Treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation

K Malottki, P Barton, A Tsourapas, AO Uthman, Z Liu, K Routh, M Connock, P Jobanputra, D Moore, A Fry-Smith and Y-F Chen*

West Midlands Health Technology Assessment Collaboration, University of Birmingham, Edgbaston, Birmingham, UK

*Corresponding author

Executive summary

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Executive summary

Background

Rheumatoid arthritis (RA) is a common inflammatory condition that typically causes a symmetrical chronic arthritis that causes joint pain, swelling and in some cases a systemic illness. The cause of RA is unknown, but important genetic influences are recognised. The goal of treatment is to achieve remission if patients present with early disease. In later disease, key goals are to control pain and inflammation and thereby reduce functional limitations and the risk of permanent joint damage.

The timely use of disease-modifying antirheumatic drugs (DMARDs) is an essential aspect of contemporary disease management, but many patients may not respond even when conventional agents are used optimally. DMARDs are defined by their ability to modify the disease process such that the risk of progressive joint damage is reduced. Biological agents designed to interrupt the inflammatory pathway have proved to be an important advance in the care of RA patients. The most widely used agents in the UK are tumour necrosis factor inhibitors [adalimumab (ADA, Humira®, Abbott), etanercept (ETN, Enbrel®, Wyeth Pharmaceuticals) and infliximab [(IFX, Remicade®, Schering-Plough Ltd)] and a monoclonal antibody targeting B lymphocytes [rituximab (RTX, Mabthera®, Roche)]. The use of these agents is subject to National Institute for Health and Clinical Excellence (NICE) guidance and all are approved for use provided specific criteria are met. Other agents such as anakinra (an interleukin-1 inhibitor), abatacept [(ABT, Orencia®, Bristol-Myers Squibb Ltd) an antibody that targets cellular interactions], and tocilizumab [(TOC, RoActemra®, Roche) an interleukin-6 inhibitor] are licensed, but currently under assessment or not approved for use by NICE, at the time when this report is being prepared.

This review considers the clinical effectiveness and cost-effectiveness of ADA, ETN, IFX, RTX and ABT when used in patients with RA who have tried conventional agents including methotrexate (MTX) and have failed to improve after trying a first tumour necrosis factor (TNF) inhibitor.

Objectives

The objectives of the assessment report were to assess:

- Whether significant differences in clinical effectiveness and cost-effectiveness exist between ADA, ETN, IFX, RTX and ABT (referred to as 'the interventions' hereafter) when used within their licensed indications in adults with active RA who have had an inadequate response to a first TNF inhibitor prescribed according to current NICE guidance.
- Whether the interventions are clinically effective and cost-effective compared with conventional DMARDs (such as MTX, sulfasalazine and leflunomide).
- Whether the interventions are clinically effective and cost-effective compared with other biologic agents [including TOC, golimumab (Simponi®, Schering-Plough Ltd) and certolizumab pegol (Cimzia®, UCB)].
- Whether the interventions are clinically effective and cost-effective compared with supportive care.

- Whether the clinical effectiveness and cost-effectiveness of the interventions differ significantly between certain subgroups of patients.

Methods

Clinical effectiveness

A systematic review of primary studies (excluding non-randomised studies with less than 20 patients in a treatment arm) of any of the technologies was undertaken. Databases searched included the Cochrane Library, MEDLINE and EMBASE along with other sources from inception up to July 2009. Further data were obtained from dossiers submitted to NICE by the manufacturers of the technologies. Inclusion decisions, quality assessment and data extraction were undertaken according to pre-defined criteria. Owing to heterogeneity between studies and insufficient data, pooling of results was not undertaken.

Cost-effectiveness

A systematic review of published studies on the costs and cost-effectiveness of the technologies for RA patients who had not responded to a TNF inhibitor and a review of the dossiers submitted to NICE by the manufacturers of the technologies were undertaken. In addition, model-based economic evaluations of the cost-effectiveness of the technologies from the perspective of the UK National Health Service (NHS) were carried out.

Results

Clinical effectiveness

Thirty-five studies were included in the systematic review. Five of these were randomised controlled trials (RCTs), one was a comparative study, one was a controlled study and 28 were uncontrolled studies (including one long-term extension of an RCT). Included RCTs compared one of the technologies with placebo and/or ongoing DMARDs/biologics to which the patients have inadequate response. No head-to-head trials directly comparing the five technologies against each other, or comparing the technologies with other biologics or previously untried DMARDs were identified.

Evidence from randomised controlled trials

The effectiveness of RTX was demonstrated in a good-quality RCT (REFLEX). At 6 months, significantly more patients treated with RTX achieved American College of Rheumatology (ACR) 20 [relative risk (RR) = 2.85, 95% confidence interval (CI) 2.08 to 3.91] and ACR70 (RR = 12.14, 95% CI 2.96 to 49.86) compared with those treated with the placebo. Significant differences between groups in favour of RTX were observed at 6 months for mean change from baseline in Disease Activity Score 28 (DAS28) (mean difference –1.50, 95% CI –1.74 to –1.26) and mean change from baseline in Health Assessment Questionnaire (HAQ) score (mean difference –0.30, 95% CI –0.40 to –0.20).

The effectiveness of ABT was demonstrated in a good-quality RCT (ATTAIN). At 6 months, significantly more patients treated with ABT achieved ACR20 (RR = 2.56, 95% CI 1.77 to 3.69) and ACR70 (RR = 6.70, 95% CI 1.62 to 27.80) compared with those treated with the placebo. Significant differences between groups in favour of ABT were observed at 6 months for mean change from baseline in DAS28 score (mean difference –1.27, 95% CI –1.62 to –0.93) and mean change from baseline in HAQ score (mean difference –0.34, insufficient data for calculating 95% CI).

One small RCT (OPPOSITE, $n = 27$) compared switching to IFX versus staying on ETN in patients who had incomplete response to ETN. The study population was not well defined and the comparator was considered inappropriate for this assessment. Two additional RCTs evaluated concurrent use of ABT and TNF inhibitor, which is not recommended in its licence. These studies were not further assessed.

Evidence from observational studies

One non-randomised study found greater but not statistically significant improvement in DAS28 for patients switched to RTX compared with those who switched to an unspecified alternative TNF inhibitor (mean difference –0.35, 95% CI –0.71 to 0.01). Another prospective cohort from the British Society for Rheumatology Biologics Registry showed significantly greater reduction in HAQ score for patients who switched to an unspecified alternative TNF inhibitor compared with switching to non-biologic DMARDs. Twenty-eight uncontrolled studies observed significant improvement in various measures of effectiveness compared with before switching, in patients who switched to ADA, ETN or IFX after discontinued previous TNF inhibitor(s), for various reasons including lack of efficacy, adverse events (AEs) and other reasons.

Subgroup analyses

Evidence from the REFLEX trial suggested that the effectiveness of RTX does not vary significantly depending on reasons for withdrawal, baseline rheumatoid factor status and number of prior TNF inhibitors tried (one vs more than one).

No significant differences in the effectiveness of ABT between subgroups, defined by the number of prior TNF inhibitors (one vs two) and the identity of the prior TNF inhibitor received (ETN vs IFX), were observed in the ATTAIN trial. Some of these subgroup analyses; however, may be underpowered.

Evidence from observational studies showed that the proportion of patients responding to a subsequent TNF inhibitor might vary according to the reason for withdrawal of the previous TNF inhibitor (higher response in patients who withdrew due to intolerance/AEs compared with those who withdrew due to lack of efficacy). The proportion of patients who respond to a subsequent treatment (including TNF inhibitors, RTX and ABT) decreases as the number of prior TNF inhibitor(s) that the patients have tried increases.

Cost-effectiveness

Systematic review

Four studies were included in the systematic review: two studies evaluated ABT and two RTX. One of the RTX studies was UK based. All but one study carried out a cost–utility analysis and reported results in cost per quality-adjusted life-year (QALY). One study carried out a cost-effectiveness analysis and reported results in cost per additional case of low disease-activity state gained (DAS28 less than or equal to 3.2) and cost per additional remission gained (DAS28 less than 2.6). All studies used a decision-analytic model.

Models varied in some important aspects: the type of model used, the sequence of drugs, comparator therapies and time horizon. There was disparity in the selection of perspectives chosen for the analyses. One study reported costs that include both those from a health-care perspective as well as indirect costs and costs of informal care; inclusion of these costs improves the cost-effectiveness of the drug.

A direct comparison of incremental cost-effectiveness ratios (ICERs) between studies was not possible because of the different approaches to modelling, in particular time horizon, country of origin and perspective chosen.

Independent economic assessment

In the reference case all biologic agents were compared with a newly initiated DMARD and against each other. Compared with DMARDs the ICERs were £34,300 (per QALY) for ADA, £38,800 for ETN, £36,200 for IFX, £21,200 for RTX, and £38,600 for ABT. RTX dominates the TNF inhibitors and the ICER for ABT compared with RTX is over £100,000 (per QALY). These results are subject to considerable uncertainty. Important drivers of that uncertainty were found in the scenario analysis to include the assumptions about HAQ progression on biologic treatments, the equation relating HAQ to quality of life, and for comparisons involving RTX the assumed time between treatments. The inclusion of AE costs for biologic therapy made little difference to the results.

Discussion

The limitations predominantly relate to factors outside the control of the assessment group. The major limitation of the assessment was the paucity of evidence from RCTs for assessing the clinical effectiveness of the three TNF inhibitors and a complete absence of genuine head-to-head trials comparing the five technologies against each other, against other biologics or against newly initiated, previously untried DMARDs. Many observational studies were identified. Data from these studies can be confounded by many factors such as patients' baseline disease activity, past history of therapy and methods of selecting and following up patients and analysis of data. Pooling of data was not performed owing to heterogeneity between studies on these respects.

Conclusions

There is lack of good-quality evidence directly comparing the effectiveness of the five technologies against each other. This imposes significant uncertainties with regard to any assessment of their relative cost-effectiveness. Adjusted indirect comparison suggests that there is no significant difference in the effectiveness between RTX and ABT, both of which are supported by good-quality RCT evidence. Existing data do not allow reliable quantification of the effectiveness of TNF inhibitors compared with RTX and ABT. Independent modelling comparing each of the other four technologies with RTX (recommended in the current NICE guidance) suggests RTX dominating ADA, ETN and IFX and an estimated ICER of £131,000 (per QALY) for ABT compared with RTX.

There is lack of evidence comparing the effectiveness of the five technologies to newly initiated, previously untried DMARDs. Independent modelling based on certain assumptions suggests the following ICERs: £34,300 (per QALY) for ADA, £38,800 for ETN, £36,200 for IFX, £21,200 for RTX and £38,600 for ABT.

There is lack of evidence directly comparing the effectiveness of the five technologies with other biologic agents.

Good-quality evidence from RCTs suggests RTX and ABT are more effective than supportive care (including ongoing DMARDs which had provided inadequate control of the disease). Data from observational studies suggest that the use of an alternative TNF inhibitor after patients have experienced an inadequate response to a first TNF inhibitor may offer some benefit, but there remain significant uncertainties with regard to the magnitude of treatment effects and how these translate into cost-effectiveness.

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