Scottish Medicines Consortium

rituximab 100mg/10ml, 500mg/50ml ml solution for intravenous infusion (MabThera®) (No. 323/06)

Roche

6 October 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rituximab (MabThera®) is accepted for restricted use within NHS Scotland in combination with methotrexate for treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor. It is restricted to use by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Rituximab in combination with methotrexate improves signs and symptoms and quality of life and prevents joint damage compared to methotrexate, in adults with rheumatoid arthritis who have had an inadequate response to methotrexate and an inadequate response or intolerance to at least one TNF-antagonist. Treatment should only be repeated in patients who continue to achieve an American College of Rheumatology (ACR) response of at least 20.

Rituximab is cost effective if the average dosing interval for those patients who respond to initial treatment does not fall below six months.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Dosing information

1000mg by intravenous infusion initially and after two weeks. If necessary this course can be repeated after at least 16 weeks. Data are limited on repeat courses, although some patients have received two to five courses.

UK launch date

July 2006

Comparator medications

Patients with rheumatoid arthritis (RA) who have had an inadequate response or intolerance to disease modifying anti-rheumatic drugs (DMARDs) including at least one tumour necrosis factor (TNF) inhibitor may have treatment options within conventional DMARDs (leflunomide, sulphasalazine, methotrexate, sodium aurothiomalate ('intramuscular gold'), auranofin ('oral gold'), penicillamine, azathioprine, hydroxychloroquine and ciclosporin) and TNF-antagonists (etanercept, adalimumab and infliximab) depending on previous treatment history. An initial appraisal consultation document by the National Institute for Health and Clinical Excellence (NICE) on TNF-antagonists for RA recommends sequential use of these only in the event of toxicity, with sequential use due to lack of efficacy restricted to studies designed to generate relevant outcome data including measures of quality of life and disease progression.

Cost per treatment period

Drug	Dose	Annual cost (£)
Rituximab	**1g iv on day 1 and 15, repeat if necessary**	**3493-6985***
Etanercept	25mg sc twice weekly or 50mg sc once weekly	9295
Adalimumab	40mg sc every two weeks	9295
Infliximab	3mg/kg iv on weeks 0, 2, 6 then every 8 weeks	8183#
Ciclosporin	2.5-4mg/kg po daily	1135-1772
Methotrexate	7.5-15mg sc or im weekly	772-861
Leflunomide	10-20mg po daily	620
Auranofin	6-9mg po daily	306-459
Sodium aurothiomalate	50mg im every week to every four weeks	146-584
Azathioprine	1-3mg/kg po daily	145-265
Sulphasalazine	2-3g po daily	110-164
Penicillamine	500-750mg po daily	108-162
Hydroxychloroquine	200-400mg po daily	33-66
Methotrexate	7.5-15mg po weekly	18-36

Costs from eVadis accessed on 1st August 2006 and the 51st edition of the British National Formulary and based on a patient weighing 70kg; *costs of rituximab based on one to two courses per year; # cost of infliximab in first year would be £11015; doses are shown for

general comparison and do not imply therapeutic equivalence; iv = intravenous infusion; sc= subcutaneous injection; po = orally; im = intramuscular injection.

Summary of evidence on comparative efficacy

Rituximab is an antibody to the CD20 surface protein on pre-B and mature B lymphocytes that causes depletion of B lymphocytes in the peripheral circulation. Its mechanism of action in RA is not fully understood, but may involve an effect on B lymphocytes in the synovium to disrupt inflammatory processes.

A double-blind study recruited adults with RA for at least six months that was active, as defined by a swollen joint count ≥8 of 66 joints assessed, a tender joint count ≥8 of 68 joints assessed and elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and who had at least one joint with an erosion due to RA. All patients had experienced an inadequate response to at least one TNF-antagonist and had received a weekly dose of methotrexate 10-25mg (orally or parenterally) for at least 12 weeks prior to screening. They were randomised in a 3:2 ratio, with stratification for region (non-US or US) and rheumatoid factor (positive or negative), to 2 doses of rituximab 1000mg by intravenous (iv) infusion separated by two weeks or placebo. All patients received methylprednisolone 100mg iv infusion prior to each dose of rituximab or placebo; oral prednisolone 60mg on days 2-7 and 30mg on days 8-14 after the first infusion; oral methotrexate 10-25mg once a week and weekly oral folic acid ≥5mg. The primary outcome was the proportion of the intention-to-treat population, which included all randomised patients receiving study drug, who achieved a response defined by the American College of Rheumatology (ACR) criteria as an ACR20 response at week 24. This was significantly greater with rituximab compared to placebo: 51% (153/298) vs. 18% (36/201). Proportions of patients achieving ACR50 (27% vs. 5%) and ACR70 (12% vs. 1%) responses with rituximab were also significantly greater than those given placebo. Mean changes from baseline to week 24 in individual components of the ACR score core set and in disease activity score (DAS28) were significantly greater with rituximab: -1.9 vs. -0.4 for the DAS28 score.

Quality of life
Rituximab, compared to placebo, was associated with significant improvements in mean change from baseline to week 24 on the short-form (SF-36) physical summary score (5.8 vs. 0.9) and mental summary score (4.7 vs. 1.3) and on the functional assessment of chronic illness therapy-fatigue (FACIT-F) score (-9.1 vs. -0.5).

Radiologically-assessed joint damage
Radiological data at baseline and week 24 were available for 268/298 (90%) of patients from the rituximab group and 177/201 (88%) of patients from the placebo group including placebo patients who received rescue therapy with rituximab prior to the 24-week visit. Differences in favour of rituximab compared to placebo were observed in mean change from baseline for the following: total Genant-modified Sharp score (0.6 vs. 1.2, respectively), erosion score (0.4 vs. 0.8, respectively) and joint space narrowing (0.2 vs. 0.5, respectively, p=0.0156), with only the difference for the latter score reaching significance. In the respective groups 66% and 60% of patients showed no worsening of erosions. Similar additional analyses were conducted on data from 272 and 184 patients from the rituximab and placebo groups, respectively, who had baseline and week 24 or 56 radiographs. Mean changes at 24 weeks were extrapolated to 56 weeks for 29% and 32% of patients in the respective groups without radiographs at week 56. There were significant differences in favour of the group originally randomised to rituximab, compared to the original placebo group, in mean change from baseline to week 56 for the following: total Genant-modified Sharp score (1.0 vs. 2.3), erosion score (0.6 vs. 1.3), joint

space narrowing (0.4 vs. 1.0) and the proportions of patients with no change in erosion score, 61% vs. 52%.

Summary of evidence on comparative safety

In the trial described previously adverse events with rituximab plus methotrexate were similar to those with methotrexate plus placebo infusion, except for a higher incidence of infusion reactions and infections. In the phase 2 and 3 studies, the incidences of infusion reactions upon initial treatment with rituximab plus methotrexate and placebo plus methotrexate were 15% and 5%, respectively, despite pre-dose iv methylprednisolone. In common with the TNF-antagonist, infliximab, which is associated with infusion reactions that can be severe, rituximab must be administered in an environment where resuscitation facilities are available. This contrasts with the other two TNF-antagonists, which are not subject to this restriction. In the trial described previously the incidences of infections in the rituximab plus methotrexate and placebo plus methotrexate were 41% and 37%, respectively, with severe or life-threatening systemic infections reported by 3.6% and 1.4% of patients, respectively, and clinically significant infections (serious or requiring iv antibiotics) occurring at rates of 5.2 and 3.65 per 100-patient years in the respective groups. In common with rituximab, many drugs used to treat RA, including TNF-antagonists and some DMARDs, affect the immune system, and thus may cause patients to be more susceptible to infections. There is also a concern that drugs which modify the immune system may be associated with an increased risk of malignancies. Although there is no evidence of a causal relationship, long-term data are required to exclude this. No trials directly compare rituximab with any TNF-antagonists or DMARDs, except methotrexate; therefore, the adverse effect profile of rituximab relative to these can only be compared indirectly in general terms.

Summary of clinical effectiveness issues

In practice rituximab would be used for patients who had failed to respond or were intolerant to at least one TNF-antagonist and at least two DMARDs (one of which is methotrexate), as the latter is a requirement for treatment with a TNF-antagonist in accordance with guidance from NICE and the British Society for Rheumatology (BSR). In the trial described previously 60%, 31% and 9% of patients had previously received one, two and three TNF-antagonists, respectively, with mean (median) numbers of previous DMARD, excluding methotrexate, in this population of 2.5 (2) and all patients having active disease despite methotrexate prior to study entry. Therefore, in terms of previous medication history the study population appears similar to the patients who may receive rituximab in practice.

In the analysis of data from patients previously treated with a TNF antagonist, median time to retreatment with this regimen was approximately 52 weeks. In practice some patients may require treatment with two rituximab infusions within one year. There are, however, limited data on multiple repeat treatments with rituximab.

In the trial described previously patients had active disease at study entry despite at least three months' treatment with methotrexate and could be considered to be not responding to this drug. The relative difference in ACR response rates with rituximab plus methotrexate compared to methotrexate alone in the trial may not be observed in practice in patients who are methotrexate-naïve. There are no trials directly comparing rituximab plus methotrexate with other DMARDs or TNF-antagonists; therefore efficacy and safety relative to them are unknown.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The manufacturer provided a micro-simulation model examining the costs and benefits of using rituximab plus methotrexate in two different treatment pathways following treatment failure with a first line TNF-antagonist. Treatment scenarios are shown in the table below.

Scenario 1 (NICE recommended treatment)		Scenario 2 (Scottish clinical practice/sequential TNF-antagonist use)	
Intervention sequence	Comparator sequence	Intervention sequence	Comparator sequence
Rituximab + MTX Leflunomide + MTX Gold Ciclosporin MTX / palliative care	Leflunomide + MTX Gold Ciclosporin MTX / palliative care	**Rituximab + MTX** Etanercept + MTX Infliximab + MTX Leflunomide + MTX Gold Ciclosporin MTX / palliative care	Etanercept + MTX Infliximab + MTX Leflunomide + MTX Gold Ciclosporin MTX / palliative care

MTX = methotrexate

An indirect comparison was necessary to estimate effectiveness due to limited information being available on treatment options and outcomes in patients that have failed on a first-line TNF-antagonist treatment. To derive outcomes in the model, ACR response categories were associated with fixed improvements in the disability index of the health assessment questionnaires (HAQ) scores which were then converted into utility scores. Utilities were estimated using a published equation based on HAQ scores and the effect of using different methods to calculate utility gains was tested**.** The model assumed a constant deterioration in HAQ- scores over time on all treatments rather than asserting that particular treatments may arrest disease progression. The model assumed that retreatment with rituximab was given after nine months. Appropriate one-way and probabilistic sensitivity analyses were provided.

The results of the model indicated that in scenario one, where there was no sequential use of TNF-antagonists, the incremental cost per quality-adjusted life year (QALY) was £14800. The result for scenario two, where sequential use of TNF-antagonist drugs was considered, gave an incremental cost per QALY of £11600 when rituximab was added to the sequence. The results were sensitive to the assumption regarding repeat dosing of rituximab. If a repeat dose was given at six months rather than nine months, the incremental cost-effectiveness ratio (ICER) in scenario two rose to £24300 but if given at twelve months the ICER fell to £4700. Changes to the methods used in the indirect comparison did not significantly alter the result.

The model structure was appropriate and the analysis well-described. The feedback received from Scottish clinical experts suggests that the sequential TNF-antagonist usage scenario is likely to be the relevant comparator for the model. The economic case for rituximab was demonstrated provided the average interval for repeat rituximab dosing, for those patients who respond to initial treatment, does not fall below six months.

Patient and public involvement

Patient Interest Group Submission: National Rheumatoid Arthritis Society

Budget impact

The manufacturer estimated that the drug acquisition cost of introducing rituximab into the treatment sequence was to be £1.8m, £2.2m, £1.5m, £1.9m and £3.5m in years one to five following introduction. However, rituximab may replace other treatments and not all eligible patients may receive therapy therefore the net budget impact is likely to be less.

Guidelines and protocols

The March 2002 NICE guidance on the use of etanercept and infliximab for the treatment of RA notes that there is no evidence for the consecutive use of these agents, and therefore this is not recommended. NICE is currently conducting a health technology appraisal of these drugs plus adalimumab for RA that is to be published in September 2006. The initial appraisal consultation document from this recommends the sequential use of these drugs only in the event of toxicity developing to an individual agent. Sequential use on the basis of lack of response to an individual agent is not recommended outside the context of a study designed to generate robust and relevant outcome data, including the direct measurement of health-related quality of life and disease progression over long-term follow-up.

The 2005 update of the BSR guidelines for prescribing TNF-α blockers in adults with RA recommend biologic therapies for patients who have active RA, defined by a DAS28 score >5.1 on two occasions at least one month apart, and have failed to respond to or tolerate adequate therapeutic trials of methotrexate and at least one other standard DMARD. It is recommended that therapy should be stopped after 3 months if a response is not achieved, where response is defined as improvement in the DAS28 score of >1.2 or a DAS28 score $\leq$3.2. It is noted that there is no evidence to suggest that any TNF-antagonist is more efficacious than the others. There are a limited number of studies that have suggested that some patients who have shown no, or only a partial, response to a TNF-antagonist can benefit from transferring to an alternative TNF-antagonist. The current evidence suggests that infliximab can be useful when etanercept has failed and vice versa. There is also evidence for adalimumab substitutions (currently in abstract form).

The December 2000 Scottish Intercollegiate Guidelines Network (SIGN) publication number 48 on early management of RA recommends that early treatment with DMARDs is important to maintain function and reduce later disability and that DMARD therapy should be sustained in inflammatory disease to maintain disease suppression. Sulphasalazine, methotrexate, intramuscular gold and penicillamine are equally effective DMARDs. No recommendations are made about TNF-antagonists.

Additional information

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 5th July 2002 that anakinra (Kineret®) is not recommended for use in NHS Scotland. At present, anakinra offers no proven clinical advantage over the other available biological agents (infliximab and etanercept) for the treatment of RA. No economic model was provided with the submission. Economic assessment performed in-house suggests that numbers needed to treat to achieve a 20% clinical response was higher for anakinra than for other biological agents, and that the cost per responder was also higher with anakinra treatment. No evidence was provided that patients who do not respond to the anti-TNF biological agents respond to anakinra.

After review of a full submission, SMC issued advice on 8th December 2003 that adalimumab (Humira®) is accepted for restricted use within NHS Scotland for the treatment of RA. It should be initiated only by specialist physicians experienced in the diagnosis and treatment of RA, and used in accordance with the BSR guidelines on prescribing TNF-α blockers in adults [which have been endorsed by NICE and QIS]. The BSR have established a Biologics Registry and details of patients treated with TNF-antagonists including adalimumab should be entered into this database. Adalimumab is the third TNF-antagonist licensed for the treatment of RA.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

The undernoted reference was supplied with the submission.

Keystone E, Emery P, Peterfy CG. Prevention of joint structural damage at 1 year with rituximab in rheumatoid arthritis patients with an inadequate response to one or more TNF inhibitors (REFLEX study). Abstract presented at EULAR 2006, abstract number OP0016