Rituximab for the treatment of rheumatoid arthritis

A Bagust, A Boland, J Hockenhull, N Fleeman, J Greenhalgh, Y Dundar, C Proudlove, T Kennedy, R Moots, P Williamson and R Dickson*

Liverpool Reviews and Implementation Group, UK

*Corresponding author

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Abstract

This paper presents a summary of the evidence review group's critical review of the evidence for the clinical effectiveness and cost-effectiveness of rituximab for the treatment of severe rheumatoid arthritis (RA) following failure of previous therapy, including one or more tumour necrosis factor-α inhibitors (TNFi), compared with current standards of care, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's clinical evidence came from one randomised, placebo-controlled, double-blind trial (REFLEX – Random Evaluation of Long-term Efficacy of Rituximab in Rheumatoid Arthritis) comparing rituximab plus methotrexate (MTX) with placebo plus MTX in 517 patients with long-standing refractory RA. Rituximab plus MTX was more effective than placebo plus MTX across a range of primary and secondary outcome measures, e.g. American College of Rheumatology (ACR) responses, Health Assessment Questionnaire (HAQ). However, this evidence cannot be used directly to address the manufacturer's analysis of the decision problem because, in the REFLEX trial, rituximab was not compared with a relevant comparator (e.g. leflunomide or second or third TNFi). Long-term efficacy data for retreatment with rituximab are favourable, with an estimated mean time to retreatment of 307 days ($n = 164$). Evidence from a further five trials is presented as the basis for indirect comparisons with other disease-modifying antirheumatic drugs (DMARDs); however, it is not clear that all relevant clinical studies

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List of authors:
A Bagust, A Boland, J Hockenhull, N Fleeman, J Greenhalgh, Y Dundar, C Proudlove, T Kennedy, R Moots, P Williamson and R Dickson

Contact details:
Rumona Dickson (LRiG Director), Liverpool Reviews and Implementation Group, Sherrington Buildings, University of Liverpool, Ashton Street, Liverpool L69 3GE, UK

E-mail: LRiG@liv.ac.uk

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have been included in the indirect comparison exercise, the rationale for the choice of indirect comparison method adopted is unclear and the indirect comparison method used to adjust the ACR responses only uses a single value for the reference placebo. The submitted microsimulation Markov model was based upon the REFLEX trial. For the 'NICE-recommended' scenario and the 'sequential TNFi' scenario, the original submission reports incremental cost-effectiveness ratios (ICERs) of £14,690 and £11,601 per quality-adjusted life-year (QALY) gained respectively. After model assumptions were adjusted to more realistic estimates by the ERG, the ICERs for the NICE-recommended scenario and the sequential use of TNFi range from £37,002 to £80,198 per QALY gained and from £28,553 to £65,558 per QALY gained respectively. The guidance issued by NICE in August 2007 states that rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs including treatment with at least one TNFi therapy.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of rituximab for the treatment of rheumatoid arthritis.[2]

Description of the underlying health problem

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder, which is primarily characterised by inflammation and swelling of multiple synovial joints. The primary symptoms of pain, fatigue and disability are chronic and related to the underlying inflammatory disease process. Furthermore, patients with RA have a reduced life expectancy.[3–7] There is no cure for RA and so the therapeutic goals are a remission of symptoms involving the joints, a return of full function and the maintenance of remission.

RA affects between 0.5% and 1% of the population, equating to approximately 400,000 people in England and Wales, with the prevalence being three times higher in women than in men.[8–11] Diagnosis is generally between the ages of 40 and 80 years[8–11] and within 5 years one-third of patients are unable to work,[12] increasing the substantial economic burden of RA.

Scope of the ERG report

The ERG report presents the results of the assessment of the manufacturer's (Roche Products) evidence submission regarding the use of rituximab for the treatment of severe RA following failure of previous therapy, including one or more tumour necrosis factor-α inhibitor (TNFi), compared with current standards of care. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer.

Rituximab (known as MabThera® in the UK and Rituxan® in the USA) is a monoclonal antibody that depletes the CD20+ B cells implicated in the immunopathogenesis of RA. In July 2006 rituximab plus methotrexate (MTX) was licensed in Europe for the treatment of severe RA following the failure of conventional treatments, including at least one TNFi. The licensing submission was supported by a phase III study[13] comparing rituximab plus MTX with placebo plus MTX along with evidence from phase II trials.[14–15] It is restricted to use by specialist physicians experienced in the diagnosis and treatment of RA.

Methods

The ERG report comprised a critical review of the evidence of the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. The ERG assessed the quality of the manufacturer's clinical effectiveness review using a standard checklist. The ERG conducted a detailed evaluation of the manufacturer's economic model. Cost–utility estimates were recalculated taking changes in parameters and assumptions into account. For example, mortality rates, the evidence base for progression rates for Health Assessment Questionnaire (HAQ) scores, the calculation of treatment costs and errors/omissions in the estimation of inpatient costs were explored. Some other issues were identified as potentially influencing model results, and the ERG carried out sensitivity analyses to show their impact on model results.

Results

Summary of submitted clinical evidence

The manufacturer's submission provides clinical evidence from one randomised, placebo-controlled, double-blind trial (REFLEX – Random Evaluation of Long-term Efficacy of Rituximab in Rheumatoid Arthritis) that compares the effects of rituximab plus MTX with placebo plus MTX in a study population of 517 patients with long-standing refractory RA. Data from other randomised controlled trials (RCTs) are pooled to demonstrate the retreatment efficacy of rituximab and for the analysis of safety data. Evidence from a further five trials is presented as the basis for indirect comparisons with other disease-modifying antirheumatic drugs (DMARDs).

The results from the REFLEX trial at 24 and 48 weeks confirm that rituximab plus MTX is more effective than placebo plus MTX (*Table 1*). These findings are consistent across a range of primary and secondary outcome measures including American College of Rheumatology (ACR) responses (ACR20/50/70), disease activity score (DAS28), European League Against Rheumatism (EULAR) response, HAQ, disability index (DI) and radiographic scores. Given that the patients in the trial are difficult to treat and have severe disabling disease with marked impairment of quality of life, the results of the REFLEX trial are convincing for this trial population. However, whether or not the patients in the REFLEX trial are similar enough to the patients described in the rituximab management strategies put forward in the manufacturer's submission is debateable, as 40% of the REFLEX trial patients had received at least two previous TNFi before receiving rituximab.

Long-term efficacy data for retreatment with rituximab from the REFLEX trial are favourable, but the results are limited by the small number of patients available for follow-up. The estimated mean time to retreatment from the REFLEX trial is 307 days ($n = 164$). The available safety data from the REFLEX trial show that rituximab patients had slightly higher rates of adverse reactions than the placebo patients. The European Medicines Evaluation Agency (EMEA) particularly stresses the risks of infusion reactions and infection associated with rituximab. This mirrors the belief that patients taking any of the newer biological drugs require close surveillance and monitoring.

The only RCT evidence available for rituximab is the comparison with placebo plus MTX. It is therefore appropriate for the manufacturer to conduct indirect comparisons to calculate absolute efficacy values for use in the economic model in order to answer the questions outlined in their statement of the decision problem. However, the ERG is not confident that the adjusted ACR scores described by the manufacturer are valid. In particular, it is not clear from the evidence presented by the manufacturer that all relevant clinical studies have been included in the indirect comparison exercise. The rationale for the choice of the indirect comparison method adopted is unclear and the indirect comparison method used to adjust the ACR responses only uses a single value for the reference placebo.

Summary of submitted cost-effectiveness evidence

The economic model submitted in support of the manufacturer's submission is a microsimulation Markov model based upon the phase III RCT of rituximab plus MTX versus placebo plus MTX (REFLEX trial). Patient disease progression is tracked within the model according to HAQ score. By using microsimulation of 10,000 RA patients, patient history is kept in memory and cost–utility values are assigned to each individual at each cycle. The manufacturer concludes that rituximab is considered to be a cost-effective treatment option in RA. For the 'NICE-recommended' scenario, the original manufacturer's submission reports an incremental cost-effectiveness ratio (ICER)

TABLE 1 *Key results from the REFLEX trial*

Outcome[a]	Placebo (*n* = 201)	Rituximab (*n* = 298)
Primary		
ACR20 (%) 24 weeks	18	51
ACR20 (%) 48 weeks	4	19
Secondary (24 weeks)		
ACR50 (%)	5	27
ACR70 (%)	1	12
Change in DAS, mean (SD)	–0.4 (1.17)	–1.9 (1.6)
EULAR response (%):		
None	78	35
Moderate	20	50
Good	2	15
Change in ACR core set, mean (SD):		
Swollen joint count	–2.6 (10.35)	–10.4 (12.95)
Tender joint count	–2.7 (15.48)	–14.4 (17.48)
Patient global assessment	–5.3 (22.88)	–26.0 (29.56)
Physician global assessment	–6.2 (27.70)	–29.5 (27.40)
Health assessment questionnaire[b]	–0.1 (0.45)	–0.4 (0.60)
Pain assessment	–2.5 (23.30)	–23.4 (29.35)
CRP (mg/dl)	0.0 (3.59)	–2.1 (3.48)
ESR (mm/hour)	–4.1 (25.05)	–18.5 (22.56)
Change in SF-36 domains, mean (SD):		
Mental health[c]	1.3 (9.43)	4.7 (11.75)
Physical health[d]	0.9 (5.65)	5.8 (8.47)
Changes in FACIT-F,[e] mean (SD)	–0.5 (9.84)	–9.1 (11.3)

ACR, American College of Rheumatology; DAS, diseases activity score; EULAR, European League Against Rheumatism; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SD, standard deviation; SF-36, Short Form-36 Health Survey.
a For SF-36 a positive change is an improvement; for all other continuous variables a negative change is an improvement.
b Clinically relevant improvement = decrease > 0.22.
c Clinically relevant improvement = increase > 6.33.
d Clinically relevant improvement = increase > 5.42.
e Clinically relevant improvement = decrease > 4.

of £14,690 per quality-adjusted life-year (QALY) gained. For the 'sequential TNFi' scenario, the ICER is estimated at £11,601 per QALY gained.

Commentary on the robustness of submitted evidence

The main strength of the submitted evidence is that the manufacturer makes a convincing case for the use of rituximab plus MTX versus placebo plus MTX using clinical evidence from the REFLEX trial in a specific population who are difficult to treat and who have severe disabling disease with marked impairment of quality of life. However, this evidence cannot be used directly to answer the questions raised in the manufacturer's analysis of the decision problem because, in the REFLEX trial, rituximab was not compared with a relevant comparator (e.g. leflunomide or second or third TNFi).

To compare the management strategies using rituximab described in their analysis of the decision problem the manufacturer carried out an indirect comparison exercise. However, given the criticisms previously outlined, the ERG is not confident that the adjusted ACR responses used in the economic evaluation are wholly valid.

TABLE 2 *Cost-effectiveness results incorporating the ERG corrections/amendments*

	Rituximab simulation			Comparator simulation			Incremental			ICER
Scenario	**Life-years**	**QALYs**	**Costs**	**Life-years**	**QALYs**	**Costs**	**Life-years**	**QALYs**	**Costs**	**Cost/QALY**
Base case (no TNFi) – revised model	12.747	3.045	£41,279	12.568	2.318	£30,588	0.179	0.728	£10,691	£14,694
Base case – revised model + ERG changes	15.940	5.489	£44,636	15.890	5.157	£31,069	0.050	0.332	£13,567	£40,873
Base case – ERG changes – 50% HAQ gains	15.792	4.626	£44,793	15.767	4.456	£31,212	0.025	0.169	£13,581	£80,198
Base case – ERG changes + longer interval	15.940	5.489	£43,351	15.890	5.157	£31,069	0.050	0.332	£12,282	£37,002
Alternate (TNFi) – revised model	13.028	3.963	£69,901	12.866	3.457	£63,996	0.162	0.506	£5905	£11,666
Alternate – revised model + ERG changes	15.999	5.954	£77,701	15.947	5.684	£68,853	0.053	0.269	£8847	£32,855
Alternate – ERG changes – 50% HAQ gains	15.843	4.870	£77,800	15.823	4.737	£69,070	0.021	0.133	£8730	£65,558
Alternate – ERG changes + longer interval	15.999	5.948	£73,173	15.948	5.678	£65,456	0.051	0.270	£7717	£28,553

ERG, evidence review group; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; TNFi, tumour necrosis factor-α inhibitor.
Note: all results are discounted at 3.5% per annum.

The ERG identified problems with the manufacturer's submitted model in two stages. Early examination by the ERG of the submitted economic model identified some aspects of its implementation that caused concern as to its reliability for generating estimates of cost-effectiveness. The manufacturer then submitted a revised model and addressed some of the ERG's concerns. However, the ERG subsequently identified a number of additional clinical and economic issues that called into question the validity of key assumptions in the revised economic model, and the credibility of the ICERs generated. In particular, the ERG commented upon the use of evidence for progression rates for HAQ scores, the calculation of treatment costs and the estimated duration of effective treatment for each of the active agents considered.

Most importantly, the ERG questioned whether the size of benefit from each RA treatment is overstated, because loss of efficacy is assumed to be instantaneous rather than cumulative. The manufacturer's probabilistic sensitivity analyses (original and revised), because of limitations described by the ERG, were also considered to be unreliable aids to decision-making.

In summary, after model assumptions were adjusted to more realistic estimates by the ERG, the ICER for the NICE-recommended scenario ranges from £37,002 per QALY gained to £80,198 per QALY gained and the ICER or the sequential use of TNFi ranges from £28,553 per QALY gained to £65,558 per QALY gained (*Table 2*).

Conclusions

The consequences of the corrections and amendments made by the ERG demonstrate that the economic results for the use of rituximab no longer appear as unequivocally advantageous as suggested in the manufacturer's submission, and may more reasonably be termed 'borderline' at best. There remain important areas in which there is substantial uncertainty, which could easily invalidate economic results generated by the manufacturer's model, most especially in relation to the long-term progression of disease and its effect on HAQ scores, and the duration of effective treatment for each of the active agents considered.

The ERG concludes that the robustness of the evidence base used in the manufacturer's economic model is uncertain.

Summary of NICE guidance issued as a result of the STA

At the time of writing the guidance issued by NICE (August 2007) states that:

Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying antirheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor-α (TNF-α) inhibitor therapy.

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