS treated with a first anti-TNF will still be on treatment at 2 years. Sequential treatment with anti-TNFs can be worthwhile but the drug survival response rates and benefits are reduced with second and third anti-TNFs, with the proportion of BASDAI 50 responders falling approximately 10% with each subsequent anti-TNF and the median BASDAI and BASFIs achieved increasing (worsening).

Adverse effects

Data from large systematic reviews, which included patients with a wide range of diseases, suggest that, in the short term, anti-TNFs as a group are associated with significantly higher rates of serious infections, tuberculosis reactivation, non-melanoma skin cancer, total adverse events (AEs) and withdrawals because of AEs than control treatments. Specifically, infliximab is associated with significantly higher rates of total AEs and withdrawals because of AEs and certolizumab pegol is associated with significantly higher rates of serious infections and serious AEs. The available open-label data on AEs were limited by the small sample sizes and non-randomised study designs.

Cost-effectiveness reported in existing published studies and manufacturer's submissions

A total of six UK studies reporting on the cost-effectiveness of anti-TNFs were identified, all for the treatment of AS. There appear marked differences between the results of the previously published industry-funded assessments in AS and the results reported in a previous independent assessment. Although all models reviewed used changes in BASDAI and/or BASFI to quantitatively model the short- and longer-term costs and quality-of-life effects, there appeared significant variation in the assumptions employed. We identified important conceptual issues with all existing models relating to the subsequent projection of BASDAI and BASFI scores over a longer time horizon.

Manufacturers submitted de novo analyses for both AS (AbbVie, UCB, Pfizer, Merck Sharp & Dohme) and nr-AxSpA (AbbVie, UCB, Pfizer) populations. Despite the different model structures and assumptions applied across the various manufacturer's submissions, the incremental cost-effectiveness ratios (ICERs) reported for the anti-TNFs versus conventional care (CC) appeared consistent in AS. Across the separate base-case analyses, the ICERs ranged from £16,391 to £44,448 for the alternative anti-TNFs compared with CC alone. Infliximab was routinely reported to have the highest ICER. When infliximab was excluded from consideration, the ICERs ranged from £16,391 to £21,972 for the other anti-TNFs.

The differences in structural and parameter assumptions appear more evident in the cost-effectiveness results for the nr-AxSpA population. The ICERs for adalimumab, certolizumab and etanercept ranged between £12,866 and £50,692 per QALY. Importantly, when the results in the separate populations were compared, no consistent relationship appeared to emerge across the manufacturer's submissions regarding the cost-effectiveness on anti-TNFs in AS compared with the nr-AxSpA population. In addition, many of the same conceptual concerns identified from the review of published cost-effectiveness studies were also still evident.

An independent model was developed to address the conceptual concerns and areas of remaining uncertainty. Although it shared several of the assumptions and parameter estimates from the manufacturer models, it has a different conceptual structure (linking BASFI progression to evidence from radiographic assessments) and applies a more generalised framework for the synthesis of clinical-effectiveness data. The extended synthesis approach showed the effectiveness of the different anti-TNFs to be similar. Consequently, the treatment effects for the anti-TNFs were assumed to come from a 'common' distribution, that is a 'class effect'. We developed a simulation model that allowed prediction of the conditional change scores for responders/non-responders to BASDAI 50 at 12 weeks and to explore differences in the baseline BASDAI/BASFI scores according to response status.

Base-case cost-effectiveness results were presented for two alternative 'rebound' assumptions. In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs varied between £19,240 [certolizumab with the proposed patient access scheme (PAS)] to £40,467 per additional QALY (infliximab) in AS patients. In the rebound to CC scenario, the ICER of the alternative anti-TNFs varied between £33,762 (certolizumab with the proposed PAS) to £66,529 per additional QALY (infliximab) in AS patients.

In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs for nr-AxSpA patients varied between £28,247 (certolizumab with the proposed PAS) to £29,784 per additional QALY (etanercept) in AS patients. In the rebound to CC scenario, the ICER of the alternative anti-TNFs for nr-AxSpA patients varied between £32,528 (certolizumab with the proposed PAS) to £34,232 (etanercept) per additional QALY.

Discussion

The key strengths of the systematic review are the rigorous methods used and the extensive breadth of the types of study included. The York model confers several advantages over current cost-effectiveness studies by linking changes in function to a more explicit clinical/biological process and facilitating a more formal consideration of the potential impact of anti-TNFs on function, via the specific effects these drugs have on the different processes which independently relate to this parameter.

The meta-analysis results derived from a substantial and generally high-quality evidence base demonstrated that anti-TNFs produce clinically important benefits to AS patients in terms of improved function and reduced disease activity following around 3 months of treatment with an anti-TNF. Smaller benefits were seen across outcomes in patients with nr-AxSpA, which was a more heterogeneous population. Less reliable data were available on long-term efficacy, although it appears that around half of patients still achieve a good level of response after around 2 years of treatment.

Although there are a number of important differences in approaches both among the different manufacturer models and compared with the York model, the comparison of ICERs based on the York rebound equal to gain scenario appears broadly consistent with that reported by the manufacturers in both populations.

Conclusions

- In both AS and nr-AxSpA populations anti-TNFs produce clinically important benefits to patients in terms of improving function and reducing disease activity. The efficacy estimates were consistently slightly smaller for nr-AxSpA than for AS.
- Statistical (and clinical) heterogeneity was more apparent in the nr-AxSpA analyses than in the AS analyses; both the reliability of the nr-AxSpA meta-analysis results and their true relevance to patients seen in clinical practice are questionable.
- In AS anti-TNFs can be assumed to have a class effect, with the treatments being equally effective.
- Effectiveness appears to be maintained over time in about 50% of patients at 2 years.
- Evidence for an effect of anti-TNFs delaying disease progression was limited; results from ongoing long-term studies should help to clarify this issue.
- Sequential treatment with anti-TNFs can be worthwhile but the drug survival response rates and benefits are reduced with second and third anti-TNFs.
- The de novo model, which had addressed many of the issues of earlier evaluations, generated ICERs ranging from £19,240 to £66,529 depending on anti-TNF and modelling assumptions.

Suggested research priorities

Randomised trials are needed to identify the nr-AxSpA population that will benefit the most from anti-TNFs. Long-term studies are needed to clarify the effect of anti-TNFs on the progression of structural damage in AS and to help clarify the characteristics of nr-AxSpA patients who go on to develop AS. Studies are also needed to better inform the efficacy estimates relating to sequential use of anti-TNFs.

Study registration

This study is registered as PROSPERO CRD42014010182.

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