Rituximab for treatment of inflammatory myositis refractory to treatment with prednisolone plus at least TWO conventional immunosuppressive medications

South Australian Medicines Evaluation Panel

September 2014
Summary of SAMEP review

| Receipt of High Cost Medicine (HCM) formulary application: | 4th February 2014 |
| Date of SAMEP meeting: | 14th May 2014 |

Name of medicine | Rituximab (Tradename: MabThera®)
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Dosage form | Injection, concentrated
--- | ---

Strength | 500mg and 100mg vials
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For treatment of inflammatory myositis including dermatomyositis, polymyositis, undifferentiated inflammatory myositis (IMM), and necrotising myopathy for the following scenarios:

- myositis which has been refractory to treatment with prednisolone plus any three conventional immunosuppressive medications, used preferably in combination
  - either methotrexate, azathioprine, mycophenolate mofetil, cyclosporin
  - refractory denoting any one of the following: persisting proximal muscle weakness, persistent elevation of serum CK, flare on prednisolone dose

- myositis clinically deemed to be very aggressive/high risk after high dose corticosteroids plus short period of two immunosuppressive medications

- myositis with poor prognostic features and clinical grounds likely to be resistant/refractory to treatment with high dose corticosteroid treatment plus short period of two immunosuppressive medications

Average cost of medicine per treatment course | The proposed adult dose in the application is 1g every two weeks for 2 doses. The cost of two 1g doses of rituximab is $9,054.
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Projected future usage for the proposed indication | The South Australian Myositis Database (SAMD) for patients with biopsy-proven idiopathic inflammatory myositis is a register (established in 1980) of adult patients with a histological diagnosis of dermatomyositis (DM), polymyositis (PM) or inclusion body myositis (IBM)[1]. In the 5 years from 2007 to 2011, 144 patients were identified (average of 28-29 patients per year). The applicant estimates that up to one third of patients may be refractory to corticosteroids + 2 immunosuppressants, indicating that 9-10 patients may be eligible for treatment under the proposed protocol. This does not include patients who relapse and may require additional treatment.
--- | ---
A treatment course of two 1g doses of rituximab costs $9054. If ten patients per annum receive the treatment course, this would cost SA Health $90,540.

It is expected that some of this cost would be offset by a reduction in the usage of intravenous immunoglobulin (IVlg) (see Appendix 2).
SAMEP recommendations

Following review of the current available evidence (Appendix 1), assessment of the pharmacoeconomics (Appendix 2) and the outcome data for patients who have already been treated with rituximab for IMM at the Royal Adelaide Hospital, and consideration of formal feedback from rheumatology, neurology and immunology department heads, or their delegates/clinicians with an interest in this area, SAMEP recommend the following:

- Listing rituximab “for initial therapy of myositis which has been refractory to treatment with prednisolone plus at least TWO conventional immunosuppressive medications for a duration of three months each”.
  - maintenance rituximab is not recommended for formulary listing for IMM
  - The words ‘preferably in combination’ should not be included in the proposed formulary listing, with regards to immunosuppressive medications.
  - The second and third scenarios proposed, ‘clinically deemed to be very aggressive/high risk’ and ‘likely to be resistant/refractory’ were not supported by SAMEP. Evidence from the single RCT suggests the effect of rituximab in myositis appears to be slow acting.

- Rituximab for induction treatment of IMM should not be in combination with maintenance IVIg.
  - While SAMEP acknowledge that the effectiveness of rituximab is highly uncertain, there is also limited evidence for the effectiveness of the alternate treatment IVIg, which is more expensive, a limited resource, and more time consuming to administer than rituximab. In the two years to October 2013, over $2.7 million was spent on IVIg in this patient population (see appendix 1). The comparative effectiveness of rituximab and IVIg is unknown as there are no head-to-head trials in the patient population, therefore it was difficult for the panel to estimate cost-effectiveness. Although there is high uncertainty, for patients who would otherwise be treated with IVIg, it is likely to be cost-effective or cost-neutral to use rituximab instead. Members agreed that listing rituximab for myositis is likely reduce the cost of treatment of myositis by reducing the amount of IVIg used in SA for this condition.

- Immunosuppressive medications can include any TWO of the following: methotrexate, azathioprine, mycophenolate mofetil, cyclosporin, or cyclophosphamide.
  - Cyclophosphamide was added to the proposed immunosuppressive medications as feedback from the WCH stated that cyclophosphamide was occasionally used in severe cases.
  - Extensive feedback to consultation was received regarding the proposed pathway which recommended combination immunosuppressive therapy. The majority of feedback from clinicians disagreed with the recommended proviso of prescribing immunosuppressives in combination, in order to be eligible for rituximab.
  - In clinical practice, combination therapy with methotrexate (MTX) and azathioprine (AZA) is uncommon as there is no evidence of efficacy and safety.
SAMEP felt that combination therapy should be at the discretion of the prescriber, but that at least two immunosuppressives should be trialled.

- ‘Refractory’ should include persisting proximal muscle weakness AND either persistent elevation of serum CK or flare on prednisolone dose reduction. (Note: The application proposed just one of the above criteria to define refractory, however SAMEP agreed two of the criteria should be required, and must include ‘persisting proximal muscle weakness’).

- Rituximab treatment for induction of remission is defined as 1g every two weeks for 2 doses.

- SAMEP recommends that diagnostic criteria for children (MRI as opposed to biopsy) and paediatric dosing are incorporated into the proposed clinical pathway.

- The prescriber agrees to provide the following objective measures of outcome to the DTC:
  - Manual muscle testing (MMT) - the most widely used measure to assess strength in myositis (Rider, Koziol et al. 2010). 0 – 10 point or 0 – 5 point scale to include proximal, distal and axial muscles in adults and children. If < 4 years of age (CMAS).
  - Creatinine kinase levels
  - Dose of corticosteroids required

  (Note: The application proposed using the Myositis Disease Activity and Assessment Tool (MDAAT) which are currently used at the RAH, however feedback from consultation was not in favour of this)

- Basis of recommendations: The evidence to support the use of rituximab in this population is not strong, with only one industry-funded, randomised controlled delayed-start trial (RIM study), which no significant difference in achieving primary or secondary endpoints in patients with refractory myositis who were administering rituximab earlier, rather than eight weeks later (Oddis, Reed et al. 2013). Although the study was randomised, SAMEP agreed that the poor design of the trial may have prevented the detection of a treatment effect. Although they reported that 83% of patients met the Definition of Improvement (DOI), because all patients received rituximab it is not known what proportion of patients in the trial may have obtained a DOI at 44 weeks without rituximab. The RIM study demonstrates that there is potentially a large placebo effect or regression to the mean. All other published evidence to support rituximab to treat inflammatory myositis is from approximately 20 case series/reports or uncontrolled open label studies, including 4 studies with greater than 10 patients (see appendix 1).
Appendix 1  Review of the evidence

Evaluation by other jurisdictions:

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>Rituximab has not been evaluated by PBAC for inflammatory myositis</td>
</tr>
<tr>
<td>Canadian Agency for Drugs and Technologies in Health (CADTH)</td>
<td>Rituximab has not been evaluated by CADTH for inflammatory myositis</td>
</tr>
<tr>
<td>Scottish Medicines Consortium (SMC)</td>
<td>Rituximab has not been evaluated by SCM for inflammatory myositis</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>Rituximab has not been evaluated by NICE for inflammatory myositis</td>
</tr>
<tr>
<td>All Wales Medicines Strategy Group (AWMSG)</td>
<td>Rituximab has not been evaluated by AWMSG for inflammatory myositis</td>
</tr>
<tr>
<td>Food and Drug Administration (FDA)</td>
<td>Rituximab is not registered by the FDA for use in inflammatory myositis</td>
</tr>
</tbody>
</table>

Rituximab for treatment of inflammatory myositis is an off-label indication in Australia.

Summary of efficacy data

Evidence base: C (NHMRC rating guide – see under references)
Consistency: C-D
Clinical impact: C
Generalisability: B
Applicability: C

Search strategy

Population  Inflammatory myopathy (dermatomyositis, polymyositis, undifferentiated inflammatory myositis, or necrotizing myopathy), refractory to treatment with prednisolone plus any three conventional immunosuppressive medications (preferably used in combination)

Intervention  Rituximab (Tradename: Mabthera®)

Comparator  Either a fourth line immunosuppressive medication or intravenous immunoglobulin

Outcome(s)  
- Improvement in muscle strength (on MRC 5-point grading scale)
- Normalisation of Creatinine Kinase (CK) levels
- Clinical improvement in cutaneous features
- Resolution of alveolitis on high resolution CT chest, or improvement in lung diffusing capacity (DLCO) on spirometry
- Prednisolone dose requirements
- Adverse effects of treatment
- Health-related quality of life
- Mortality
Databases searched (refer to appendix for search terms)

- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Medline

Selection criteria: Randomised controlled trials, Systematic reviews. No language restrictions.

Clinical Trials Registries searched

- Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
- US National Institutes of Health Trial Registry www.clinicaltrials.gov
- European Clinical Trials Register www.clinicaltrialsregister.eu
- World Health Organisation International Clinical Trials Registry Platform http://apps.who.int/trialsearch

Identified on-going trials (from registries listed above):

<table>
<thead>
<tr>
<th>Database and ID number</th>
<th>Title</th>
<th>Condition</th>
<th>Intervention</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClinicalTrials.gov NCT00774462</td>
<td>Rituximab for the treatment of refractory inflammatory myopathies and refractory myasthenia gravis</td>
<td>Myositis, Myasthenia Gravis</td>
<td>Rituximab</td>
<td>Completed</td>
</tr>
<tr>
<td>ClinicalTrials.gov NCT00106184</td>
<td>Rituximab for the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis</td>
<td>Myositis, Polymyositis, Dermatomyositis, Juvenile Dermatomyositis</td>
<td>Rituximab (RIM study)</td>
<td>Completed</td>
</tr>
<tr>
<td>ClinicalTrials.gov NCT01632124</td>
<td>Rituximab-induced pulmonary function changes</td>
<td>Inflammatory myositis, Rheumatoid arthritis</td>
<td>Rituximab</td>
<td>Recruiting</td>
</tr>
<tr>
<td>ClinicalTrials.gov NCT01862926</td>
<td>Rituximab versus cyclophosphamide in connective tissue disease</td>
<td>Idiopathic Inflammatory myositis, Interstitial lung disease, scleroderma, mixed connective tissue disease</td>
<td>Rituximab, Cyclophosphamide</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>EudraCT 2012-003633-42</td>
<td>A randomised, double blind controlled trial, comparing rituximab against intravenous cyclophosphamide in connective tissue disease associated with interstitial lung disease</td>
<td>Connective tissue disease associated with interstitial lung disease</td>
<td>Rituximab, cyclophosphamide</td>
<td>Ongoing</td>
</tr>
<tr>
<td>EudraCT 2005-002463-88</td>
<td>Efficacy and safety of a human normal immunoglobulin product</td>
<td>Idiopathic DM and PM with insufficiently improved muscle</td>
<td>IVIg</td>
<td>Completed</td>
</tr>
</tbody>
</table>
for IV administration (IVIg) strength under
in the treatment of conventional therapy
dermatomyositis and (glucocorticosteroids with polymyositis: prospective, immunosuppressors)
randomised, double blind

Recommended dose

The dose regimen proposed by the applicant is two 1g IV infusions, administered two weeks apart.

The dose used in adults in the largest RCT published to date (the RIM study) was 750mg/m² up to a maximum of 1g per infusion, with two infusions being administered one week apart (Oddis, Reed et al. 2013). Although the body surface area of patients was not provided, most adults have a BSA of >1.3m², therefore the dose in these patients would have been two infusions of 1g.

A proposed dosage regimen for children was not provided in the application, however the RIM study used two infusions at a dose of 575mg/m², one week apart (Oddis, Reed et al. 2013).

The applicant has also suggested that “Repeated administration of rituximab may be required in the event of clinical relapse of disease”.

Revised – 11 - A1

Public – I1 - A1

8
OVERVIEW OF INFLAMMATORY MYOSITIS

The inflammatory myopathies are a heterogeneous group of diseases, including polymyositis (PM), dermatomyositis (DM) and inclusion body myositis. These diseases are characterized by the gradual development of progressive motor weakness affecting the arms and legs, as well as the trunk, in association with histologic evidence of muscle inflammation. Inflammation predominantly involves striated muscle, but smooth muscle and even cardiac muscle may (though less commonly), be affected (Gelber, Levine et al. 2010).

At the most severe end of the disease spectrum, patients may develop profound impairment in swallowing solid foods and in full lung expansion, arising from pathologic involvement of visceral muscle affecting the oesophageal and diaphragmatic muscle tissues, respectively. These disease manifestations may result in nasal regurgitation of swallowed liquid beverages and in profound respiratory compromise (Gelber, Levine et al. 2010).

Epidemiology

The inflammatory myopathies are relatively rare disorders:

- Polymyositis has been estimated to occur with an annual incidence rate of approximately 5 cases per million (Gelber, Levine et al. 2010). Women are affected twice as often as men.
- Dermatomyositis has a bimodal distribution in terms of age at onset; the first peak occurs in childhood, and the second peak occurs in mid and late adult life (Gelber, Levine et al. 2010).

In the cohort of patients registered in the SA Myositis Database (SAMD) since 1980, there is a female predominance (59%), and the mean age for patients with DM is 55.1 years, PM is 59.0 years and IBM is 67.5 years (Basnayake, Blumbergs et al. 2014).

Pathophysiology

Polymyositis and dermatomyositis share several similar pathologic features but possess distinct ones as well. These include patchy involvement, presence of inflammatory infiltrates, and areas of muscle damage and regeneration.

Polymyositis:

- Inflammation is located around individual muscle fibres (“perimysial”);
- the infiltrate is T-cell (CD8+ > CD4+) and macrophage predominant;
- Inflammation in polymyositis is proposedly driven by autoantigens expressed in the muscle environment.
- Proinflammatory cytokines may induce a striking up regulation of MHC class I molecules seen on affected muscle cells but not adjacent normal myocytes. This MHC class I upregulation may lead to muscle damage through antigen-specific interactions with infiltrating CD8+ T cells, or through indirect mechanisms, by triggering a cell-damaging unfolded protein response (“UPR” or “ER stress”) in the muscle itself. Further damage occurs when infiltrating T cells degranulate and release perforin and proteolytic granzymes at specific sites of contact within the affected muscle (Gelber, Levine et al. 2010).
Dermatomyositis:

- Pathology different to polymyositis, but the outcome—profound muscle weakness—is the same;

- Major pathologic hallmarks of dermatomyositis include atrophy at the periphery of muscle bundles ("perifascicular atrophy"), and a predominantly B-cell and CD4+ T-cell infiltrate localized to the perifascicular space and surrounding capillaries (which are reduced in number). Activation of the complement cascade is seen as well (Gelber, Levine et al. 2010).

- The cutaneous features of dermatomyositis can be debilitating and include a painful, burning sensation of affected skin, as well as skin cracking and even breakdown with open ulceration. “Mechanic’s hands” refers to rough, cracked skin at the tips of the fingers forming irregular dirty-appearing lines.

The inflammatory myopathies characteristically begin over a number of weeks to a few months. The hallmark symptom of both polymyositis and dermatomyositis is weakness, usually involving the upper and lower extremities and is predominantly proximal rather than distal in location (Gelber, Levine et al. 2010). While muscle pain or myalgia may be present, weakness is the predominant symptom.

A major subgroup in inflammatory muscle disease (up to 30 percent of patients with dermatomyositis or polymyositis) is the “antisynthetase syndrome”, characterised by the presence of anti-synthetase antibodies and systemic clinical manifestations including relatively acute disease onset, constitutional symptoms (eg, fever and weight loss), myositis, the Raynaud phenomenon, mechanic’s hands, arthritis that is generally non-erosive, and interstitial lung disease (Tzioufas 2001; Miller and Vleugels 2013).
## SUMMARY OF EVIDENCE FOR THE USE OF RITUXIMAB IN INFLAMMATORY MYOSITIS

### Systematic reviews

A Cochrane review assessing the effects of immunosuppressive and immunomodulatory treatments for dermatomyositis and polymyositis has been published (Gordon, Winer et al. 2012). The review only included randomised controlled trials (RCTs) or quasi-RCTs. 10 of the 14 identified trials were included in the review, however no trials of rituximab were included.

### Randomised controlled trials

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Funding of study</td>
<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases Intramural program of the National Institute of Environmental Health Sciences General Clinical Research Center/ Clinical and Translational Science Award to the University of Kansas Medical Center Rituximab provided by Genetech</td>
</tr>
<tr>
<td>ClinicalTrials.gov identifier</td>
<td>NCT00106184</td>
</tr>
<tr>
<td>Design</td>
<td>Multicentre, randomised, double-blind, placebo-phase trial</td>
</tr>
<tr>
<td>Study duration</td>
<td>44 weeks</td>
</tr>
</tbody>
</table>
| Patient population | Inclusion criteria:  
1. Adults with definite or probable PM or DM; or children ≥ 5 years with definite or probable juvenile DM; and  
2. Refractory myositis defined as: Intolerance or inadequate response to glucocorticoids and at least one other immunosuppressive or immunomodulatory agent (intolerance defined as 'side effects that require discontinuation of the medication or an underlying condition that precludes further use of the medication'),(Oddis 2005); and  
3. Demonstrable muscle weakness:  
   o Adults: Maximum Manual Muscle Testing$^1$ (MMT8) score of 125/150 + 2 other abnormal core set measures  
   o Juvenile DM: MMT8 score of 125/150 + 2 other abnormal core set measures; or MMT8 score > 125/150 + 3 abnormal core set measures.  
Exclusion criteria:  
   · Drug-induced myositis  
   · Juvenile PM  
   · Inclusion-body myositis  
   · Cancer-associated myositis (myositis diagnosed within 2 years of a cancer diagnosis)  
   · Myositis in overlap with another connective tissue disease  
   · Previous treatment with rituximab |

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Juvenile DM with baseline IgG or IgM levels below the age-adjusted lower level of normal

Adults with IgM levels ≥ 30% below lower level of normal

**Intervention**

Rituximab early: Active drug at week 0 and week 1, placebo at weeks 8 & 9.

(Dose based patient’s BSA: Children with BSA ≤ 1.5m² → 575mg/m² at each infusion; Adults & children with BSA > 1.5m² → 750mg/m² to max 1g per infusion).

**No. of patients on intervention** 96

**Comparator**

Rituximab late: Placebo infusions at weeks 0 & 1, rituximab at weeks 8 & 9.

(Dose based patient’s BSA: Children with BSA ≤ 1.5m² → 575mg/m² at each infusion; Adults & children with BSA > 1.5m² → 750mg/m² to max 1g per infusion).

**No. of patients on comparator** 104

**Primary efficacy outcome(s)** Time to achieve definition of improvement (DOI)

**Secondary outcome(s)** Time to achieve 20% improvement in MMT-8 on two consecutive visits.

Proportion of patients achieving DOI at week 8 (rituximab vs placebo).

**Blinding of patients** Yes

**Blinding of outcome assessors** Yes

**Allocation concealment** Yes

**Withdrawals from intervention arm of study** 3 (3.1%)

**Withdrawals from placebo arm of study** 2 (1.9%)

**Primary Outcome:**

Median time to DOI

**Secondary Outcomes:**

Median time to 20% ↑ in MMT-8

% of patients achieving DOI at 8 wks

<table>
<thead>
<tr>
<th></th>
<th>Rituximab early</th>
<th>Rituximab late</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to DOI</td>
<td>20.0 weeks</td>
<td>20.2 weeks</td>
<td>0.74</td>
</tr>
<tr>
<td>Median time to 20% ↑</td>
<td>Not provided</td>
<td>Not provided</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>MMT-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients achieving DOI at 8 weeks</td>
<td>15%</td>
<td>20.6%</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Events:**

There was no significant difference in adverse events reported at week 8.

67 serious adverse events occurred in 64 patients: Infections & infusion reactions were the most common adverse events.

The above trial is the only randomised controlled trial investigating the use of rituximab to treat inflammatory myositis. Rather than using the conventional placebo controlled design, the investigators used a delayed start design, where one group received active treatment during the first period of the trial, and the second group receiving active treatment at a later time-point.

The following diagram shows the trial design:
The delayed-start design potentially can measure improvement in the active treatment group versus placebo up until the end of the first period of the trial, before the second group is administered active drug. The assumption in the above trial was that the disease-modifying effect of rituximab would be obtained within the first 8 weeks. The authors reported that there was no significant difference in the two treatment arms for the primary or secondary end points. Although they reported that 83% of patients met the Definition of Improvement (DOI), because all patients received rituximab it is not known what proportion of patients in the trial may have obtained a DOI at 44 weeks without rituximab.

**Level III or IV evidence**

Most publications reporting on the use of rituximab in inflammatory myopathies are case series or case reports. The applicant referred to a number of published case series and case reports in the formulary submission (Arlet, Dimitri et al. 2006; Rios Fernandez, Callejas Rubio et al. 2009; Valiyil, Casciola-Rosen et al. 2010; Mahler, Blom et al. 2011; Limaye, Hissaria et al. 2012; Basnayake, Cash et al. 2013; Basnayake, Blumbergs et al. 2014).

Most case series are retrospective, however the study by Mahler et al was prospective and followed 13 adult patients with inflammatory myositis refractory to conventional therapy who were treated with rituximab for a median of 27 months (Mahler, Blom et al. 2011).

**Overview of Evidence**

**Study Design and Quality**

There is one randomised controlled trial identified, investigating rituximab in inflammatory myositis. All other published studies are low level evidence, either case series or case reports.

**Effectiveness**

The randomised controlled delayed-start trial (RIM study) showed no significant difference in achieving primary or secondary endpoints in patients with refractory myositis who were administering rituximab earlier, rather than eight weeks later (Oddis, Reed et al. 2013). Although the study was randomised, the duration of first phase (where one group received active drug and the other placebo) was only 8 weeks and because the onset of effect may be longer than 8 weeks, the design of the trial may have prevented the detection of a treatment effect.

Most published reports of rituximab to treat inflammatory myositis are from uncontrolled studies, case series and case reports only. A prospective study including 13 adult patients with inflammatory myositis refractory to conventional therapy, who were treated with two 1g doses of rituximab, with a two week interval between the doses (Mahler, Blom et al. 2011). Median
follow-up was 27 months, with none lost to follow-up. Refractory was defined as having failed to respond to corticosteroids and one immunosuppressive medication. 10 of the 13 patients (77%) had been treated with methotrexate and 8 with azathioprine. Other medication included IV corticosteroids, infliximab, etanercept, cyclosporin, adalimumab, cyclophosphamide and one patient had previously had IVIg. The authors reported a significant reduction in creatinine kinase (CK) levels in all patients at 6 weeks, however normalisation of CK levels was not achieved in two patients. In 11 patients (85%) muscle strength was reported improved, as measured by hand-held dynamometry (Mahler, Blom et al. 2011). However 10 of the 13 patients (77%) relapsed after a median of 7.4 months and received additional courses of rituximab.

Intravenous immunoglobulin (IVIg) is considered the main comparator treatment in this patient population. The National Blood Authority (NBA) of Australia has listed the inflammatory myopathy as a condition “for which IVIg has an established therapeutic role” (National Blood Authority Australia 2012). The indications listed are:

1. Patients with PM or DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents;
2. Patients with inclusion body myositis (IBM) who have dysphagia affecting function;
3. Patients with rapidly progressive IBM.

IVIg is not recommended to treat the limb weakness of IBM based on expert consensus (National Blood Authority Australia 2012). The NBA recommends that IVIg should be used monthly for three to six months before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned (National Blood Authority Australia 2012). The NBA recommends effectiveness be demonstrated by objective findings of either:

- Improvement in functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment; or
- Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores (National Blood Authority Australia 2012).

The dose of IVIg recommended by the NBA is:

<table>
<thead>
<tr>
<th>Induction</th>
<th>2g/kg in 2 to 5 divided doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>0.4 – 1g/kg 4-6 weekly</td>
</tr>
</tbody>
</table>

A double blind cross-over controlled trial published in 1993 in 15 biopsy-proven DM patients refractory to treatment. They were randomized to either high dose IVIg or placebo monthly for 3 months (with continuing prednisolone). The very small numbers of patients enrolled makes interpretation of the results difficult, however the authors reported that the 8 patients assigned to IVIg had a significant improvement in scores of muscle strength (p<0.018) whereas the 7 patients assigned to IVIg did not (Dalakas, Illa et al. 1993). Repeat muscle biopsy was undertaken in 5 patients and this showed histological evidence of improvement which correlated with return of endomysial capillary numbers to normal.

In summary, there appears to be some evidence to suggest that rituximab may decrease symptoms of inflammatory myositis, improve muscle strength, and reduce the on-going steroid dose in some patients refractory to other treatment, however the magnitude of the treatment effect compared to IVIg or the addition of a fourth-line immunosuppressive medicine is unclear.
due to insufficient data, as is the duration of effect and the proportion of patients expected to respond.

**Safety**

Treatment with rituximab is associated with a small, but well documented, risk of fatal infusion reactions, tumour lysis syndrome (TLS), severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML) (FDA 2012).

Infusion reactions are common and typically occur during the first infusion, with time to onset between 30 and 120 minutes. Reactions include urticarial, hypotension, angioedema, hypoxia, bronchospasm, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylaxis or death. In clinical trials, the observed incidence of infusion reactions was ≥ 25% (FDA 2012).

JC virus infection resulting in PML can occur in rituximab-treated patients with autoimmune diseases who have had prior or concurrent immunosuppressive treatment, with most cases diagnosed within 12 months of the last infusion of rituximab (FDA 2012).

In the RIM study, a total of 67 serious adverse events were reported, occurring in 64 patients. Infections were the most common serious adverse event including pneumonia (6 cases), cellulitis (6 cases), urosepsis (2 cases), herpes zoster (2 cases), septic arthritis, histoplasmosis & urinary tract infections (Oddis, Reed et al. 2013).
Appendix 2  Comparative costs and pharmacoeconomics

Current usage and cost to the State

Since the implementation of the SA Health *High Cost Medicines Policy* in October 2011, there have been 11 Individual Patient Use (IPU) requests for rituximab for these indications in SA. Details of the cost & hospital are provided below:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hospital</th>
<th>Date</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisynthetase syndrome</td>
<td>RAH</td>
<td>Oct-11</td>
<td>$9,054</td>
</tr>
<tr>
<td>Myositis</td>
<td>RAH</td>
<td>Apr-12</td>
<td>$9,052</td>
</tr>
<tr>
<td>Myositis</td>
<td>RAH</td>
<td>Aug-12</td>
<td>$9,054</td>
</tr>
<tr>
<td>Dermatomyositis / Antisynthetase syndrome</td>
<td>RAH</td>
<td>Sep-12</td>
<td>$9,056</td>
</tr>
<tr>
<td>Polymyositis / Antisynthetase syndrome</td>
<td>RAH</td>
<td>Sep-12</td>
<td>$9,056</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>RGH</td>
<td>Feb-13</td>
<td>$9,055</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>RAH</td>
<td>Mar-13</td>
<td>$9,054</td>
</tr>
<tr>
<td>Antisynthetase syndrome / Inflammatory myopathy</td>
<td>RAH</td>
<td>Apr-13</td>
<td>$9,054</td>
</tr>
<tr>
<td>Refractory dermatomyositis</td>
<td>RGH</td>
<td>Apr-13</td>
<td>$9,054</td>
</tr>
<tr>
<td>Resistant dermatomyositis</td>
<td>RAH</td>
<td>Jun-13</td>
<td>$9,054</td>
</tr>
<tr>
<td>Refractory antisynthetase syndrome</td>
<td>RAH</td>
<td>Dec-13</td>
<td>$9,054</td>
</tr>
</tbody>
</table>

Total cost: $99,597

(RAH = Royal Adelaide Hospital; RGH = Repatriation General Hospital)

Note: It is not clear from the data we have whether some of the requests are repeat treatments for the same patient.

Cost of medicine per treatment course

Rituximab 500mg vial = $2263.57

The proposed dose in the application is 1g every two weeks for 2 doses. The cost of two 1g doses of rituximab is $9,054.

Projected cost of rituximab per year to SA Health for proposed indication

The South Australian Myositis Database (SAMD) for patients with biopsy-proven idiopathic inflammatory myositis is a register (established in 1980) of adult patients with a histological diagnosis of dermatomyositis (DM), polymyositis (PM) or inclusion body myositis (IBM)(Basnayake, Blumbergs et al. 2014). In the 5 years from 2007 to 2011, 144 patients were identified (average of 28-29 patients per year). The applicant estimates that up to one third of patients may be refractory to corticosteroids + 2 immunosuppressants, indicating that 9-10 patients may be eligible for treatment under the proposed protocol. This does not include patients who relapse and may require additional treatment.

A treatment course of two 1g doses of rituximab costs $9054. If ten patients per annum receive the treatment course, this would cost SA Health $90,540. It is not clear what proportion of these patients will relapse and require further rituximab.
Cost of comparator – Intravenous immunoglobulin (IVIg)

The dose of IVIg recommended by the NBA for inflammatory myositis is:

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2g/kg in 2 to 5 divided doses</td>
<td>0.4 – 1g/kg 4-6 weekly</td>
</tr>
</tbody>
</table>

In the two year period between October 2011 and October 2013, a total of $24,954g of IVIg was administered to 55 patients in SA public hospitals for the treatment of inflammatory myositis (data provided by the state IVIg nurse). The total cost was $2,730,440 of which 37% ($1,010,263) was a direct cost to SA Health. In the two year period, the 55 patients treated with IVIg received an average of 9 treatments each (range 1-28), with the median total cost per patient being $26,316 ($9,736 to SA Health). The total cost per patient ranged from $5,183 to $263,162.

Comparative cost per patient

Rituximab

The proposed dose of rituximab is 1g every two weeks for 2 doses. The cost of two 1g doses of rituximab is $9,054. The entire cost of the drug is a cost to SA Health as it is not funded on by the Commonwealth through the PBS.

IVIg:

Under the National Blood Supply (NBS) arrangements, the cost of the product is shared between the Commonwealth and state governments. The brands currently used in SA are Intragam and Kiovig.

Comparative costs per gram (as of October 2013) are provided below:

<table>
<thead>
<tr>
<th>IV Ig product</th>
<th>Local or imported?</th>
<th>Cost per gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intragam</td>
<td>Australian</td>
<td>$132.91</td>
</tr>
<tr>
<td>Kiovig</td>
<td>Imported</td>
<td>$60.00</td>
</tr>
</tbody>
</table>

In SA in the last 5 years, the average dose of IVIg per patient (who has received IV Ig for inflammatory myositis) is 77.1g, equating to $4,626 to $10,247, depending upon the brand used. Currently in South Australia, about 65% of IVIg used is the domestic product (Intragam) and 35% imported (Kiovig). Therefore the average cost per gram of IV Ig used in SA is $106.13 and therefore, currently in SA, the cost on average to treat a patient with inflammatory myositis is $8,182 per treatment. Under current contract arrangements, IV Ig products are funded 37% by the state and 63% by the Commonwealth. Therefore on average, the cost to SA health per patient is $3,027 and the cost to the Commonwealth is $5,155 per treatment.

The NBA recommend an induction dose of 2g/kg in 2 to 5 divided doses which for a 70kg patient would cost $14,858 ($5,498 cost to SA Health, $9,360 to Commonwealth). The recommended maintenance dose of 0.4 – 1g/kg 4-6 weekly (based on a 70kg patient) would
The annual on-going cost would therefore be between $25,757 and $96,577 per patient ($9,530 to $35,733 to SA Health)

The comparative costs* (for a 70kg patient) are shown in the table below:

<table>
<thead>
<tr>
<th>Total cost</th>
<th>Cost funded by Commonwealth</th>
<th>Cost to SA Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 1g x 2 doses</td>
<td>$9,054</td>
<td>---</td>
</tr>
<tr>
<td>IVlg induction 2g/kg</td>
<td>$14,858</td>
<td>$9,360</td>
</tr>
<tr>
<td>IVlg maintenance 0.4-1g/kg 4-6 weekly</td>
<td>$25,757 - $96,577</td>
<td>$16,227 - $60,844</td>
</tr>
</tbody>
</table>

*Drug cost only – does not include administration costs

It is unclear what proportion of patients require maintenance therapy with IVlg. If just IVlg induction dosing is required, the cost to SA health is cheaper ($5,498) compared to rituximab ($9,054). However if ongoing maintenance is required, the annual cost to SA Health of IVlg is potentially up to $41,231 ($32,177 more expensive compared to rituximab, assuming only one course of rituximab is administered). In the last two years, patients administered IVlg for inflammatory myositis received on average 9 treatments each.

Cost-effectiveness

The comparative effectiveness of rituximab and IVlg is unknown as there are no head-to-head trials in the patient population, therefore it is difficult to estimate cost-effectiveness. The effectiveness of rituximab is highly uncertain, however there is also limited evidence for the effectiveness of the alternate treatment IVlg, which is more expensive and more time consuming to administer than rituximab.

In addition, being a biological product, IVlg is a limited resource and the NBA recommend that where safe, effective and affordable alternative therapies exist, these are considered preferable to IVlg (National Blood Authority Australia 2012).

Although there is high uncertainty, for patients who would otherwise be treated with IVlg, it is likely to be cost-effective or cost-neutral to use rituximab instead.
Appendix 3: References


FDA (2012). Rituximab (Rituxan) Full Prescribing Information. Silver Spring, Maryland, Food and Drug Administration [Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5362lbl.pdf].


<table>
<thead>
<tr>
<th>Rating guide – adapted from NHMRC 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
</tr>
<tr>
<td>2. Consistency (if only one study was available, rank this component as 'not applicable')</td>
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<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>D</td>
</tr>
<tr>
<td>NA</td>
</tr>
<tr>
<td>3. Clinical impact (indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the Formulary Submission?)</td>
</tr>
<tr>
<td>A</td>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
</tr>
<tr>
<td>5. Applicability (is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)</td>
</tr>
<tr>
<td>A</td>
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<td>B</td>
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<tr>
<td>C</td>
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<td>D</td>
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Disclaimer: This review was produced as an advisory note for the SA Medicines Advisory Committee. The data used to compile the report comes from various sources. The Department is not able to guarantee that different sources have compiled or reported data in a consistent way. The Department uses its best endeavours to ensure the quality of the information available in this report. Before relying on the information within this report, users should carefully evaluate its accuracy, currency, completeness and relevance for their purposes, and should obtain any appropriate professional advice relevant to their particular circumstances. The Department cannot guarantee and assumes no legal liability or responsibility for the accuracy, currency or completeness of the information.