East Lancashire Medicines Management Board

Commissioning Policy: Rituximab (MabThera®)

Treatment of Anti-neutrophil Cytoplasmic Antibody Positive Vasculitis

(incl. Wegener's Granulomatosis)

Date of Issue: July 2010 (amended Feb 2012) ***Review Date: July 2013***

BNF Therapeutic Class: 8 Malignant disease and immunosuppression > 8.2 Drugs affecting the immune response > 8.2.3 Rituximab and alemtuzumab > RITUXIMAB

Licensed Indications: *Unlicensed for use in ANCA positive vasculitis*

Dosage and Administration: *As per SPC or see section 'Dose later' in document.*

Recommendation – RED Traffic light

Rituximab should only be prescribed by a consultant for eligible patients for the management of anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis in situations where standard treatment (cyclophosphamide, methotrexate, azathioprine, corticosteroids, and plasma exchange) is not appropriate, not tolerated or not effective.
Further policy criteria are given in section 4.

Whether the use of rituximab in accordance with the above criteria is appropriate in any particular case is a matter for the treating clinician's professional judgment, having weighed the risks and benefits to the patient (and discussed these with the patient) and acting in accordance with a responsible body of medical opinion as this is an unlicensed use of rituximab. This document is in no way intended to endorse or approve the use of Rituximab in a particular patient and is a general statement of policy only.

Introduction

- Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis affects approximately 8.4 per million/population per annum, with a prevalence in the UK population of 64.8 per million/population in 2005. ANCA antibody is associated with three types of disease, Wegener's granulomatosis and microscopic polyarteritis, and Churgs Strauss syndrome. Wegener's granulomatosis is associated with destructive lesions within the nose, throat, lungs and kidneys, whereas microscopic polyarteritis tends to affect the small blood vessels causing rash and kidney failure.

- The aetiology of the disease is unclear. Patients develop the ANC antibody and then they also require a second trigger to stimulate their lymphocytes to initiate the disease process itself. The trigger is often a viral infection which accounts for the seasonal variation in the disease and the fact that often clusters of the disease occur.

- Without treatment, mortality is 100%. Current treatment involves induction therapy with cyclophosphamide and steroids followed by maintenance with drugs such as azathioprine, methotrexate and mycophenolate mofetil. Some patients require plasma exchange.

- A small proportion of patients will either not respond to cyclophosphamide or be intolerant of it – at initial presentation or at relapse after initial successful treatment. Other patients will fail to stay in remission and have progressive disease despite the best maintenance therapy.

- In vasculitis a crucial step is the autoimmune process and the production of antibodies directed against the body's own proteins. Although rituximab is not licensed for treatment of these conditions, there is evidence that it is beneficial in some of these conditions, including ANCA vasculitis (see Appendix A). However, the level of evidence for this indication is currently low and sparse. The mode of action of

rituximab involves reduction in the activity of B lymphocytes that contain the CD20 receptor, which leads to reduction in antibodies generally dampening down the autoimmune process.

- Clinicians consider rituximab to be a relatively well tolerated drug, although it is not without short or long term risks. Adverse effects tend to be infusion site reactions and increase in the incidence of infections. These adverse effects are considered to be less serious than those caused by cyclophosphamide which is routinely used for treatment of ANCA positive vasculitis. Cyclophosphamide carries a significant risk of neutropenia related sepsis (and related complications) and is associated with 20 fold increase in risk of bladder cancer.

1. Clinical Evidence

1.1. There are a number of small case series and cohort studies that have been published with small numbers of patients (see appendix II), the majority of cases are in relapsed or refractory disease. Response rates in all of these are very high, although lack of long term, randomised and properly controlled and comparative data is lacking. There is a single comparative trial comparing rituximab versus cyclophosphamide in the induction of patients with ANCA positive renal vasculitis, some of whom were dialysis dependent. This demonstrated that in the short term, rituximab was non-inferior to the standard treatment of cyclophosphamide, although long term outcome and safety data are still lacking to support its use in the induction phase. However, many units on the basis of the case series have applied to use rituximab as part of the pathway for patients with relapsed or life threatening disease.

1.2. Rituximab offers a potential and significant financial saving over the use of IV immunoglobulin therapy and plasmaphoresis, both of which are sometimes used as a second line therapy for Connective Tissue Disease on the basis of case series and anecdotal reports.

2. Safety

2.1. There is a lack of long term outcome, and therefore safety data on the use of rituximab in ANCA positive vasculitis. Rituximab is widely used in a variety of other indications for which long term safety data is available. There is the short term risk of infusion reactions, including hypersensitivity, which are well documented and can be managed appropriately.

2.2. Cyclophosphamide therapy will lead to widespread immune depression and as such are unsuitable for patients who are known to be vulnerable to infection. Additionally its use may be limited by the development of recurrent infections in patients. Rituximab does not lead to alteration of overall immunoglobulin levels and during the period of B cell depletion no increase in the incidence of infections has been observed.

2.3. The incidence of haemorrhagic cystitis and bladder carcinoma correlates with the duration and cumulative dose of cyclophosphamide. No significant risk of neoplasia has been identified with rituximab therapy.

3. Rationale

3.1. A need for development of this policy was identified through a case request from the Rheumatology Physicians at East Lancs Hospitals NHS Trust.

3.2. It is estimated that about ~1-2 patients per annum across East Lancashire Health Economy would require rituximab due to failure or intolerance or contraindications to standard treatments. Assuming an induction dose of 2 grams over 2 weeks and an average maintenance dose of rituximab 1 gram twice a year per patient which costs £3,500 per annum, the total financial impact will be around £7,000 per annum.

3.3. The benefits of treatment proposed by clinicians include a reduction in: renal failure and complications of renal failure, hospital admissions and hospital stay. Clinicians at other hospitals such as Leeds Teaching Hospitals & Hull & Riding Hospitals Trusts have tried the drug and have documented evidence of the benefits. This drug is routinely used in this way at University Hospitals in Birmingham and the Vasculitis Centre in Cambridge.

3.4. Evidence supporting the benefit of rituximab in vasculitis is summarised in Appendix II. The number of patents involved in these trials is small due to the rarity of these conditions. However, the proportion of

patients experiencing remission as a result of this therapy is remarkably high from the case studies presented.

3.5. There is no cost-effectiveness analysis but considering that rituximab from the case studies presented 'appears' to be very effective at inducing remission in patients not suitable for cyclophosphamide or relapsing despite treatment with cyclophosphamide, the cost of rituximab may easily be outweighed by avoiding serious consequences of not controlling the disease process.

3.6. The Cambridge group have data on nearly 100 patients with refractory Vasculitis and SLE treated in UK with Rituximab. The response to therapy has been dramatic in the case studies presented, and associated with very few side effects.

3.7. Rituximab is not licensed for this indication, and is still being investigated in larger scale trials to judge its comparative and relative effectiveness.

3.8. The British Society of Rheumatology guidelines from 2007 state that in 'Refractory disease: The use of infliximab, intravenous immunoglobulin, antithymocyte globulin, CAMPATH-1H (alemtuzumab, anti-CD52), deoxyspergualin and ***rituximab*** in refractory disease is still under investigation (C).

4. Policy

4.1. **NHS Blackburn with Darwen and NHS East Lancashire Primary Care Trusts approve the use of rituximab for management of ANCA positive vasculitis in situations where standard treatment (cyclophosphamide, methotrexate, azathioprine, steroids and plasma exchange) is not tolerated, not effective or not appropriate.**

4.2. If appropriate (i.e. standard treatment not tolerated or not effective) the drug may be used at induction stage or at relapse stage. Induction dose is 2 grams over 2 weeks. Maximum of two maintenance doses per annum are allowed.

4.3. Rituximab should be discontinued if there is no response as indicated by relevant disease markers.

4.4. Specialist units providing this treatment should produce annual reports covering the following issues:

4.4.0. Number of patients treated with rituximab
4.4.1. Criteria for initiating treatment
4.4.2. Dosage of rituximab (including frequency of administration)
4.4.3. Other drugs used as part of the treatment
4.4.4. Response to treatment
4.4.5. Adverse effects thought to be attributable to rituximab

4.5. For patients who do not meet the above criteria but are considered to have personal circumstances which might make them an exception to the policy, individual funding may be sought from the PCT. In order for funding to be agreed, it must be demonstrated that:

4.6. The patient is significantly different from the general population of patients with the condition in question and at the same stage AND due to this difference, they are likely to gain significantly more benefit from the intervention than might be expected for the similar patient with the condition.

5. Rationale behind the decision

5.1. Although the quantity and quality of evidence on the efficacy and safety of rituximab is low, it is a rare condition and bigger, more rigorous trials may never take place. The current evidence for drugs already used in second line treatment is also weak. However, the evidence that we do ve indicates that more than 90% of patients respond to rituximab and that it has a good side effect profile, and costs are low to moderate per patient. There is little research into the cost effectiveness of rituximab, but due to the high response rates seen and the cost of alternative treatments or management of further complications it is likely to be a good use of NHS resources. In addition, the evidence we have supports the case made that it will have little financial impact on either PCT.

Acknowledgements :

Warrington and Coventry PCTs: Commissioning Policy: Rituximab (MabThera®) for Treatment of Anti-neutrophil Cytoplasmic Antibody Positive Vasculitis and Sysemic Lupus Erythematosus. Text from this policy was directly reproduced in this policy, with additions. The original policy document can be found online at http://www.coventrypct.nhs.uk/documents/general/2010216144150_Enc%20N1%20-%20Rituximab%20Report.pdf and has a review date of November 2010.

References:

1. Watts RA et al. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. Arthritis Rheum. 2009 Oct 15;61(10):1412-6.

2. Walsh and Jayne, *Kidney International* (2007) 72, 676-682.

3. Jones R et al. WCN 2009: Rituximab Comparable to Standard Cyclophosphamide Regimen for ANCA-Associated Renal Vasculitis. World Congress of Nephrology 2009: A Joint Meeting of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and the International Society of Nephrology (ISN): Abstract Sa773. Presented May 24, 2009.

4. Lapraik et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitisRheumatology 2007;46:1615–1616. Downloaded from http://rheumatology.oxfordjournals.org on July 9, 2010.

Appendix A : Summary of references (Taken (& updated with Jones 2009 paper) from Walsh and Jayne, *Kidney International* (2007) **72**, 676-682)

Study	No. of patients (with nephritis)	Dose of rituximab	Concomitant treatments	Remission	B cell depletion	No. of relapses and time to relapse
Vasculitis						
Jones (2009)	44 in total = 33 rituximab & 11 cyclophosphamide (44)	Rituximab Group: 4 doses 375mg/m2 weekly plus 2 of intravenous cyclophosphamide 15 mg/kg Cyclophosphamide Group: 6 to 10 infusions of cyclophosphamide 15 mg/kg	Standard protocol plus prednisolone	Ritux: 27/33(82%) Cyc: 10/11(91%)	Ritux: 33/33 (100%) Cyc: ~66%	Sustained remission (BVAS = 0) for 2 evaluations Ritux: 25/33 (76%) Cyc: 9/11 (82%)
Aries (2006)	8 (2)	4 doses 375mg/m_2 weekly	Cyclophosphamide, mycophenolate, methotrexate, steroids	2/8 (1/2)	8/8	Not reported
Eriksson (2005)	9 (7)	4 doses 500mg weekly or 500mg day 1 and day 15	Mycophenolate, azathioprine, cyclophosphamide, steroids	8/9 complete 1/9 partial (7/7 with nephritis)	9/9	2 (12 and 13 months)
Keogh (2005)	11 (4)	4 doses 375mg/m_2 weekly	Plasma exchange for nephritis, steroids	10/11 complete 1/11 partial (4/4 with nephritis)	11/11	2 (7 and 12 months)
Keogh (2006)	10 (7)	4 doses 375mg/m_2 weekly	Steroids	10/10 (7/7 with nephritis)	10/10	1 (9 months)
Smith (2006)	11 (6)	4 doses 375mg/m_2 weekly 1g every other week for 2 doses for retreatment	Mycophenolate, steroids	9/11 complete 1/11 partial	11/11	6 (median 16.5 months)
Stasi (2006)	10 (6)	4 doses 375mg/m_2 weekly	Steroids	9/10 complete 1/10 partial	10/10	3 (12, 16 and 24 months)

Guidance above to be read in conjunction with the manufacturer's SPC.
For NHS use only – Not to be used or reproduced for commercial purposes
***Red** light = only to be prescribed within secondary care, specialist initiation only: GPs should not be asked to prescribe*
***Amber** light = only to be initiated in secondary care with follow up prescribing by primary care without a shared care agreement*
***Amber light with Shared Care** = only to be initiated in secondary care with follow up prescribing by primary care with a shared care agreement*
***Green** light = prescribing is appropriate in both primary and secondary care within the specified conditions*
***Black** list = Not included in the East Lancs Joint Formulary. Not recommended for prescribing in primary or secondary care. This may be due to lack of good clinical evidence or more suitable alternatives available.*