Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation

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Scientific summary

Biologic DMARDs for the treatment of rheumatoid arthritis

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Scientific summary

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive, irreversible, joint damage, impaired joint function, and pain and tenderness caused by swelling of the synovial lining of joints and results in increasing disability and reduced quality of life. The primary symptoms are pain, morning stiffness, swelling, tenderness, loss of movement, fatigue and redness of the peripheral joints. RA is associated with substantial costs, both direct (associated with drug acquisition and hospitalisation) and indirect (owing to reduced productivity).

In 2010 the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) jointly published Rheumatoid Arthritis Classification Criteria, which focused on features at earlier stages of disease that are associated with persistent and/or erosive disease rather than defining the disease by its late-stage features. The classification criteria allocate scores to characteristics of joint involvement, serology, acute-phase reactants and duration of symptoms, to produce a score between 0 and 10, inclusive, with those scoring ≥ 6 and with obvious clinical synovitis being defined as having 'definite RA' in the absence of an alternative diagnosis that better explains the synovitis.

There are an estimated 400,000 people in England and Wales with RA, and approximately 10,000 incident cases per year. The disease is more common in females (1.16%) than in males (0.44%), with the majority of cases being diagnosed when patients are aged between 40 and 80 years and with peak incidence in patients in their seventies.

Objectives

The key objectives of this report are twofold: to estimate the clinical effectiveness of seven biologic disease-modifying antirheumatic drugs (bDMARDs) – adalimumab (ADA; Humira®, AbbVie), etanercept (ETN; Enbrel®, Pfizer), infliximab [IFX; Remicade®, Merck Sharp & Dohme Corp. (MSD)], certolizumab pegol (CTZ; Cimzia®, UCB Pharma), golimumab (GOL; Simponi®, MSD), tocilizumab (TCZ; RoActemra®, Roche) and abatacept (ABT; Orencia®, Bristol-Myers Squibb) – in defined populations; and to estimate the cost-effectiveness of these interventions compared with conventional disease-modifying antirheumatic drugs (cDMARDs). These analyses incorporated the use of bDMARDs with and without methotrexate (MTX) where this was within licence.

Three populations were defined: population 1, adults with severe active RA not previously treated with cDMARDs; population 2, adults with severe active RA that has been previously treated with cDMARDs but not bDMARDs; and population 3, adults with moderate to severe active RA that has been previously treated with cDMARDs only, including MTX (unless contraindicated or inappropriate).

Methods

A systematic review of clinical effectiveness and safety evidence for interventions of interest was conducted. Where trials narrowly missed criteria (because of a small proportion of patients with prior bDMARD exposure or low prior MTX exposure), they were considered to inform sensitivity analyses. Separate network meta-analyses (NMAs) were undertaken for randomised controlled trials (RCTs) reporting EULAR and ACR data.

A mathematical model was constructed to simulate the experiences of hypothetical patients. The model was based on EULAR response data as these are most commonly used in clinical practice in England and Wales. Large observational databases, published literature and the results of the NMAs were used to provide data for the model. The primary outcome measure was incremental cost per quality-adjusted life-year (QALY) gained.

Results

Sixty RCTs met the inclusion criteria for the systematic review of clinical effectiveness and safety evidence. Of these, 38 trials provided relevant ACR and EULAR response data for the NMA. In addition, 14 additional trials not meeting review criteria contributed data to NMA sensitivity analyses. Other relevant efficacy and safety outcomes were tabulated and discussed in a narrative synthesis. Generally, risk of bias was low overall, and low for baseline comparability, blinding, analysis by allocated treatment group and inclusion of $\geq 80\%$ of participants randomised in the final analysis. There was greater risk of bias and a lack of clarity in many included trials for allocation sequence generation and concealment, and selective reporting of outcomes.

Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in population 1, IFX plus MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups: (1) intensive cDMARDs and ADA plus MTX; (2) ETN, GOL plus MTX and step-up combination cDMARDs; and (3) ADA and cDMARDs.

Although there was uncertainty in, and overlap between, the effects of treatment on EULAR for interventions in populations 2 and 3 in the main trials, ETN plus MTX and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) TCZ, GOL plus MTX, ADA plus MTX, ABT intravenous (i.v.) plus MTX and grouped biologics; and (2) ETN, IFX plus MTX, ADA and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although CTZ plus MTX was associated with an even bigger response than ETN plus MTX and TCZ plus MTX.

Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions in populations 2 and 3 in the main trials, ETN plus MTX, TCZ and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) ETN, GOL plus MTX, ABT subcutaneous plus MTX, ADA plus MTX, IFX plus MTX and ABT i.v. plus MTX; and (2) CTZ plus MTX, intensive cDMARDs and ADA. The inclusion of the additional studies in which patients received prior biologics suggested that CTZ plus MTX and ETN plus MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and ADA which are associated with even smaller response rates.

The incremental cost per QALY of bDMARDs compared with a cDMARD-alone strategy is typically £40,000 when used in populations 2 and 3 and is greater in individuals with moderate to severe disease. The incremental cost per QALY increases (£50,000) for those who receive a bDMARD without MTX and is approximately £60,000 in population 1. A key parameter that affected the results is the assumed Health Assessment Questionnaire (HAQ) while on cDMARDs; if the values used in previous National Institute for Health and Care Excellence (NICE) appraisals were instead used, the incremental cost per QALY fell to approximately £38,000 for bDMARDs compared with cDMARDs alone. Fully incremental analyses were undertaken, but these could be misleading owing to the similarity in incremental costs per QALY for each bDMARD compared with cDMARDs alone, and the uncertainty in efficacy parameters. The data source used for establishing the relationship between HAQ and pain was also seen to influence the results markedly; the Assessment Group base case uses the estimate most favourable to the bDMARDs.

Discussion

There is no reason to believe that the results detailed in this report are not generalisable to the English and Welsh populations.

A strength of this report is that a systematic review of RCTs for bDMARDs in bDMARD-naive patients has been conducted. The primary outcome measures are EULAR or ACR response at 6 months and a formal NMA has been conducted to assess relative efficacy. Different analyses have been undertaken to assess the impact of including RCTs with a small proportion on patients with prior bDMARD use, and/or including RCTs when patients may have not had adequate prior MTX treatment.

A major strength of the cost-effectiveness analyses presented is that the Assessment Group has constructed a EULAR-based model that is much more appropriate to practice in England and Wales than previous ACR-based models. Estimates of incremental cost-effectiveness ratios (ICERs) for both EULAR data only, and when mapping ACR data to EULAR data indicate that the conclusions were not altered by restricting the selection of RCTs to only those that reported EULAR data.

An additional strength is that large observational databases were used to generate data on parameters such as HAQ change conditional on EULAR response and HAQ progression while on cDMARDs. This is preferable to data taken from relatively small RCTs of limited follow-up.

The model has known limitations. The plausible reduced efficacy of treatments when used subsequent to other treatments has not been formally incorporated. It is expected that this omission will favour bDMARDs. Lost productivity has not been included in the model, which may favour bDMARDs if it were included.

The analyses have assumed that the discontinuation rule specified by NICE has been strictly adhered to; data from the British Society for Rheumatology Biologics Register show that this is not the case. If such non-adherence continues, the ICERs will be considerably higher than those presented. Analysis of the impact has not been undertaken due to the possibility of back-calculation of commercial-in-confidence discounts offered through Patient Access Schemes.

Conclusions

The implications for the NHS are not known and it will be heavily dependent on the guidance produced by NICE.

Key research priorities include establishing, more precisely, HAQ progression while on cDMARDs; the relationship between HAQ score and utility; and the relationship between HAQ score and pain. Better evidence on the relative efficacies of bDMARDs and the reduction in efficacy when used after a different bDMARD would be beneficial, but it is acknowledged that large RCTs would be required to provide definitive answers.

Study registration

This study is registered as PROSPERO CRD42012003386.

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