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Title **Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After The Failure of a Tumor Necrosis Factor Inhibitor: A Systematic Review and Economic Evaluation**

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Aim

To assess the clinical and cost effectiveness of adalimumab (ADA), etanercept (ETN), infliximab (IFX), rituximab (RTX), and abatacept (ABT) in patients with RA who have tried conventional agents, but failed to improve after a first tumor necrosis factor (TNF) inhibitor.

Conclusions and results

The systematic review included 35 studies: 5 randomized controlled trials (RCTs), 1 comparative study, 1 controlled study, and 28 uncontrolled studies. One RCT (REFLEX) assessed the effectiveness of RTX. At 6 months significantly more patients treated with RTX achieved 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) response compared with placebo. Differences between groups in favor 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 in Health Assessment Questionnaire (HAQ) score (mean difference –0.30, 95% CI –0.40 to –0.20). One RCT (ATTAIN) assessed the effectiveness of ABT. 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 to those treated with placebo. Significant differences between groups in favor 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 in HAQ score (mean difference –0.34, insufficient data to calculate 95%CI). Twenty-eight uncontrolled studies observed improvement in patients who switched to ADA, ETN, or IFX after discontinuing previous TNF inhibitor(s). The systematic review included 4 studies on cost-effectiveness. Independent economic evaluation undertaken by the assessment group showed that compared with disease-modifying antirheumatic drugs, the incremental cost-effectiveness ratios (ICERs) were 34 300 pounds sterling (GBP) per quality-adjusted life-year (QALY) for ADA, GBP 38 800 for ETN, GBP 36 200 for IFX, GBP 21 200 for RTX, and GBP 38 600 for ABT. RTX dominates the TNF inhibitors and the ICER for ABT compared with RTX is over GBP 100 000 per QALY. RCT evidence suggests that RTX and ABT are more effective than supportive care. Data from observational studies suggest that use of an alternative TNF inhibitor may offer some benefit, but uncertainties remain as to the magnitude of treatment effects and their cost effectiveness. Future research should include head-to-head trials comparing the clinical and cost effectiveness of the technologies against each other and emerging biologics.

Recommendations

See Executive Summary www.hta.ac.uk/project/2055.asp.

Methods

Clinical effectiveness: A systematic review of primary studies (excluding nonrandomized studies with <20 patients in a treatment arm) was undertaken. Databases searched included the Cochrane Library, MEDLINE, and EMBASE and other sources up to July 2009. Further data were obtained from dossiers submitted to NICE by manufacturers of the technologies. Inclusion decisions, quality assessment, and data extraction were undertaken according to predefined criteria. Owing to heterogeneity between studies and insufficient data, results were not pooled. Cost effectiveness: A systematic review of published studies on the costs and cost effectiveness of the technologies and a review of the dossiers submitted to NICE by the manufacturers were undertaken. Model-based economic evaluations of the cost effectiveness of the technologies from the perspective of the UK National Health Service (NHS) were carried out.

Further research/reviews required

See Executive Summary www.hta.ac.uk/project/2055.asp.

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