Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

rituximab 100mg, 500mg solution for infusion (MabThera®) SMC No. (894/13)

Roche Products Limited

09 August 2013

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.

Indication under review: In combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

SMC restriction: to use in patients who have relapsed following treatment with cyclophosphamide or who are intolerant to or unable to receive cyclophosphamide.

One course of rituximab (an intravenous infusion weekly for four weeks) was non-inferior to three to six months of oral cyclophosphamide for the proportion of patients achieving remission at six months. The study was conducted in patients with severe proteinase 3- or myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis who were treatment-naïve or previously treated.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Published 09 September 2013

Indication

In combination with glucocorticoids, rituximab is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Dosing Information

Rituximab infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.

Rituximab 375mg/m^2 body surface area, administered as an intravenous (iv) infusion once weekly for 4 weeks (four infusions in total).

Methylprednisolone given intravenously for 1 to 3 days at a dose of 1,000mg per day is recommended prior to the first infusion of rituximab (the last dose of methylprednisolone may be given on the same day as the first infusion of rituximab). This should be followed by oral prednisone 1mg/kg/day (not to exceed 80mg/day, and tapered as rapidly as possible based on clinical need) during and after rituximab treatment.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended during and following rituximab treatment, as appropriate. Pre-medication with analgesic/anti-pyretic and anti-histaminic medicines should be given prior to each infusion.

Product availability date

22 April 2013

Summary of evidence on comparative efficacy

Severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are also known as antineutrophil cytoplasmic antibody [ANCA] associated vasculitis [AAV]). AAV is an autoimmune disease where the proportion of activated peripheral blood B lymphocytes correlates with disease activity and treatment with rituximab results in their depletion.[1] Small vessels and medium arteries are primarily affected and, if left untreated, AAV is a rapidly progressing, fatal disease with a mean survival of five months.

One phase III, multi-centre double-blind comparative study recruited 197, treatment-naïve or relapsed patients aged ≥15 years with Wegener's granulomatosis or microscopic polyangiitis.[1] Patients were required to have a positive serum assay for proteinase 3-ANCA or myeloperoxidase-ANCA, manifestations of severe disease and a Birmingham Vasculitis Score for Wegener's granulomatosis (BVAS/WG) of ≥3 (scores range from 0 to 63; with higher scores indicating more active disease). Patients previously treated with rituximab were excluded as were patients with a serum creatinine >4.0mg/dL due to renal impairment associated with the current episode. Patients were randomised to double-blinded treatment with rituximab 375mg/m^2 iv infusion once weekly for four weeks and no further treatments (n=99) or oral cyclophosphamide 2mg/kg/day (dose adjusted for renal insufficiency) for three to six months followed by oral azathioprine 2mg/kg/day when in remission (n=98). All patients received pre-medication with methylprednisolone 1g iv infusion daily for one to three days followed by oral prednisone 1mg/kg/day. By week four, the dose was reduced to 40mg/day and then

reduced every two weeks with the aim for discontinuation by six months. In addition, all patients received *Pneumocystis* and osteoporosis prophylaxis during the study

The primary end-point was the proportion of patients in complete remission (defined as a BVAS/WG of 0 with successful completion of the prednisolone taper at six months). Non-inferiority was demonstrated if the lower limit of the 95.1% confidence interval for the mean difference in remission rates (rituximab minus cyclophosphamide) was greater than -20%. At baseline, patients had a mean BVAS/WD score of 8.2 to 8.5. In the intent-to-treat population, using worst case imputation, the primary endpoint was reached in 64% (63/99) of rituximab patients and 53% (52/98) of cyclophosphamide patients (difference 10.6%, 95.1% confidence interval (CI): -3.2% to 24.3%) and non-inferiority, but not superiority, was demonstrated. The analysis of the primary endpoint in the sub-group of patients with relapsing disease at baseline demonstrated rituximab was superior to cyclophosphamide: 67% (34/51) versus 42% (20/50); treatment difference 25% (95% CI: 5.8% to 44%), (p=0.01). Sub-group analyses also demonstrated a similar treatment difference in complete remission rates in patients older than 65 years of age compared to younger patients.

Results of the secondary endpoints were supportive of the primary endpoint. The proportion of patients in the respective rituximab and cyclophosphamide groups with BVAS/WG of 0 and prednisone dose <10mg/day was 71% (70/99) versus 62% (61/98); difference 8.5%, 95.1% CI: -4.7% to 21.7%. Rates of severe disease flare (an increase in BVAS/WG ≥3 points or one major BVAS/WG item requiring treatment with cyclophosphamide) and limited flare (new occurrence or worsening of ≥1 minor BVAS/WG items) were comparable between groups. There were similar improvements for rituximab versus cyclophosphamide for the short form 36 and vasculitis damage index quality of life measures. At 12 months, 42% of patients in the rituximab group and 38% of patients in the cyclophosphamide group remained in complete remission off glucocorticoids, and at 18 months, the proportions were 36% versus 31%, respectively.[2] The median time to complete remission off glucocorticoids (number of days from baseline visit to attaining the primary endpoint) was 180 days for rituximab versus 183 days for cyclophosphamide.[3] A total of 15 patients received re-treatment with rituximab following relapse (based on investigator judgment) within six to 18 months after initial rituximab treatment.

A supportive, phase III, open-label study has been conducted in 44 patients with newly diagnosed AAV, ANCA positivity and renal involvement.[4] Patients were randomised in a 3:1 ratio to rituximab 375mg/m^2 iv infusion once weekly for four weeks plus cyclophosphamide 15mg/kg iv infusion with first and third rituximab doses (n=33) (a third cyclophosphamide infusion could be given if the patient had progressive disease within the initial six months) or to cyclophosphamide 15mg/kg iv infusion every two weeks for three doses then every three weeks until stable remission (a minimum of six and maximum of 10 doses), followed by azathioprine 2mg/kg/day (n=11). The groups received the same glucocorticoid regimen. At baseline, patients had a median BVAS score of around 19. The primary endpoint was sustained remission rate (absence of disease activity [BVAS of 0] for at least six months) assessed at 12 months. Sustained remission occurred in 76% (25/33) of rituximab- and 82% (9/11) of cyclophosphamide-treated patients; difference -6%, 95% CI: -33% to 21%, p=0.68.

Summary of evidence on comparative safety

There were no significant differences between rituximab and cyclophosphamide in terms of total adverse events, serious adverse events, non-disease related adverse events, or the number of patients with at least one non-disease related adverse event. The proportion of patients who discontinued due to adverse events was 14% (14/99) in the rituximab group and 17% (17/98) in the cyclophosphamide group. The proportion of patients with pre-defined ("selected") adverse events was lower in the rituximab group (22% [22/99]) than in the cyclophosphamide group (33% [32/98]), mainly accounted for by the difference in incidence of leucopenia, and the annual rates were 5% and 6%,

respectively. The "selected" adverse events included leucopenia (≥grade 2) (3 versus 10 patients), thrombocytopenia (≥grade 3) (3 versus 1 patient), infection (≥grade 3) (7 patients each), haemorrhagic cystitis (1 patient each), cerebrovascular accident (no patients), hospitalisation due to disease or treatment (8 versus 2 patients) and infusion reaction preventing further infusions of investigations drug (1 versus no patients).

Up to month six, there was one malignancy reported in each group, and beyond six months, four patients in the rituximab group (including one patient with two malignancies) and one patient in the cyclophosphamide went on to develop malignancies. The specific malignancies reported were prostate cancer (n=2), colon cancer (n=2), uterine cancer (n=1), lung cancer (n=1), bladder cancer (n=1), and papillary thyroid cancer (n=1). When the data were analysed "as treated" for rituximab there was a higher proportion of patients who developed one malignancy in the group having received rituximab versus the group who never received rituximab (4.9% [6/124] versus 1.4% [1/73], p=0.26). However, five of the rituximab treated patients also received other immunosuppressive agents either during or before the study that might have contributed to the development of malignancy.

Summary of clinical effectiveness issues

Cyclophosphamide (given with glucocorticoids) has been the standard treatment for AAV for over 30 years and treated patients have an estimated five year survival rate of 82%.[5] However, its use is associated with significant adverse events. Clinical experts consulted by SMC report the use of iv cyclophosphamide (with glucocorticoids) for remission induction. In addition, they highlight a lack of therapeutic options in patients refractory to cyclophosphamide or who have contraindications/previous toxicity which preclude its use.

In the pivotal study, rituximab was shown to be non-inferior to oral cyclophosphamide for the proportion of patients in remission at six months in a population including treatment-naïve and previously treated patients. Superiority was not shown for the whole population; however, rituximab was superior to cyclophosphamide in the sub-group of patients with relapsing disease at baseline (n=101). Results of the secondary endpoints were supportive of the primary endpoint. In addition, a supportive, open-label, comparative study showed similar sustained remission rates between treatments.

The pivotal study has some limitations. Firstly, the comparator (oral cyclophosphamide) may be less relevant for Scottish practice. However, it has been reported that iv and oral cyclophosphamide are equally effective at inducing remission[5] which provides some reassurance. Secondly, patients were required to be ANCA-positive and also have severe ANCA-associated vasculitis. Therefore, there are no data on treatment effects in patients with limited Wegener's granulomatosis or in those who are ANCA-negative. Thirdly, the pivotal study excluded patients with creatinine >4mg/dL due to renal involvement of current episode. Finally, patients were required to be rituximab-naïve and limited data on rituximab re-treatment mean the efficacy of subsequent courses of rituximab is not known.

In the pivotal study, approximately two-thirds of patients had proteinase 3-ANCA positivity. This group is more likely to relapse (mean relapse rate per patient per year has been reported as being 0.2), compared to patients with myeloperoxidase-ANCA positivity.[6]

Patients treated with rituximab did not receive immunosuppressants for maintenance of remission in the pivotal study. This may not be the approach used in clinical practice. The use of immunosuppressive therapy for prevention of relapse in patients in remission and at high risk of relapse (e.g. with history of earlier relapses and granulomatosis with polyangiitis, or patients with reconstitution of B-lymphocytes in addition to proteinase 3-ANCA at monitoring) is noted as an option in the summary of product characteristics (SPC) for rituximab.

Fewer adverse events were anticipated with rituximab compared to oral cyclophosphamide but this was not observed in the study. Overall, five patients treated with rituximab developed malignancies (with one patient developing two malignancies). However, no particular pattern to the types of malignancies was observed and analysis was confounded by cross-over as well as previous exposure to immunosuppressive agents.

Patients may prefer four, weekly iv infusions of rituximab compared to three to six months treatment with cyclophosphamide followed by azathioprine. Infusion related reactions were reported in 12% of patients in the rituximab arm of the pivotal study. The SPC for rituximab advises that infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing rituximab with cyclophosphamide in patients with severe AAV. Expert responses confirmed that iv cyclophosphamide is the predominant treatment in Scotland. The base case analysis assumed 72% of patients would receive iv cyclophosphamide and 28% would received oral cyclophosphamide. A lifetime Markov model was used consisting of four health states: non-remission, complete remission, uncontrolled disease and death. In the cyclophosphamide arm, patients could receive a maximum of two treatment cycles before receiving best supportive care, whereas in the rituximab arm, patients could receive a maximum of two rituximab cycles followed by one cycle of cyclophosphamide.

The clinical data used in the model were taken from the non-inferiority study described above and the results from the primary endpoint were used in the model. Once patients achieved complete remission they were assumed to be at risk of relapse. The relapse rates from the study were extrapolated using an exponential curve to provide relapse rates over the lifetime of the model. This resulted in constant relapse rates of 16% and 15% for the rituximab and cyclophosphamide arms respectively. The efficacy of cyclophosphamide retreatment was taken from the remission rates of relapsing patients in the pivotal study where the probability of achieving remission was reduced by 35%. The efficacy of rituximab retreatment was not investigated in the study but was assumed to reduce by the same rate. A key assumption in the model was that the probability of obtaining remission on cyclophosphamide would be the same regardless of prior rituximab therapy.

The utility values for the 'complete remission' and 'non-remission' health states were derived from the pivotal study. Quality of life data were collected using SF-36, which was administered at baseline and at month 6. The SF-36 scores were converted to utility values using a published utility mapping algorithm. The resultant utility values were 0.837 and 0.754 for the 'complete remission' and 'non-remission' health states respectively. The utility value for patients with uncontrolled disease was based on assumption and was estimated to be 0.671.

Resource use included outpatient visits, monitoring, administration and adverse event costs. In the 'non-remission' health state patients were assumed to require 1.5 outpatient visits per week with different proportions of patients requiring different specialties based on the corresponding organ involvement at baseline in the pivotal study. In the 'remission' health state the frequency was reduced to every 3 months. In the 'uncontrolled disease' state the company assumed patients would receive best supportive care 1.5 times weekly. These estimates were based on clinical opinion.

The company estimated a base case incremental cost-effectiveness ratio (ICER) of £8,544 per quality-adjusted life-year (QALY) based on an incremental cost of £1,391 and a QALY gain of 0.1628. The

probabilistic sensitivity analysis showed the probability that rituximab is cost-effective at willingness to pay thresholds of £20,000 and £30,000 per QALY was 61.7% and 68.9% respectively.

The company also conducted an exploratory subgroup analysis to simulate the cost-effectiveness in patients who are intolerant to cyclophosphamide. For this subgroup, due to the lack of available data, the company used data from patients who are yet to receive induction therapy as a proxy for patients who are intolerant to cyclophosphamide. In this analysis, it was assumed that patients in the rituximab arm transition straight to the uncontrolled disease health state following relapse. In the comparator arm patients were assumed to only receive best supportive care. The results of this analysis indicated that rituximab was the dominant treatment (estimated savings of £4,885 and a QALY gain of 0.5386). Expert responses indicated this would be a clinically relevant subgroup.

The following limitations were noted:

- The base case analysis assumed rituximab treatment was associated with a higher probability of complete remission. However, the pivotal study was a non-inferiority study which showed no difference between treatments. When equal complete remission rates were used the ICER increased to £25k per QALY. The company also provided some additional analysis to show the impact of removing all other non-significant differences in the model i.e. not just complete remission rates. The result was an ICER of £5,199 with the analysis being driven by the additional line of treatment. However, there were some concerns about how the relapse rates were derived and therefore whether it was appropriate to assume no difference in these rates.
- The results were sensitive to the assumed treatment pathway. When alternative treatment pathways were tested in the sensitivity analysis, the results ranged from rituximab being the dominant treatment to rituximab being dominated by cyclophosphamide. SMC expert responses indicated that rituximab would likely be used in patients who were unable to receive cyclophosphamide treatment or in patients who had relapsed or not achieved remission with cyclophosphamide. The remission rate with rituximab was significantly higher in the relapsed patients subgroup in the clinical study but the ICER in this subgroup was high due to the higher relapse rate in this population. However, the company noted that this high relapse rate would be unlikely to happen in practice and therefore it may be more appropriate to use the whole trial population relapse rates. When these estimates were used, rituximab was the dominant treatment in the subgroup of relapsed patients.
- The assumption that the probability of achieving remission with cyclophosphamide was the same regardless of prior rituximab therapy may not be appropriate. Sensitivity analysis was requested to test this assumption; however, the company was unable to provide this analysis because of the model structure. This remains an area of uncertainty.

Despite these uncertainties, the economic case was considered demonstrated in relapsed patients and in patients who are intolerant to or unable to receive cyclophosphamide.

Summary of patient and public involvement

A Patient Interest Group Submission was received from the UK Vasculitis Trust (Vasculitis UK).

Additional information: guidelines and protocols

The British Society for Rheumatology (BSR)/British Health Professionals in Rheumatology (BHPR) published guidelines for the management if adults with ANCA associated vasculitis in 2007.[5]

Remission induction

Cyclophosphamide 2mg/kg/day orally or 15mg/kg iv infusion at 2 to 3 week intervals for 3 to 6 months in conjunction with a reducing dose of oral prednisolone (staring dose, 1mg/kg/day).
Remission maintenance
Replace cyclophosphamide with azathioprine 2mg/kg/day or methotrexate.
Relapsing disease
Increase prednisolone dose to 30mg/day then gradual taper for minor relapse
Initiate cyclophosphamide (as for remission induction) and increase prednisolone dose to 30mg/day for major relapse. Also, iv methylprednisolone and plasma exchange may be considered.

The guideline notes that rituximab may be considered for treatment of refractory vasculitis or the treatment of vasculitis when conventional agents are contra-indicated. It is noted that there is insufficient current evidence to recommend the routine use of rituximab in induction or maintenance regimens. [NB: the guideline predates the publication of the pivotal rituximab study and licensing of rituximab for remission induction].

The 2007 guideline is currently under review with the updated version expected to be ratified soon.

Additional information: comparators

Intravenous (or oral) cyclophosphamide. SMC clinical experts have indicated that a number of treatment options may be used that are off-label, unlicensed or non-medicine (plasma exchange) but noted that some could be considered experimental.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Rituximab	**375mg/m^2 iv weekly for 4 weeks**	**4,890**
Cyclophosphamide	2mg/kg orally daily for 3 to 6 months	up to 99
Cyclophosphamide	15mg/kg iv at 2 to 3 week intervals for 3 to 6 months	up to 101

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 May 2013, and www.mims.co.uk (for rituximab). All costs are excluding cost of concurrent glucocorticoid treatment. Cyclophosphamide costs are excluding azathioprine 2mg/kg/day used for remission maintenance (cost approximately £49 for 6 months treatment). Costs are based on body surface area of 1.8m^2 or a body weight of 70kg.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 146 in all 5 years with an estimated uptake rate of 13.5% in year 1 and 32% in year 5.

The gross impact on the medicines budget was estimated to be £191k in year 1 and £445k in year 5. The net impact on the medicines budget was estimated to be £189k in year 1 and £441k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Stone JH, Merkel PA, Spiera R, et al. (RAVE-ITN Research Group). Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010 Jul 15;363(3):221-32.

2. Specks U, Stone J. Long-term efficacy of rituximab in ANCA associated vasculitis. Ann Rheum Dis 2011;70(Suppl3):85

3. www.clinicaltrials.gov

4. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS). N Engl J Med 2010;363(3):211–220

5. Lapraik, C., Watts, R., & Bacon, P. BSR and BHPR guidelines for the management of adults with ANCA. Rheumatology 2007;46:1–11

6. Tervaert J. Rituximab in ANCA-associated vasculitis: a revolution? Nephrol Dial Transplant. 2011; 26:3077-79

This assessment is based on data submitted by the applicant company up to and including 12 July 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.