The Technology Assessment Unit of the McGill University Health Centre (MUHC)

The effectiveness and safety of rituximab (anti-CD20) in neurologic autoimmune diseases

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by

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PRINCIPAL MESSAGES

Rituximab, an anti-CD20 (white cell marker) antibody, has been used off-label for the treatment of four rare autoimmune diseases, myasthenia gravis (MG), neuromyelitis optica (NMO), dermatomyositis, and chronic inflammatory demyelinating polyneuropathy (CIDP).

Although the evidence to support its use for these conditions is slender, their rarity indicates that better evidence will be hard to accumulate.

The scanty evidence available is sufficient to justify conditional and temporary approval for use of rituximab in the MUHC for patients with MG and NMO who are refractory to or intolerant of standard therapy. Evidence is insufficient to support its use for dermatomyositis or CIDP.

All relevant patient data should be collected and maintained in a regularly updated registry which should be examined at the latest in two years at which time the issue of approval should be reconsidered.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChR</td>
<td>Acetylcholine receptor</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AIR</td>
<td>Autoimmunity in Rituximab (registry)</td>
</tr>
<tr>
<td>CD19, CD20</td>
<td>B-cell surface markers</td>
</tr>
<tr>
<td>CIDP</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Research and Dissemination</td>
</tr>
<tr>
<td>BIOGEAS</td>
<td>Biologicals registry for the Study Group in Autoimmune Diseases (Spain)</td>
</tr>
<tr>
<td>DM</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
</tr>
<tr>
<td>EMBASE</td>
<td>Excerpta Medica Database</td>
</tr>
<tr>
<td>GRAID</td>
<td>German Registry of Autoimmune Diseases</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>INC</td>
<td>Inflammatory Neuropathy Consortium (Italy)</td>
</tr>
<tr>
<td>INCAT</td>
<td>Inflammatory Neuropathy Cause and Treatment Score</td>
</tr>
<tr>
<td>IVIg</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>MG</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>MGFA</td>
<td>Myasthenia Gravis Foundation of America</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MUHC</td>
<td>McGill University Health Centre</td>
</tr>
<tr>
<td>MuSK</td>
<td>Muscle specific receptor kinase</td>
</tr>
<tr>
<td>NHL</td>
<td>Non Hodgkin lymphoma</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NMJ</td>
<td>Neuromuscular junction</td>
</tr>
<tr>
<td>NMO</td>
<td>Neuromyelitis optica</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PE</td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>PM</td>
<td>Polymyositis</td>
</tr>
<tr>
<td>PML</td>
<td>Progressive multifocal leucoencephalopathy</td>
</tr>
<tr>
<td>QMG</td>
<td>Quantitative Myasthenia Gravis</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RIM</td>
<td>Rituximab in Myositis (study)</td>
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<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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</table>
EXECUTIVE SUMMARY

Background
Myasthenia gravis (MG), neuromyelitis optica (NMO), dermatomyositis (DM), and chronic inflammatory demyelinating polyneuropathy (CIDP) are four rare autoimmune diseases with neurological and neuromuscular manifestations. Standard treatment options are corticosteroids, immunosuppressants, intravenous immunoglobulin (IVIg), and plasmapheresis (PE). Rituximab, a monoclonal antibody to the leukocyte cell surface antigen CD20, is approved for the treatment of refractory rheumatoid arthritis and has been used off-label for treating patients with numerous other autoimmune diseases. The TAU was asked to review the efficacy and cost impact of the use of rituximab in the above-listed indications.

Method
A systematic literature search of PubMed, EMBASE (Ovid), Cochrane, DARE, ISI Web of Sciences, and grey literature sources for “rituximab” and the indications as listed above, as text- and keywords. The search was extended to include overarching terms such as “inflammatory myositis”, where indicated.

Results: Literature review
We found no systematic reviews or HTAs. With the exception of a single RCT for rituximab in inflammatory myositis including dermatomyositis, the evidence consisted of case series and case reports. Because of the paucity of available evidence, we included data derived from abstracts as well as from complete reports.

Myasthenia gravis We retrieved ten case series (seven reported in full and three in abstract) describing 112 patients with mainly severe and refractory disease who had received rituximab for MG. We also found case reports describing the response of MG to rituximab in a further 48 patients. The majority of patients showed improvement, particularly those with antibodies to muscle receptor kinase (MuSK). Three articles documented reductions in use of IVIg and/or PE following treatment. Across all reports, two patients were hospitalized with infections and one had to discontinue treatment due to an infusion reaction.

Neuromyelitis optica We found one guideline document prepared by The European Federation of Neurological Societies (EFNS) 2010. This guideline included rituximab as first-line immunosuppressive therapy for NMO. We retrieved fifteen case series (seven reported in full and eight in abstract) that contributed data for 250 patients, and case reports for a further 22 patients. A summary of individual patient data for 114 patients in seven studies showed that rituximab reduced the annualized relapse rate from a median 1.8 per year (range 0.13 to 12) before treatment to a median of 0 (range 0 to 15.6). Level of disability also improved, from a median Extended Disability Status Scale measure of 6 to a median of 3.5. There were no data for a comparison of use of IVIg and PE before and after rituximab treatment. Across all
reports, five patients died, two of NMO relapse and three of infection, and three patients were hospitalized due to possibly related adverse events (two infections).

**Dermatomyositis** One study observed the time to improvement of 200 patients (dermatomyositis 76 patients, juvenile dermatomyositis 38, polymyositis 76), randomised to 2 groups, one receiving rituximab at onset and one receiving it after a delay of eight weeks. Overall, 83% of the patients reached the predefined improvement endpoint, but there was no difference in time to improvement between the two arms. Twenty-seven patients were described in four case series, and 21 in case reports. Criteria for improvement varied and improvements, where observed, were generally modest. Assessment is complicated by the fluctuating nature of the condition. In the RIM study, one patient died of unrelated causes, one withdrew due to an adverse event, and there were 26 serious adverse events, mainly infectious.

**Chronic inflammatory demyelinating polyneuropathy** Up to fifty-one patients have been described in three case series, with an unknown degree of overlap, and 12 patients in case reports. Of the 21 patients in the case series whose outcomes were adequately reported, approximately half were considered improved, either by scale measures of disease activity or by clinical judgement.

**Safety**
Rituximab has the potential to cause serious side effects such as tumour lysis syndrome (in patients with malignancies), severe mucocutaneous reactions, and progressive multifocal leucoencephalopathy (PML). The reported adverse events were consistent with the known safety profile of rituximab, with infections and infusion reactions predominating, and with the severity of the underlying medical condition. There were no reports of PML in patients with MG, NMO, or CIPD, and one report of PML in a patient with DM who had received multiple immunotherapies. However, reporting of non-serious, non-fatal adverse events in these case series was generally confined to infections and infusion reactions, and was likely to be incomplete.

**MUHC experience**
Of ten patients with MG treated with rituximab within the MUHC over the past five years, nine showed improvement and one did not respond. Two responded well enough to be discharged after prolonged requirement for artificial ventilation (3-4 months). Three of the ten discontinued IVIg treatment, three discontinued PE treatment, and one discontinued both.

**Costs**
Approximate direct costs of six months trial therapy and two year maintenance therapy for MG would be approximately $10,000 and $30,000 per patient respectively. There are insufficient data on which to base estimates of net cost, but
in patients in whom use of IVIg or PE could be reduced or eliminated net treatment costs would be reduced and in some cases there might be net gains.

**CONCLUSIONS**

The available evidence is based on case series and case reports involving small numbers of subjects, and therefore should be interpreted with caution. However, the rarity of these disorders means that higher quality data may never be obtained.

**Efficacy**

*Myasthenia gravis*

- There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with severe MG that is refractory to standard treatment, or who cannot tolerate standard treatment, may respond to rituximab, with in some cases marked clinical improvement to the point of remission.

- There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with MG who require very frequent dosing (eg, weekly) with IVIg and/or PE to avoid deterioration may be able to abolish or reduce their dependence. In such cases, use of rituximab may result in savings in cost and reduction in need for resources.

*Neuromyelitis optica*

- NMO is a distinct disease entity with a more severe prognosis than multiple sclerosis. Recurrent relapses early in the disease result in rapid accumulation of disability.

- There is a small but consistent body of evidence from uncontrolled studies that patients with NMO experience less frequent relapses following rituximab treatment (although a few may suffer exacerbations). On the basis of this evidence, rituximab with corticosteroids has entered guidelines and practice as first-line treatment.

*Dermatomyositis*

- In a randomized placebo-phase trial of rituximab in dermatomyositis (adult and juvenile) and polymyositis there was no difference between groups in the primary endpoint of time to improvement. By the end of the 44-week trial, most patients in both groups had reached the pre-defined measure of improvement. The evidence from a small number of case series for improvement is inconsistent. Some patients have experienced a modest improvement.

*Chronic inflammatory demyelinating polyneuropathy*
There is an extremely small body of evidence from uncontrolled studies that suggests rituximab can produce improvement in patients with CIDP, with results ranging from modest improvement to remission.

**Safety**

Adverse events were reported for all the MG, DM and CIDP case series, and all the full-length reports of NMO case series. On-treatment deaths were reported for patients with NMO and DM, and hospitalizations due to infection were reported for patients with MG, NMO, and DM. The small size of the dataset means that it is difficult to assess increased risk of adverse events due to rituximab.

**RECOMMENDATIONS**

The data are of insufficient quantity and quality to support a recommendation for the routine use of rituximab in any of these four conditions.

There is sufficient evidence to support the use of rituximab in the treatment of a limited number of patients, as described below.

**Myasthenia gravis**

There is sufficient evidence to support *temporary* and *conditional* approval of rituximab in the treatment of patients with myasthenia gravis under the conditions outlined below:

- Hospitalized patients whose disease is refractory to other therapies
- Hospitalized patients whose treatment options are limited due to intolerance or contraindications to more accepted therapies.
- Patients who require very frequent use (more frequently than 10 days) of IVIg or PE
- The number of new patients treated per year be limited to 10.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a *regularly updated* registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of permanent approval should be considered.

**Neuromyelitis optica**

There is sufficient evidence to support *temporary* and *conditional* approval of rituximab in the treatment of patients with neuromyelitis optica under the conditions outlined below.
• Patients diagnosed with NMO who have positive NMO-IgG and have experienced one or more severe relapses.
• The number of new patients treated per year be limited to a maximum of three.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a regularly updated registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of continued/permanent approval should be considered.

Dermatomyositis

There is insufficient evidence to justify the use of rituximab in dermatomyositis other than in the context of a formal research study.

Chronic inflammatory demyelinating polyneuropathy

There is insufficient evidence to justify use of rituximab in CIDP other than in the context of a formal research study.

General Recommendation

To treat patients with rare diseases such as MG and NMO without collecting, coordinating, and publishing the results would constitute a serious waste of opportunity and resources. Accordingly, every effort should be made to enlist colleagues at associated institutions to share in a treatment and reporting protocol that would allow significant information concerning the benefits and indications for the use of rituximab to be accumulated and published.
SOMMAIRE

Contexte
La myasthénie gravis (MG), la neuromyélite optique aiguë (NOA), la dermatomyosite (DM) et la polyneuropathie inflammatoire démyélinisante chronique (PIDC) sont quatre maladies autoimmunes rares présentant des manifestations neurologiques et neuromusculaires. Les options de traitement standards pour ces maladies sont l’administration de corticostéroïdes, d’immunosuppresseurs, d’immunoglobulines intraveineuses (IgIV) et la plasmaphérèse (PE). Le rituximab, un anticorps monoclonal dirigé contre l’antigène de surface CD20 des leucocytes, est homologué pour le traitement de la polyarthrite rhumatoïde résistante et est administré hors indication pour le traitement de patients ayant de nombreuses autres maladies autoimmunes. L’Unité d’évaluation des technologies (TAU) a été sollicitée afin d’examiner l’efficacité et l’impact budgétaire de l’utilisation du rituximab dans les indications ci-haut mentionnées.

Méthodologie
Une recherche documentaire systématique a été effectuée dans PubMed, EMBASE (Ovid), Cochrane, DARE, ISI Web of Sciences ainsi que dans la littérature grise ciblant le « rituximab » et les indications mentionnées ci-dessus, et ce, en texte et mots-clés. Lorsque requis, la recherche a été étendue en incluant des termes plus généraux comme « myosite inflammatoire ».

Résultats. Revue de la littérature
Nous n’avons identifié aucune revue systématique ni rapport d’évaluation. À l’exception d’un essai clinique randomisé (ECR) portant sur l’utilisation du rituximab pour le traitement de la myosite inflammatoire, incluant la DM, toutes les données probantes répertoriées consistent en des séries de cas et des études de cas cliniques. En raison de la rareté des données probantes, nous avons inclus des données tirées de résumés de congrès ainsi que de rapports complets.

Myasthénie gravis
Nous avons retrouvé 10 études de série de cas cliniques (sept publiées et trois présentées en abrégés) décrivant 112 patients principalement atteints d’une maladie grave ou réfractaire ayant reçu du rituximab pour de la MG. Nous avons aussi identifié des études de cas cliniques décrivant la réponse de la MG au rituximab chez 48 patients supplémentaires. Une amélioration a été montrée chez la majorité des patients, particulièrement chez ceux ayant des anticorps contre le récepteur
tyrosine-kinase spécifique du muscle (MuSK). Trois articles ont documenté des diminutions de l’utilisation d’IgIV et/ou de PE suivant le traitement. Au total des études, deux patients ont été hospitalisés pour des infections et un a dû cesser le traitement en raison d’une réaction lors de la perfusion.

**Neuromyélite optique aiguë**

Nous avons identifié un guide de pratique clinique de la Fédération européenne des sociétés de neurologie (EFNS) publié en 2010. Ce guide de pratique inclut le rituximab parmi les traitements immunosuppresseurs de première intention de la NOA. Nous avons répertorié 15 études de série de cas cliniques (sept publiées et huit en abrégés) fournissant des données sur 250 sujets, ainsi que des études de cas cliniques portant sur 22 patients supplémentaires. Un résumé des données individuelles des patients pour 114 sujets de sept études a montré que le rituximab a permis de réduire le taux annualisé de récidive d’une médiane de 1,8 récidive par année (étendue de 0,13 à 12) avant le traitement à une médiane de 0 récidive par année (étendue de 0 à 15,6). Le degré d’invalidité des sujets s’est aussi amélioré, passant d’une médiane de 6 à 3,5 sur l’échelle Extended Disability Status Scale. Aucune donnée permettant de comparer l’utilisation d’IgIV et de PE avant et après le traitement au rituximab n’était disponible. Dans l’ensemble des études, cinq patients sont décédés, soit deux d’une récidive de la NOA et trois d’une infection. Trois patients ont été hospitalisés en raison d’événements indésirables possiblement liés au traitement (deux infections).

**Dermatomyosite**

Une étude a mesuré le temps avant d’observer une amélioration clinique chez 200 patients (76 atteints de dermatomyosite, 38 de dermatomyosite juvénile, 76 de polymyosite), randomisés entre deux groupes, l’un recevant du rituximab à l’apparition des symptômes et l’autre le recevant après un délai de huit semaines. Globalement, 83% des patients ont atteint le niveau d’amélioration prédéterminé, mais il n’y avait pas de différence entre les groupes quant au temps écoulé avant d’observer l’amélioration. Vingt-sept patients ont été décrits dans quatre séries de cas et 21 dans des études de cas cliniques. Les critères pour définir une amélioration et les améliorations elles-mêmes, lorsqu’observées, étaient généralement modestes. L’évaluation est compliquée par la nature fluctuante de la maladie. Dans l’étude RIM, un patient est décédé de causes non reliées, un a abandonné l’étude en raison d’un événement indésirable et il y a eu 26 effets indésirables graves, principalement des infections.
Polyneuropathie inflammatoire démyélinisante chronique
Jusqu'à 51 patients ont été décrits dans trois séries de cas, avec un degré de duplication inconnu, et 12 patients dans des études de cas cliniques. Parmi les 21 sujets dans les séries de cas pour lesquels les résultats ont été rapportés adéquatement, approximativement la moitié ont été considérés comme ayant eu une amélioration, que ce soit selon des mesures sur une échelle d'activité de la maladie ou selon le jugement clinique.

Innocuité
Le rituximab peut causer des effets secondaires graves dont un syndrome de lyse tumorale (chez les patients ayant des tumeurs malignes), des réactions mucocutanées graves et une leucoencéphalopathie multifocale progressive (LEMP). Les effets indésirables rapportés étaient cohérents avec le profil de sécurité connu du rituximab, les infections et les réactions lors de l'administration du médicament étant prédominantes, ainsi qu'avec la gravité de la condition médicale sous-jacente. Aucun cas de LEMP n'a été rapporté chez les sujets atteints de MG, NOA ou PIDC. Un cas de LEMP a été rapporté chez un sujet atteint de DM ayant reçu plusieurs immunothérapies. Toutefois, la déclaration des effets indésirables non graves et non fataux rapportés dans les séries de cas était généralement limitée aux infections et aux réactions lors de la perfusion et elle est probablement incomplète.

Expérience du CUSM
Au CUSM, parmi les dix personnes atteintes de MG traitées avec du rituximab au cours des cinq dernières années, neuf ont connu des améliorations cliniques et un n'a pas répondu au traitement. La réponse au traitement de deux patients a été suffisamment bonne pour recevoir leur congé après un période de ventilation artificielle prolongée (trois à quatre mois). L'administration d'IgIV a pu être cessée chez trois des 10 patients, le recours à la PE a été abandonné chez trois autres et une personne a cessé ces deux traitements.

Coûts
Les coûts directs approximatifs pour six mois de traitement avec du rituximab et pour un traitement d'entretien de deux ans pour les personnes atteintes de MG seraient respectivement d'environ 10 000 $ et 30 000 $ par personne. Il n'y a pas suffisamment de données sur la base desquelles il est possible d'estimer le coût net du traitement, mais chez les patients chez qui l'utilisation d'IgIV ou de PE pourrait
être réduite ou éliminée, les coûts nets du traitement seraient diminués et dans certains cas il pourrait y avoir des gains nets.

CONCLUSIONS
Les preuves disponibles sont constituées d'études de séries de cas cliniques et d'études de cas cliniques impliquant de petits nombres de sujets et, conséquemment, devraient être interprétées avec prudence. Toutefois, de par la nature rare des pathologies étudiées, il est probable que de meilleures données probantes ne puissent jamais être disponibles.

Efficacité
Myasthénie gravis :
- Des preuves faibles mais constantes provenant d'études non contrôlées suggèrent que les personnes atteintes de MG grave réfractaire au traitement standard et celles qui ne tolèrent pas le traitement standard, pourraient répondre au rituximab et même, dans certains cas, démontrer une amélioration clinique marquée allant jusqu’à une rémission.
- Des preuves faibles mais constantes provenant d'études non contrôlées suggèrent que les personnes atteintes de MG qui nécessitent un dosage très fréquent (e.g. hebdomadaire) avec des IgIV et/ou de la PE pour éviter une détérioration de leur condition clinique pourraient cesser ou réduire leur dépendance. Dans de tels cas, l'utilisation du rituximab pourrait générer des économies de coûts et réduire l’utilisation des ressources.

Neuromyélite optique.
- La NOA est une maladie distincte de la sclérose en plaques et présentant un pronostic plus sombre. Les fréquentes récidives, tôt dans l’évolution de la maladie, entraînent une progression rapide de l’invalidité.
- Des preuves faibles mais constantes provenant d'études non contrôlées suggèrent que les personnes atteintes de NOA connaissent des récidives moins fréquentes après un traitement avec le rituximab (bien que quelques-unes puissent souffrir d’exacerbations de la maladie). Sur la base de ces données probantes, l’administration de rituximab en concomitance avec l’administration de corticostéroïdes a été incluse dans les guides de pratique et implantée en pratique comme traitement de première intention.

Dermatomyosite
- Dans un essai clinique randomisé contrôlé par un placebo évaluant l’efficacité du rituximab chez les personnes atteintes de dermatomyosite (adulte ou juvénile) et de polymyosite, il n’y avait pas de différence entre les groupes pour ce qui est de l’indicateur primaire qui était le délai avant l’observation
d'une amélioration clinique. Après un suivi de 44 semaines, la majorité des patients dans les deux groupes avaient atteint le seuil d'amélioration prédéterminé. Les preuves issues d'un petit nombre de séries de cas concernant l’amélioration clinique sont inconstantes. Certains patients ont connu une amélioration modeste.

**Polyneuropathie inflammatoire démyélinisante chronique**

Des données probantes d'un niveau extrêmement faible tirées d'études non contrôlées suggèrent que le rituximab peut mener à une amélioration clinique chez les patients atteints de PIDC, les résultats variant d'une amélioration modeste à une rémission.

**Innocuité**

Des effets indésirables ont été rapportés dans toutes les séries de cas de personnes atteintes de MG, DM et PIDC et dans tous les rapports complets de séries de cas de NOA. Des décès pendant le traitement ont été rapportés chez des patients atteints de NOA et de DM, et des hospitalisations causées par des infections ont été rapportées chez des patients ayant de la MG, de la NOA et de la DM. En raison de la faible quantité de données disponibles, il est difficile d'évaluer l'augmentation du risque d'effets indésirables attribuables au rituximab.

**RECOMMANDATIONS**

Les données probantes actuellement disponibles sont en quantité et qualité insuffisantes pour recommander l'utilisation routinière du rituximab pour le traitement de l’une ou l’autre de ces quatre maladies.

Les preuves disponibles sont suffisantes pour soutenir l'utilisation du rituximab comme traitement d’un nombre limité de patients, tel que décrit ci-bas.

**Myasthénie gravis**

Les preuves sont suffisantes pour soutenir une approbation temporaire et conditionnelle du rituximab pour le traitement de patients atteints de myasthénie gravis répondant aux critères suivants :

- patients hospitalisés dont la maladie est réfractaire aux autres traitements;
- patients hospitalisés dont les options de traitement sont limitées en raison d'une intolérance ou de contre-indications aux thérapies plus courantes;
- patients requérant l'utilisation fréquente (plus fréquente qu’aux dix jours) d'IgIV ou de PE;
- le nombre de nouveaux patients traités par an sera limité à 10.
Puisque les preuves disponibles concernant l'utilisation du rituximab sont limitées, toutes les données pertinentes concernant ces patients devraient être collectées et maintenues dans un registre régulièrement mis à jour. Il devrait contenir les informations sur le diagnostic, les raisons du traitement, la symptomatologie avant et après le traitement, la posologie et les effets indésirables.

Les données de ce registre devraient être analysées lorsque nécessaire, au plus tard dans deux ans, et la question de l'approbation permanente devrait alors être considérée.

**Neuromyélite optique aiguë**

Les preuves sont suffisantes pour soutenir une approbation temporaire et conditionnelle du rituximab pour le traitement de patients atteints de neuromyélite optique aiguë répondant aux critères suivants :

- patients ayant un diagnostic de NOA positive pour les IgG ayant connu une récidive grave ou plus;
- le nombre de nouveaux patients traités par an sera limité à trois.

Puisque les preuves disponibles concernant l'utilisation du rituximab sont limitées, toutes les données pertinentes concernant ces patients devraient être collectées et maintenues dans un registre régulièrement mis à jour. Il devrait contenir les informations sur le diagnostic, les raisons du traitement, la symptomatologie avant et après le traitement, la posologie et les effets indésirables.

Les données de ce registre devraient être analysées lorsque nécessaire, au plus tard dans deux ans, et la question de maintenir l'approbation ou de la rendre permanente devrait alors être considérée.

**Dermatomyosite**

Il n'y a pas suffisamment de preuves pour justifier l'utilisation du rituximab pour traitement de la dermatomyosite dans un contexte autre que le cadre d'un projet de recherche formel.

**Polyneuropathie inflammatoire démyélinisante chronique**

Il n'y a pas suffisamment de preuves pour justifier l'utilisation du rituximab pour traitement de la PIDC dans un contexte autre que le cadre d'un projet de recherche formel.
Recommandation générale

Traiter les patients atteints de maladies rares telles que la MG et la NOA sans recueillir, coordonner et publier les résultats constituerait un grave gaspillage d’opportunités et des ressources. En conséquence, tous les efforts doivent être faits pour inciter des collègues des institutions partenaires à contribuer à un protocole de traitement et documentation des résultats qui permettrait de recueillir, accumuler et publier des informations significatives concernant les bénéfices et les indications de l’utilisation du rituximab.
The effectiveness and safety of rituximab (anti-CD20) in autoimmune diseases

1. BACKGROUND

Rituximab is a chimeric monoclonal antibody directed at the B-cell surface marker CD20. Its exact mechanism of action is unclear, but its biological effect is to deplete B-lineage white cells that express CD20 (pre-B cells to lymphoplasmacytic cells), through a combination of direct signaling, complement dependent cellular cytotoxicity and antibody dependent cellular cytotoxicity. For most patients, depletion lasts 6 to 12 months. Rituximab is effective in the treatment of B-cell malignancies, but has also received regulatory approval for the treatment of refractory rheumatoid arthritis (RA), Wegener’s granulomatosis and microscopic polyangiitis. It has been used off-label in the treatment of a number of other autoimmune diseases, particularly in patients whose disease is unresponsive to or who have unacceptable toxicity from prednisone and immunosuppressants.

The Technology Assessment Unit (TAU) was asked by Céline Dupont, Secretary of the MUHC Pharmacy and Therapeutic committee (P&T) to review the efficacy and costs of use of rituximab in four rare autoimmune diseases (myasthenia gravis, neuromyelitis optica, dermatomyositis, and chronic inflammatory demyelinating polyneuropathy) and to develop recommendations concerning its use in the MUHC.

The methods of the review are described in Section 3, and the background and literature results for rituximab in each individual disease in the following sections: Myasthenia gravis, Section 4; Neuromyelitis optica, Section 5; Dermatomyositis, Section 6; Chronic inflammatory demyelinating polyneuropathy, Section 7.

2. OBJECTIVE(S)

- To assess evidence for the efficacy and safety of rituximab in the four indications listed above
- To determine the direct costs of use of rituximab
- To develop recommendations for the use of rituximab therapy in the MUHC
3. METHODS

3.1. Literature search and quality assessment

3.1.1. Databases, key terms/words, and filters

Because of the paucity of available evidence and the limited number of cases reported, we included data derived from abstracts as well as from complete reports, except where otherwise noted.

The Cochrane Collaboration and the Centre for Research and Dissemination (CRD) Databases were searched from inception to April 12, 2012, for systematic reviews, health technology assessments and economic assessments, using keyword “Rituximab” and review of the retrieved titles. The Cochrane Collaboration Clinical Trial registry was searched from inception to April 12, 2012 using the keyword “Rituximab” in combination (AND) with terms for each of the conditions of interest. The search was updated to October 15, 2012.

PubMed (inception to April 12, 2012), OVID EMBASE (1966 to 2012 Week 16), and ISI Web of Science to April 12, 2012 were searched using keywords “Rituximab” as a text term and mapped to subject headings in combination (AND) with terms for the conditions of interest. The PubMed search was automatically updated weekly, with emailed results via the MyNCBI service, and the searches for the other databases were updated to October 15, 2012.

Exploratory searches did not suggest any additional value in using alternative terms for rituximab (eg, Rituxan, MabThera) in the major databases which allowed for keyword mapping. If keyword mapping was not available, then the search incorporated alternative terms.

The conditions of interest were: myasthenia gravis, neuromyelitis optica, dermatomyositis (also searched for as “inflammatory myopathy” or “myositis” or “polydermatomyositis”), and chronic inflammatory demyelinating polyneuropathy (also “chronic inflammatory demyelinating polyneuritis”, “CIDP”, and “inflammatory neuropathy”). Searches included mapping to subject headings (where offered) and text words.

There were no language restrictions, but review of non-English or non-French language papers were limited to those that provided an English or French abstract.

Two authors (AS, IN) searched for and selected papers, and then reconciled their selections and identification of duplicates by discussion.

3.1.2. Inclusion/exclusion criteria

Papers/abstracts were retrieved for full-text review if their title suggested that they described one or more instances of patients treated with rituximab. Narrative reviews or conference summaries were retrieved for review of their citation lists. We
identified duplicate reports on the basis of included patient details, authorship and institutions.

3.2. Data extraction

For all case series/open label trials, we extracted the following (subject to variation in reporting):

- Any statement as to completeness of reporting, eg, all cases at a given centre, or within a given region or country
- Study design (prospective versus retrospective)
- Summary demographic information, time since diagnosis, antibodies, comorbidities, prognostic indicators
- Stated reasons for rituximab treatment (and therefore inclusion in the series), including any definition of “refractory” disease
- Prior treatments
- Dose and schedule of rituximab administration, number of repeat treatments, indication for retreatment
- Other treatments administered concurrently with rituximab
- Patient outcomes (disease scales before and after treatment, disability before and after treatment, reduction in medications)
- Length of follow-up, time-points for assessment
- Summary deaths, treatment discontinuations, and adverse events

From all case reports:

- Demographics, time since diagnosis, comorbidities
- Prior treatments
- Dose and schedule of rituximab treatment, number of pre-treatments and the reason for them
- Patient outcomes
- Deaths and adverse events

Two authors (AS, IN) independently extracted outcome data, and one author (AS) extracted study and demographic details, while the second author checked the data.

3.3. Summary of evidence

We tabulated study characteristics, patient characteristics, inclusion criteria (if any), definition of refractory disease (if appropriate), prior treatments, dosing schedule, disease status before and after treatment, and adverse events.

The inclusion of individual patient data in the case series for MG and NMO allowed for a simple, descriptive pooled summary of patient demographics, treatment cycles, status before and after treatment, and prior medications. Given the variability of dosing schedules, including the mixture of re-dosing upon schedule and re-dosing
upon relapse, we compared the status at first treatment with the status at end of follow-up.

### 3.4. Cost analysis

Given the small number of patients and the individual management required, we could not construct a comprehensive patient flow model for any of the four diseases. Instead, we estimated the direct cost impact of rituximab when used for a brief therapeutic trial, or when used for a two-year maintenance programme for patients with MG. We also estimated the potential impact on net costs in situations in which costly treatment could be reduced or eliminated by use of rituximab.

The inputs and results are described in Section 9 and Appendix 1. As costs were calculated over 2 years only (the planned duration of rituximab), costs were not discounted.

### 4. RITUXIMAB IN MYASTHENIA GRAVIS

#### 4.1. Myasthenia gravis background

Myasthenia gravis (MG) is an antibody-mediated autoimmune disorder of the neuromuscular junction (NMJ, the structure that transmits the electrical impulse from the nerve to the muscle cell)\(^6\)\(^7\), with an estimated prevalence of around 20 per 100,000 people\(^7\). The binding of pathogenic auto-antibodies to the acetylcholine receptor (AChR) or other proteins in the NMJ results in damage to and remodelling of the NMJ, and weakens nerve to muscle transmission. This manifests as muscle weakness that worsens with repeated effort, and which can affect walking, swallowing and breathing, to the point that a severely affected patient may become dependent on a ventilator\(^7\).

Various subtypes of MG have been identified, depending upon age of onset (before or after age 40), presence of pathogenic antibodies (anti AChR or anti muscle specific receptor kinase [MuSK]), presence of thymoma, or pattern of muscle weakness (isolated ocular, bulbar, or limbs)\(^7\). These differ in severity, prognosis, and response to treatment. Later onset, presence of thymoma, and MuSK antibodies are associated with more severe disease\(^7\). Patients with MuSK-antibody positive MG have a poorer response to anticholinesterase inhibitors (which give symptomatic relief without modifying the disease course), are more likely to develop respiratory failure, and are more likely to require longer-term immunosuppression\(^8\). Recent research has identified MuSK as an antibody to a protein that tethers the AChR to the membrane\(^7\).

In a large cohort of patients with MG followed from 1940 to 2000, the majority of patients developed their most severe symptoms within the first 2 years\(^9\). Nineteen percent required intubation, but following the introduction of respiratory intensive
care, these exacerbations were rarely fatal. In the overall cohort, the majority of those who survived the first two years either improved (57%) or entered remission (13%), while 20% remained unchanged and 4% worsened.

First line treatment for MG is with oral anticholinesterase inhibitors, which prolong the action of acetylcholine by inhibiting its degradation, with corticosteroids and other immunomodulators (azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus) used for long term disease control. Plasmapheresis, which removes pathogenic antibodies by filtration, produces rapid improvement in most patients and is used in myasthenic crisis. IV immunoglobulin, which removes pathogenic antibodies by binding to them, is used as a treatment for exacerbations.

The minority of patients with severe disease refractory to multiple agents, or who have unacceptable side effects with other modalities, are candidates for treatment with rituximab.

### 4.2. Efficacy of rituximab in myasthenia gravis

We did not find any systematic reviews, health technology assessments, or randomized controlled trials of the use of rituximab in MG. One non-systematic review (2010) collected 53 cases from case series and case reports. Thus the evidence was limited to case series and case reports describing the use of rituximab largely in refractory MG, and patients recorded in national registries. Study design of and efficacy of rituximab in case series (as described in both full text and abstracts) are tabulated in Table 1 (study design) and Table 2 (efficacy) at the end of this document, and discussed in the Section 4.2.1. Data from full reports that included individual patient data were extracted and summarized (Section 4.2.2). Results from case reports are briefly summarized in Section 4.2.3.

#### 4.2.1. Rituximab in myasthenia gravis: case series

**Results of literature search.** We found 19 reports (articles and abstracts) which described case series of five or more patients treated with rituximab for MG. We could not obtain a copy of one abstract. Elimination of duplicates left ten reports of non-overlapping series of patients (summarized in Table 1 and Table 2). Of these, seven series have been reported in full and three in abstract (one with the corresponding poster available for review). One of the series has recently been updated in abstract.

**Outcomes reported.** Reported outcomes varied, with some studies reporting individual symptoms before and after treatment, and others capturing changes according to disease scales. The most frequently used scale was the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification and Postintervention status. The MGFA clinical classification constitutes Classes I through V, in order of increasing severity from isolated eye muscle weakness to a need for intubation (with or without assisted ventilation). Classes II through IV are subdivided into a and b, where b describes patients with bulbar symptoms, difficulty in speaking and
swallowing, and describes patients without bulbar symptoms. The MGFA Postintervention Status classifies patients according to their clinical status (absolute or changed from baseline) and requirements for maintenance therapy. The Quantitative Myasthenia Gravis (QMG) Score is a numeric scale where 13 items on the neurological exam are scored from 0 to 3, to a final score of 0 to 39, with higher scores indicating more severe disease.

**Rituximab regimen.** There was no standard rituximab regimen (Table 1). The initial dosing in most studies, particularly the earlier ones, reflected the standard dosing for lymphoma, with 4 doses of 375 mg/m² (dosed according to body surface area, around 1.7 m² in an adult) given weekly followed by 1 to 2 scheduled maintenance doses of 375 mg/m² to be given at monthly, three-monthly, or 6-monthly intervals. Three studies used a dose regimen more consistent with that approved for RA, 0.5 to 1.0 g, given twice, two weeks apart. Several studies specified administration of additional cycles upon clinical deterioration, with or without B-cell recovery. In addition, patients received a variety of concomitant medications, during treatment with rituximab, including anticholinesterase-inhibitors, prednisone and immunosuppressants (until response allowed tapering), and premedications recommended to reduce the risk of rituximab infusion reactions.

**Number of patients.** The number of patients in each study ranged from five to 20, to a total of 112. The seven studies reported in full were retrospective and the three reported in abstract, prospective. In eight studies, the indication for rituximab treatment was defined as refractory disease (Definitions supplied in Table 1), with or without intolerance of standard treatments; the others did not specify.

### 4.2.2. Summary of individual patient data from case series

The seven full reports included plots and tabulations of demographics and prior disease and treatment characteristics for 88 patients (Table 2), allowing for a descriptive summary of these data. Five of these reports stated that the investigators included all MG patients who had been treated with rituximab within a given geographical area and time-interval, and one selectively reported a subset of all such patients with MuSK antibody. The coverage of the seventh report was unclear, but it was a multicenter study, therefore we deemed it likely to include a complete set of patients, and included it. Three patients were excluded from the patient summaries: one juvenile, and two with Lambert-Eaton myasthenic syndrome, bringing the total to 85.

**Baseline and demographics.** The majority of rituximab-treated patients had severe disease with bulbar symptoms: MGFA Class IIIb 16/85 (18.8%), IVb 38/85 (44.7%), and V 9/85 (10.6%). MGFA Class was not reported for 25/85 (29.5%) patients, but for the 5 patients from Lindburg et al, 2010, and 6 patients from Nowak et al, 2011, we used the MGFA clinical classification estimated by Benveniste and Hilton in their review of this literature. The median age was 48 years (range 14 to 83 years), 64/85 (75.3%) were female, and the median disease duration was 6 years
Rituximab in neurological diseases

(range 0 to 45 years). The majority of patients had AChR antibodies 51/85 (60.0%), compared with 30/85 (35.3%) for patients with MuSK antibodies, and one patient with both. In the overall MG population, 80-90% have AChR antibodies, and of the remainder, 40-70% are positive for MuSK antibodies. Patients with MuSK antibodies tend to respond more poorly to standard therapies, so are overrepresented amongst refractory patients.

**Previous therapies.** All previous therapies were reported for six of the published series. For the seventh, all previous therapies were available for 6/17 patients from an earlier publication, while only concurrent therapies were reported for the remaining 11. Patients received a mean 3.7 (range 1 to 8) different treatments prior to rituximab, with the most common being prednisone (82/85, 96.5%) and azathioprine (51/85, 60.0%). Thymectomy was reported in 49/85 (57.6%) patients. Thirty-one (31/85, 37.6%) and 26/85 (30.6%) patients had previously received IVIg and PE, respectively.

**Outcomes.** Four studies reported post-treatment status according to the post-treatment MGFA, and one study reported post-treatment status according to the MGFA Clinical Class, from which post-treatment MGFA could be estimated. For the patients from Lindburg et al, 2010, and 6 patients from Nowak et al, 2011 who had been previously reported, we used the post-treatment MGFA estimated by Benveniste and Hilton for their review. Patients with estimated outcomes could not be assessed as being in pharmacologic remission (PR) or having minimal manifestations (MM), because there was no information about their maintenance treatments; they were therefore categorized as improved (I). Of the 77 patients with quantifiable outcomes, 69 (89.6%) showed clinical improvement (classified as CSR, PR, MM, or I) and 8 (10.4%) were unchanged or worse at the end of follow-up; of the latter, one patient died of worsened disease. Figure 1 shows the outcome at the end of follow-up, with the pre-treatment status indicated by shading. There was no obvious relationship between status before treatment and status at follow-up.
Figure 1  Post-treatment MGFA at end of follow-up for MG patients treated with rituximab, with pre-treatment status indicated

Post-treatment MGFA classifications: CSR, complete stable remission (asymptomatic and off medication); PR, pharmacologic remission (asymptomatic, still requires medications); MM, minimal manifestations (includes MGFA categories MM1, MM2, and MM3; some residual weakness, still requires medications); I, improved (clinically improved and/or medications reduced); U, unchanged; W, worsened; X, died. NR, not reported.

Plots of patient characteristics (not shown) versus dichotomized outcome (improved versus unchanged/worsening) did not show any readily apparent relationship between outcome and age, disease duration, and sex. However, all 21 patients with MuSK antibody improved, while only 40/48 (83.3%) of patients with AChR antibody improved and 8/48 (16.7%) remained unchanged or worsened.

Effects on medications. We were interested in changes in treatment resulting from the use of rituximab, particularly the effect on the more costly and inconvenient treatments of plasmapheresis and IVIg. While the majority of publications reported the use of anticholinesterase inhibitors and immunosuppressants (including prednisone) before and after rituximab, the effect on IVIg dosing and need for PE was reported for only two case series and a subset of a third. In Blum et al, 2011, 6/9 patients requiring regular IVIg had a dose reduction of 50%, two had no change, and one had an increase of 100%, since IVIg was used to treat an exacerbation. Dose and schedule were not specified. Two patients were receiving regular PE, which was stopped after rituximab. Nowak et al, 2014, reported that 12 of their 14 patients received a median 7.5 cycles of PE (range 0 to 34) in the 12 months prior to
rituximab, which decreased to a median 0 cycles of PE (range 0 to 19) during follow-up of a minimum of 12 months. Nine of 12 patients were able to discontinue PE after the first cycle of rituximab, and the remainder could discontinue after the third (18 months). Collongues et al, 2012\textsuperscript{13}, did not summarize the use of IVIg and PE for patients in their case series, but an earlier report by Lebrun et al, 2009\textsuperscript{20}, which described six of these patients, indicated that prior to rituximab four patients required regular PE and all six patients required regular IVIg, and after rituximab treatment these therapies were stopped. Dose and schedule were not specified.

4.2.3. Rituximab in myasthenia gravis: case reports

In addition to the case series described above, 38 case reports were retrieved, of which two appeared to be duplicate publications. We could not retrieve two reports\textsuperscript{33,34}, leaving 34 reports\textsuperscript{32,35-67} (24 full reports and 10 in abstract) of one to three patients, for a total of 48 patients. Patients received rituximab because of disease refractory to other immunosuppressants, contraindications or intolerance to treatments, or as treatment for a comorbid condition (eg, B-cell malignancy\textsuperscript{42,57,62} or rheumatoid arthritis\textsuperscript{46,66}). Nearly a half of the patients (20/48) had anti-MuSK antibodies. Several had comorbid autoimmune disorders, including rheumatoid arthritis\textsuperscript{46}, systemic lupus erythematosus\textsuperscript{52}, CIDP\textsuperscript{58} and Morvan’s syndrome\textsuperscript{39,58,65} (antibody to voltage-gated potassium channels). Responses to rituximab in paraneoplastic MG\textsuperscript{53}, HIV-associated MG\textsuperscript{49}, MG with methotrexate-associated lymphoma\textsuperscript{64}, and MG post bone-marrow transplant\textsuperscript{67} were also described.

Treatment regimens varied but were similar to those used for the case series. In most cases these consisted of four weekly doses of 4 cycles of 375 mg/m\textsuperscript{2}, including patients who received rituximab as part of chemotherapy for lymphoma. In a few cases, follow-up maintenance dosing was according to schedule, but in the majority, re-treatment was according to clinical need. Follow-up periods ranged from around 6 months to >3 years.

With the exception of three patients\textsuperscript{48,51,62}, one of whom had well-controlled symptoms that remained unchanged during treatment for follicular lymphoma\textsuperscript{62}, all patients responded to rituximab. Eighteen patients were described at the end of follow-up (which may have included retreatment for one or more relapses) as having complete remission, being MGFA Class I, being in remission, or being asymptomatic (with or without medications). The majority of patients were also able to reduce or discontinue other medications, including ten who were described as having stopped scheduled or frequent PE, and seven who had stopped IVIg. Results were not available for 2 patients. The probability of publication bias in these reports, ie, the increased tendency to publish favourable cases, must be noted.

4.2.4. Rituximab in myasthenia gravis: registry studies

In the German Registry of Autoimmune Diseases (GRAID)\textsuperscript{68}, baseline and outcome data were available for four of five MG patients who received rituximab prior to
September 2008, two of whom had complete response to rituximab, and two, partial response (by investigator judgement).

4.3. Safety of rituximab in myasthenia gravis

In the accumulated case reports and case series described above, covering 161 patients, one patient died of heart failure considered unrelated to rituximab, two patients had a serious adverse event related to rituximab use, and there were 17 non-serious adverse events (some patients contributed more than once to this last category). Safety reports for myasthenia gravis are summarized in Table 3.

Both serious adverse events were infectious: One patient, aged 29 years, developed agranulocytosis, leucopenia, and pneumonia one month after receiving rituximab for a relapse (two doses of 1000 mg each), and being started on mycophenolate mofetil (2 g/day)\textsuperscript{22}. After recovery, the patient remained symptom-free for a follow-up of 5 years. One patient was admitted to hospital with spondylodiscitis one year after rituximab\textsuperscript{12}.

A 62 year-old man with a history of Waldenstrom's macroglobulinemia and lymphoplasmocytic lymphoma prior to developing MG was reported as having discontinued rituximab due to a severe allergic reaction\textsuperscript{57}. Overall, 16 patients experienced an infusion reaction, and four developed an infection, two of whom required hospitalization.

The majority of safety reports came from the case series, while the case reports frequently omitted any mention of safety, even to indicate that there were no significant adverse events; therefore it is likely that less severe adverse events were under-reported.

Four of the five MG patients reported to the GRAID registry (prior to 2008)\textsuperscript{68} had an infection, and two of those had a severe infection. This appeared to be higher than for other diseases in the registry, but the numbers were small and the authors could not determine whether this elevation was statistically significant. The observation period was short, 2.7 years, and the authors noted that the majority of infections occurred within the first seven months after rituximab.

4.4. Ongoing studies of rituximab in myasthenia gravis

Two trials are recorded as ongoing, although one was reported in abstract in 2008\textsuperscript{24}, and is no longer recruiting (“A pilot trial of Rituxan in refractory myasthenia gravis” NCT00619671). The second, “Rituximab for the treatment of refractory inflammatory myopathies and refractory myasthenia gravis” (FORCE, NCT00774462), aims to recruit 12 patients with MG.

4.5. Summary of rituximab in myasthenia gravis

Efficacy. The majority of patients with MG treated with rituximab had clinical improvement: 69/77 (89.6%) patients with individual outcomes reported in the case
series, and 29/34 (85.3%) patients in case reports. Most of these patients had severe disease (MGFA Class IV and V) that responded poorly to multiple standard therapies, or were dependent on frequent re-treatment with IVIg or PE. About one third of the patients in the case series and half of those in the case reports were asymptomatic or had minimal manifestations of disease at last follow-up. Use of IVIg or PE was markedly reduced in those studies that documented it: 12/15 patients receiving IVIg (2 case series) and 18/18 patients receiving PE (3 case series) ultimately discontinued PE. However, we must note that such results (85-90% response rates) reflect the results seen in individual case reports and small case series and cannot be assumed to reflect the possibility of such outcomes in general.

**Safety.** Two patients were hospitalized with infections and one patient had to discontinue treatment due to an infusion reaction. There were no adverse events of an unexpected type. Given the small number of patients, and the risk of infection associated with severe disease itself (e.g., risk of pneumonia increased by bulbar weakness), it is difficult to assess the attributable risk of infection due to rituximab.

### 5. RITUXIMAB IN NEUROMYELITIS OPTICA

#### 5.1. Neuromyelitis optica background

Neuromyelitis optica (NMO, also known as Devic’s disease) is an idiopathic inflammatory demyelinating disease of the central nervous system (CNS), which has only recently been fully characterized as an entity distinct from multiple sclerosis. Its estimated prevalence is below 5 per 100,000 people, it predominately affects women, and it is more prevalent in non-Caucasian populations. NMO presents as recurrent transverse myelitis (inflammation of the white matter of the spinal cord, sometimes extending into the brainstem) and optic neuritis (inflammation of the optic nerve). In contrast to MS, lesions tend not to develop in the brain itself, particularly early in disease evolution. The presence in serum of an antibody to aquaporin-4, NMO-IgG/AQP4 supports the diagnosis in a patient with clinical symptoms of NMO, and appears to predict a more severe course and poorer outcome.

Wingerchuk et al, 1999, described the clinical course for 71 patients followed between the years 1950 to 1997 at the Mayo Clinic. In their cohort, individual relapses were characterized by development of maximal neurological deficit over days, followed by incomplete resolution over weeks to months, usually with some residual deficit. Morbidity and mortality were high. Fifteen of their 71 patients died of neurogenic respiratory failure from myelitis extending into the brainstem, and >50% became blind in one or both eyes or were no longer able to walk independently by the end of 5 years. Reviewing the characteristics of the disease, Wingerchuk estimated that the majority of patients with NMO (80-90%) have relapsing disease,
with frequent severe relapses early in their disease course (90% of patients will relapse within 3 years of their initial presentation) resulting in early accumulation of disability. A severe initial presentation and frequent initial relapses independently predict a poor prognosis. The remaining patients have a monophasic course, with an initial, often severe, incident presentation and no relapses over the course of follow-up. Few NMO patients followed a secondary progressive course, unlike those with MS.

Initial and acute attacks are treated with high-dose methylprednisolone (2009 recommendations), with subsequent oral taper. Plasmapheresis has been shown to benefit patients with severe symptoms who do not respond to corticosteroids. Maintenance therapy with oral prednisone and azathioprine has been shown to reduce the frequency of attacks. Patients with NMO with positive NMO-IgG antibody and one or more severe relapses would be considered for rituximab treatment (Dr. Amit Bar-Or, personal communication).

5.2. Efficacy of rituximab in neuromyelitis optica

We found one treatment guideline, from the European Federation of Neurological Societies (EFNS), which included a recommendation on rituximab. We did not find any systematic reviews, health technology assessments, or randomized controlled trials of the use of rituximab in NMO, although we found several narrative and non-systematic reviews of case series and case reports. The case series and case reports are described below. Design of and efficacy of rituximab in case series (full text and abstracts) are tabulated in Table 4 and Table 5, respectively, at the end of this document, and discussed in Section 5.2.1. Data from full reports that included individual patient data were extracted and summarized (Section 5.2.2). Results of case reports are briefly summarized in Section 5.2.3.

5.2.1. Rituximab in neuromyelitis optica: case series

Results of literature search. Twenty-six articles or abstracts described case series of five or more patients treated with rituximab for NMO. Elimination of duplicates reduced this number to nineteen reports of non-overlapping series of patients, although one additional abstract (Kim et al, 2012) was retained as it added a significant number of patients to the previous full report (Kim et al, 2011). Five abstracts did not include outcome data. Of the other fifteen, seven studies were reported in full and eight in abstract (summarized in Table 4 and Table 5).

Outcomes reported. In the absence of a standardized scale for NMO, disease severity was measured in terms of frequency of exacerbations and disability. The definition of what constituted an exacerbation varied across studies (Table 4). Disability was captured according to the Expanded Disability Status Scale, which assesses disability due to multiple sclerosis in 0.5 point increments on a scale of 0 (normal neurological exam) to 10 (death from MS).
Rituximab regimen. As was the case for MG, there was no standard treatment regimen. Three studies used the RA dosing regimen, four used both the lymphoma and the RA regimens, usually starting with the lymphoma regimen for earlier cases or initial treatment, and moving to the RA regimen for later cases or re-treatment. Protocols for re-treatment also varied, within and between studies. With experience, some investigators shifted from dosing in response to relapses or CD19 cell recovery to scheduled dosing in an attempt to prevent relapse. Two abstracts did not describe the dosing regimen. Patients also received a variety of concomitant medications, during treatment with rituximab including prednisone and immunosuppressants, and premedications recommended to reduce the risk of rituximab infusion reactions.

5.2.2. Summary of individual patient data from case series

Baseline and demographics. Seven case series\textsuperscript{74,76,77,80,84,93,94} were reported in full and included individual patient data for 114 patients 14 years and older. In six of these seven series, age of rituximab initiation was either reported in the study, or could be calculated from available information. Patients were a median 40 years old when they first received rituximab (range 14 to 70 years), and the majority was female, 100/114 (88\%). The observation time before rituximab, which for most patients represented the duration of disease, was a median 35.9 months (range 2 to 262 months).

Prior to rituximab initiation, patients had a median 1.8 relapses/year (mean 2.4 relapses/year), with the rates for individual patients ranging from 0.13 to 12 relapses/year. Both duration of prior observation (an estimate of disease duration) and relapse rate varied considerably across studies, with median relapse rates ranging from 0.72 (Bedi et al, 2011\textsuperscript{74}, n=23) to 7.20 (Lindsey et al, 2012\textsuperscript{84}, n=9). Relapse rate alone does not capture the nature and severity of relapses, which, where they were described, covered the range of manifestations of disease, from loss of sight in one or both eyes, to quadriplegia, to respiratory failure. Figure 2 shows the relapse rate in individual patients before and after administration of rituximab, including the variation in duration of observation, suggesting that those patients with the highest relapse rates prior to rituximab tended to have shorter periods of observation.

As relapse rate has been reported to decrease over time we also summarized reported relapse rate in the 24 months prior to treatment, which produced similar values, with a median of 1.5 relapses/year, mean of 1.7 relapses/year, and range for individual patients of 0 to 8.0 relapses/year.
Outcomes. Patients were followed for a median of 24 months (29/30 patients in the prospective observational study by Kim et al\textsuperscript{76} had a mandated 24 months). During follow-up, the reported rate was a median 0 relapses/month (mean 0.5 relapses/month), range for individual patients 0 to 15.6 relapses/year (the latter in a patient with very short follow-up time). This, too, varied across the seven studies, with medians ranging from 0 (each of Bedi et al, 2011, n=23; Ip et al, 2012, n=7, and Pellkofer et al, 2011, n=10) to 1.2 (Lindsay et al, 2012, n=9). The majority of patients experienced less frequent relapses following rituximab treatment, 104/114 (91%).

Prior to rituximab treatment the median EDSS was 6 (mean 5.4), with individual patient scores ranging from 0 to 9.5. Following rituximab, the median EDSS improved to 3.5 (mean 4.4), with individual patient scores ranging from 0 to 10. Forty-one patients had missing assessments.

Not all papers reported prior use of medications, including IVIg and plasmapheresis, and none compared the need for IVIg/PE before and after rituximab administration.

5.2.3. Rituximab in neuromyelitis optica: case reports

In addition to the case series above, we retrieved sixteen case reports\textsuperscript{99-115} (ten full reports, six abstracts) of the use of rituximab in patients with NMO. Elimination of duplicates left 14 reports. Of these, one abstract did not report specific outcomes\textsuperscript{101}. 
and one article described NMO developing as a potential adverse event of rituximab treatment for malignancy\textsuperscript{111}. Four additional case reports detailing treatment with an alternative experimental therapy listed rituximab amongst the failed therapies\textsuperscript{116-119}.

Of the 13 patients treated with rituximab whose outcomes were reported in detail, eight showed clinical improvement, and five either did not improve or worsened. One patient, whose diagnosis was recent, had a complete remission\textsuperscript{104}, while patients whose disease was longstanding had more limited improvement, perhaps reflecting pre-existing damage from the disease. Two patients who experienced frequent relapses while receiving rituximab had an overlap diagnosis of SLE\textsuperscript{112,113}; one of these stabilized with addition of methotrexate\textsuperscript{112}. In addition to these, rituximab was listed as a failed therapy in nine patients described in four case reports dedicated to other experimental therapies\textsuperscript{116-119}.

5.2.4. \textit{Rituximab in neuromyelitis optica: registry studies}

The German national registry (GRAID) collected data on neuromyelitis optica, but reported it in the same category with multiple sclerosis\textsuperscript{68}, therefore the results from that category would predominately be reflective of multiple sclerosis.

5.2.5. \textit{Rituximab in neuromyelitis optica: treatment guidelines}

On the basis of case series data and expert opinion, the European Federation of Neurological Societies (EFNS), included the recommendation that rituximab be considered as first-line treatment for preventing relapses in NMO\textsuperscript{69}.

5.3. \textbf{Safety of rituximab in neuromyelitis optica}

In the accumulated case series and case reports reported above, covering 162 patients, five patients died, two of NMO relapse and three of infection, five experienced a serious adverse event, three of which were possibly related. Thirty-nine additional adverse events were reported (it is likely that some patients contributed more than once to this category). Safety reports for neuromyelitis optica are summarized in Table 6.

Two patients died of NMO relapse following rituximab treatment, both at 9 months post-treatment\textsuperscript{77,84}. Three patients died of infectious complications: A 47 year-old woman with NMO and comorbid Sjögren’s disease died of cardiovascular failure, following urogenital infection and thrombosis, about 17 days after the start of rituximab\textsuperscript{80}. A 53-year-old woman died of suspected sepsis six months after receiving rituximab\textsuperscript{77}. At autopsy she had confluent demyelination from the lumbar to cervical level, and bilaterally atrophic optic nerves. The third patient\textsuperscript{79}, reported in abstract, died of recurrent pneumonia, leucopenia, and sepsis (timing related to rituximab administration unknown).

Five patients experienced serious adverse events other than death, three of which were possibly related to rituximab. A 35-year-old woman with a 3-year history of
NMO developed a posterior reversible encephalopathy syndrome 24 hours after rituximab infusion\textsuperscript{111}, which resolved with discontinuation of rituximab and supportive care. Prior to her death from NMO (referred to above), a 43-year-old woman had recurrent \textit{Clostridium difficile} colitis and urinary tract infection\textsuperscript{77}. A third patient discontinued rituximab due to an AE of severe bedsore\textsuperscript{79}. Overall there were 32 reports of infection (three fatal and 2 serious) and 19 infusion reactions.

5.4. Ongoing studies of rituximab in neuromyelitis optica

We did not identify any ongoing studies of rituximab in neuromyelitis optica.

5.5. Summary of rituximab in neuromyelitis optica

\textit{Efficacy}. The majority of patients with NMO had clinical improvement following treatment with rituximab, as measured by frequency of relapse and disability. In the case series, 104/114 (91\%) patients had less frequent relapses. The median number of relapses during the pre-treatment observation period was 1.8 per year, and in the post-treatment observation period was 0. A small number of patients worsened, with more frequent relapses. In the case reports, 8/20 patients were reported as having improved with rituximab.

\textit{Safety}. Five of 162 patients died, two of severe NMO relapse and three of infection, and three patients were hospitalized due to possibly related adverse events (two infections). There were no adverse events of an unexpected type. Given the small number of patients, and the morbidity and mortality of the disease itself, it is difficult to assess whether rituximab increased the risk of death or hospitalization.

6. RITUXIMAB IN DERMATOMYOSITIS

6.1. Dermatomyositis background

Dermatomyositis (DM) is an idiopathic inflammatory disease of skin and smooth muscle\textsuperscript{120,121}, with an estimated prevalence of around 5 per 10,000 people overall\textsuperscript{122}. Based on data from Quebec billing and hospitalization databases for 2003, and with statistical adjustment for diagnostic uncertainty, the combined prevalence within Quebec of DM and the related myopathy polymyositis (PM) was estimated to be 21.5 per 100,000 (95\% credible interval 19.4 to 23.9)\textsuperscript{123}.

The clinical definition of DM includes photosensitive skin rash in a characteristic distribution over the face, upper body and hands (which may precede other symptoms), muscle weakness that may be severe enough to leave the patient bedridden and may extend to the respiratory and esophageal muscles\textsuperscript{120,121}. Extramuscular interventions include cardiac arrhythmias from conduction disturbances and interstitial lung disease. Serum muscle enzymes are often elevated and muscle biopsy shows muscle cell destruction, necrosis and regeneration, with
mononuclear cell infiltrates. Many patients have antibodies against muscle cell components, but a characteristic pattern has yet to be identified. A subset of DM patients also meet some or all of the diagnostic criteria for other autoimmune diseases (eg, scleroderma or mixed connective tissue disease). In addition, up to a third of DM patients are subsequently diagnosed with cancer. Disease-related mortality for DM and polymyositis is at least 10%, primarily due to lung disease and malignancy.

According to observations of several small long-term cohorts, outcomes have improved over time, but over a third of patients remain symptomatic, with some degree of disability, despite treatment. Lung disease, older age, and cancer are associated with poorer outcomes. In one study, 5-year survival was 95% and 10-year survival 84%.

First line therapy is with high dose corticosteroids, with slow taper to prevent relapses. Immunosuppressants are used as second line therapy, with variable results. Rituximab is one of several new agents to have been tried off-label for patients with DM refractory to other treatments.

6.2. Efficacy of rituximab in dermatomyositis

We did not find any systematic reviews or health technology assessments of the use of rituximab in dermatomyositis, but one relatively large RCT, the Rituximab in Myositis (RIM) Study, has been reported in full. Fernandez et al. accumulated 49 patients with inflammatory myopathies from case series, case reports and their own practice, including 34 patients with DM, the majority of whom (around 73%) had improvement with rituximab. Design of and efficacy of rituximab in case series (full text and abstracts) are tabulated in Table 7 and Table 8, respectively, at the end of this document, and discussed in the Section 6.2.2. Results from case series are briefly described in Section 6.2.3.

6.2.1. Rituximab in dermatomyositis: clinical trials

The Rituximab in Myositis (RIM) study randomised 200 patients with adult DM (n=76), juvenile DM (n=38), and polymyositis (n=76) into “rituximab early” and “rituximab late” groups, in which the latter received rituximab eight weeks later than the former. Rituximab was given as two 1g doses, one week apart. The study was double blinded and was maintained for 44 weeks. Although 83% of all patients met the prespecified level of improvement, the primary outcome of median time from randomisation to improvement did not differ between the two groups (20 weeks versus 20.2 weeks in early and late groups respectively). Results for the adult DM subgroup alone were similar: time to level of improvement was 20.4 versus 20.3 weeks for the early and late groups, respectively. Over the course of the study the mean prednisone dosage fell from 20.8 mg per day to 14.4 mg per day, and eight of nine patients who were retreated following relapse met the improvement criteria by a median 19.9 weeks.
These results are difficult to interpret. As recognised by the authors in retrospect, for a meaningful study rituximab treatment in the late group should have been delayed by much more than eight weeks. The eight weeks duration of the placebo phase was set by consensus, and followed guidelines that suggested that eight weeks placebo treatment was the limit ethically acceptable. The authors concluded that, “While the trial itself showed no statistical difference (time to improvement) between treatment groups, the overall response rate in a group of patients with refractory myositis, the ability to taper glucocorticoid therapy, and the response to re treatment suggest that the agent had an effect but that certain aspects of the study design made identification of such an effect difficult”.

6.2.2. Rituximab in dermatomyositis: case series

Seven case series describing the use of rituximab in dermatomyositis in at least 5 patients were identified. Elimination of duplicates left four full reports of prospective case series of 4 to 8 DM patients each, to a total of 27 patients, summarized in Table 7 and Table 8. One case series included both DM and PM patients, and did not report the two separately.

Response to treatment was measured by improvement in muscle strength on manual testing or myometry and reduction in muscle enzyme levels, but there was no consensus on the definition of clinically significant change.

Most patients received the standard treatment for RA, with the exception of those in Levine 2005, some of whom received the dose for lymphoma. Only one study, Mahler 2011, included redosing upon relapse. Patients also received a variety of concomitant medications including prednisone and immunosuppressants, and premedications recommended to reduce the risk of rituximab infusion reactions.

All patients in Levine et al met the primary endpoint of ≥12% improvement in muscle strength with no need for further treatment or change in treatment. Two of five DM patients in Sultan et al, 2008, met the clinical response criteria of >15% improvement in muscle strength with >30% reduction in CPK. Three of eight patients in Chung et al, showed partial response with ≥50% reduction in muscle strength deficit and ≥50% reduction in CPK (if elevated); a further 3 showed improvement in muscle strength alone. In Mahler et al, 2011, the mean improvement in muscle strength on MMT was 7% and the median CPK was reduced by 93.2%. This last study did not report data for their 8 DM patients separately from their 5 polymyositis patients.

6.2.3. Rituximab in dermatomyositis: case reports

In addition to the case series above, we retrieved 16 individual case reports of the use of rituximab in patients with DM. Indications for rituximab treatment included refractory disease, intolerance to other treatments, and rituximab treatment for lymphoproliferative disorder. Dosing was generally by the RA protocol, frequently accompanied by IV methylprednisolone.
Of the 21 patients whose outcomes were reported, all but two showed clinical improvement in symptoms including muscle weakness, skin rash, cardiac manifestations (symptomatic arrhythmia) and chronic organizing pneumonia. One patient had clinically active disease which did not improve, and the other had good disease control but developed transplant-associated lymphoproliferative disorder following a kidney transplant\textsuperscript{142} and needed to discontinue her current regimen. Rituximab, given to treat the lymphoproliferative disorder, also appeared to control the DM.

### 6.2.4. Rituximab in dermatomyositis: registry studies

Patients with dermatomyositis have been described in reports from the Autoimmunity and Rituximab (AIR, France)\textsuperscript{150}, the GRAID (Germany)\textsuperscript{58}, and the BIOGEAS (GEAS, Study Group on Autoimmune Diseases, Spain)\textsuperscript{151} registries, either separately, or under an overall category of inflammatory muscle disorders. We cannot, however, exclude the possibility of overlap with other reports, especially case reports.

Of six patients with DM in the AIR registry\textsuperscript{150}, five were treated with the RA regimen and one with the NHL regimen. One patient, who received rituximab according to the RA regimen, did not respond, while the other five were considered to have responded (defined as decreased creatinine phosphokinase level with decreased corticosteroid dose). Two of four were able to discontinue IVIg treatment. Of 11 patients with DM in the BIOGEAS registry\textsuperscript{151}, 9 responded (defined as disease activity decreased by at least 50% from initial observations). Of 21 patients with polydermatomyositis (inflammatory myopathy) in the GRAID registry\textsuperscript{58}, approximately half had a complete response (per investigator judgement), a quarter had a partial response, and the remainder did not respond.

### 6.3. Safety of rituximab in dermatomyositis

In the National Insitutes of Health (NIH) sponsored “Rituximab in Myositis” study\textsuperscript{125,127}, adverse events were reported according to standardized NCI Common Terminology Criteria for all patients, without separate reporting for DM. One patient died during the trial, developing a lung mass suspicious of malignancy, then stroke; the death was not listed as related. One patient withdrew early due to an adverse event, and there were 26 serious adverse events that were considered related to treatment\textsuperscript{127}, the majority of which were infectious (listed in Table 9). These included six cases of pneumonia, six of cellulitis, two of urosepsis, and 2 of herpes zoster. The most common serious adverse events (whether related or unrelated) were infection (25% patients), musculoskeletal (17.6%), gastrointestinal (11.8%), and cardiac events (7.4%)\textsuperscript{125}. There was no difference in adverse events at Week 8, prior to administration of rituximab to the “late rituximab” arm\textsuperscript{127}. There were more infusion reactions in patients receiving rituximab than with placebo (15.4% versus 5.3%), two of which required hospitalization. To avoid confounding the effect of rituximab, IV corticosteroids were not administered as premedication.
In the collected case series and case reports, describing 52 patients, two patients died, three additional patients were hospitalized, and 24 non-serious adverse events were reported (it is likely that some patients contributed more than once to this last category).

One patient died of cancer 9 months after rituximab treatment, having shown no evidence of malignancy at screening\textsuperscript{130}. A 58 year-old woman died of diverticular perforation leading to massive gastrointestinal hemorrhage and multisystem organ failure, one month after receiving rituximab\textsuperscript{134}. The three hospitalizations were for gastroenteritis, fever, and heart failure, reported for a mixed group of IMM patients, that included 8/13 DM patients\textsuperscript{133}. The other reported adverse events included infections at various sites, and infusion reactions. There was one additional diagnosis of cancer, nodular sclerosing lymphoma, although the time in relation to rituximab administration was not reported\textsuperscript{134}. Overall there were 14 infections (one leading to hospitalization) and five infusion reactions.

Authors reporting on safety in registry studies tended to include DM with other diseases under a single category of inflammatory muscle diseases. In the GRAID registry study by Tony et al\textsuperscript{68}, three of 26 patients in their category of polydermatomyositis died, two of infection and one of unspecified causes. Two of the deaths occurred 12.7 and 14.2 months after a single cycle of rituximab, respectively. In Couderc et al, 2011,\textsuperscript{150} six of 30 patients had DM. For all 30 patients, the incidence of adverse events was 30.2 per 100 patient years. Two patients had skin rashes reported as infusion reactions, two had unexplained fever soon after rituximab administration, and eight infections were reported (only one requiring hospitalization). One patient with a prior diagnosis of breast cancer was diagnosed with metastatic disease 1 year after rituximab. Ramos-Casals et al\textsuperscript{151} reported safety on 20 patients with inflammatory muscle disease, of whom two developed urinary tract infections, and one with antisynthetase syndrome died due to disease progression. However, apart from the infusion reactions and unexplained fevers, none of the above adverse events can be attributed to rituximab with any confidence.

Likewise, in view of the small number of patients, and the risk of infection associated with severe disease and disability it not possible to assess the attributable risk of infection due to rituximab.

Progressive multifocal leukoencephalopathy (PML) is a rare, catastrophic complication of autoimmune disease and/or immunosuppression, caused by reactivation of latent JC virus\textsuperscript{152,153}. In the majority of patients, PML is fatal. The initial reports of PML in patients with SLE treated off-label with rituximab led to the FDA releasing an alert in December 2006\textsuperscript{154} and subsequently to the black box warning on the label\textsuperscript{2}.

Molloy et al\textsuperscript{153} identified one report of a 41 year-old woman with DM (and possibly RA) who developed PML following treatment with rituximab and methotrexate, having previously been treated with infliximab. In addition, a case report was recently
published describing fatal PML in a 37 year-old woman with the related disorder, polymyositis\textsuperscript{155}, who had received high doses of immunosuppressants prior to rituximab.

6.4. Ongoing studies of rituximab in dermatomyositis

We did not identify any ongoing studies of rituximab in dermatomyositis.

6.5. Summary of rituximab in dermatomyositis

Efficacy. In summary, the majority of patients with DM treated with rituximab had clinical improvement. However, in a randomized placebo-phase trial of rituximab in patients with DM and polymyositis, the majority of patients in both arms improved and there was no clinically or statistically significant difference in the time to improvement between the two treatment groups. Definition of improvement varied across the case series, but most patients showed improved muscle strength and decreased levels of muscle enzymes. Nineteen of 21 patients described in case reports improved.

Safety. In the RIM study, which reported safety for both DM and PM, one patient died of unrelated causes, one withdrew due to an adverse event, and there were 26 serious adverse events, mainly infectious. Overall, 40% of patients reported an adverse event and 25% reported an infection. The case series included reports of fatal and non-fatal cancer, and serious and non-serious infections, as did the registry studies. Most of the information comes from mixed series of patients with inflammatory myopathies. This, with the small numbers, makes it difficult to assess whether rituximab affects the background risk of malignancy and infection associated with DM.

7. RITUXIMAB IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

7.1. Chronic inflammatory demyelinating polyneuropathy background

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic autoimmune neuropathy\textsuperscript{156}, even so, its estimated prevalence is only 1-7 per 100,000 adults\textsuperscript{157}. It manifests as progressive, symmetric muscle weakness affecting both proximal and distal muscles, with loss of reflexes, abnormal sensation, pain, and impaired balance\textsuperscript{156,157}. It resembles Guillain-Barré Syndrome, but according to current diagnostic criteria is distinguished by its slower development and different response to treatment. Electrophysiological testing shows features of demyelination in multiple nerves, and cerebrospinal fluid shows elevated protein. No pathogenic or pathognomonic antibody has been identified.
The disease is variable in its manifestations and prognosis. About 60% of patients have progressive disease, 30% follow a relapsing-remitting course, and 10% recover after the first episode.\textsuperscript{157}

First-line therapy is with corticosteroids, IVlg, and plasmapheresis, use of which are supported by data from randomized controlled trials which showed benefit in approximately two thirds of patients.\textsuperscript{156} Maintenance therapy is frequently used, but owing to the variable disease course, must be reassessed to avoid overtreatment.\textsuperscript{156} Immunosuppression is used for patients with refractory disease, or who cannot tolerate or need to reduce their dose of steroids. Rituximab is considered for patients who do not respond to immunosuppressants.

### 7.2. Efficacy of rituximab in chronic inflammatory demyelinating polyneuropathy

We did not find any systematic reviews, health technology assessments, or randomized controlled trials of the use of rituximab in CIDP. A Cochrane systematic review of immunomodulatory treatment for CIDP did not identify any RCTs for inclusion in their analysis, and therefore reached no conclusions about rituximab.\textsuperscript{158} Thus the evidence is limited to case series and case reports, as described in the following sections.

#### 7.2.1. Rituximab in chronic inflammatory demyelinating polyneuropathy: case series/registry reports

We retrieved three case series describing the use of rituximab in CIDP\textsuperscript{54,159,160} and one abstract reporting an informal survey of members of the Inflammatory Neuropathy Consortium (INC) as to their experience using biological agents in CIDP\textsuperscript{161}. Two of the three case series were derived from the same registry, the Italian Network for CIDP register, and have multiple co-authors in common\textsuperscript{159,160}, thus are likely to contain significant overlap of patients. Both were published in 2011 and report 13\textsuperscript{159} and 18\textsuperscript{160} patients, respectively. The third case series, reported in abstract, included 13 patients with inflammatory neuropathies, but did not indicate the specific diseases, and so will not be further discussed\textsuperscript{54}. We do not know the overlap between the survey and the other papers.

Response to treatment was measured according to disease scales, the Medical Research Council (MRC) sum score, the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, or the Rankin Scale.

Patients were treated with the standard dose for either RA or lymphoma. Patients also received a variety of concomitant medications, including prednisone and immunosuppressants, and premedications recommended to reduce the risk of rituximab infusion reactions.

Nine of 13 patients from the INC Registry responded to rituximab\textsuperscript{159}, when response was defined as improving more than 2 points on both the MRC sum score and the
INCAT disability score, or obtaining a similar benefit from rituximab as from IVIg administration. Six of 18 patients with refractory CIDP from the INC Registry\textsuperscript{160} responded to rituximab when response was defined as an improvement of more than 1 point on the Rankin scale.

In an email survey of members of the INC, reported in abstract\textsuperscript{161}, 11 member physicians had treated 20 patients, 11 of whom had a concomitant haematologic disorder. Twelve of the 20 patients were considered to have responded. Two relapsed, and one was retreated.

7.2.2. Rituximab in chronic inflammatory demyelinating polyneuropathy: case reports

In addition to the case series described above, we found 14 reports describing one to two patients\textsuperscript{58,162-174}, one of which was a small open-label trial of immune neuropathies that recruited two patients with CIDP\textsuperscript{166}. Exclusion of duplicate reports left 11 reports that described 12 patients\textsuperscript{58,163,165-172,174}. Rituximab was indicated for refractory CIDP, usually with unresponsiveness to or need for frequent IVIg/PE, or treatment for a comorbid condition: lymphoma\textsuperscript{167,168}, autoimmune disease (systemic lupus erythematosus\textsuperscript{172}, Morvan’s syndrome and MG\textsuperscript{58} [also described with the MG case reports], autoimmune haematologic disease\textsuperscript{169}), or diabetes mellitus\textsuperscript{170}. Dosing varied, but tended to reflect the use for lymphoma.

Of the 12 patients, 9 were described as having a clinical response to rituximab, with improvement in motor strength, sensory deficit, neuropathic tremor, or pain. Two patients from the open-label trial\textsuperscript{166} did not meet the trial’s primary endpoint of a >25% reduction in dose of IVIg, although one showed clinical improvement.

7.3. Safety in chronic inflammatory demyelinating polyneuropathy

For the patients (up to 63) who received rituximab for CIDP, no deaths or serious adverse events were reported, although seven of the case reports made no mention of safety. Four non-serious adverse events were reported in the two case series: flu-like symptoms, skin rash, allergic reaction (non-specified) and a rise in transaminases. Duplicate reporting is likely, as discussed above.

7.4. Ongoing studies of rituximab in chronic inflammatory demyelinating polyneuropathy

We did not identify any ongoing studies of rituximab in CIDP.

7.5. Summary of rituximab in chronic inflammatory demyelinating polyneuropathy

The reported number of patients treated with rituximab for CIDP was small. About half of the patients in the case series (up to 25/51 but likely fewer due to overlap) and 9/12 patients in the case reports showed symptomatic improvement. No deaths
or serious adverse events were reported. The small numbers and incomplete reporting mean safety cannot be assessed.

8. THERAPY AT THE MUHC

8.1. Experience with rituximab

To date, outcomes are available only for patients treated with rituximab for myasthenia gravis.

8.1.1. Rituximab in myasthenia gravis

Dr Genge reported on ten patients who had received rituximab for MG over the past five years, four of whom were non-responsive to, or intolerant of, IVIg and/or PE, as well as other modalities. Rituximab was also used as a prednisone-sparing agent for two patients with severe MG and diabetes. Rituximab was administered according to the RA regimen, with two initial doses of 1 g each given two weeks apart, followed by 1 g at 6 month intervals as a maintenance regimen.

Nine of the ten patients improved following rituximab, some markedly. Two had been ventilator-dependent for three and four months, respectively, and could discontinue ventilation after rituximab; one of these subsequently discontinued all medications except azathioprine. Three patients were able to stop use of IVIg, three were able to stop use of PE, and one was able to stop use of both. One patient did not respond, requiring ongoing IVIg and PE.

No rituximab-related adverse events have been observed in these patients to date.

9. COST ESTIMATE

We did not find any papers describing the cost or cost-effectiveness of rituximab in any of these four conditions.

Because of the absence of substantial data, variability in treatment regimens, and in patient responses, we did not attempt to estimate the cost of use of rituximab versus the cost of standard treatment with any precision. However, if such treatment is used, it will presumably start with a trial of therapy and rituximab will be discontinued if there is found to be no benefit. We having made very approximate estimates of the gross direct cost of use of rituximab for MG to the MUHC, initially ignoring costs of complications of treatment and offset costs of possible reductions in other treatment costs. (See Appendix 1)
**Gross direct cost of therapeutic trial**

Assuming that rituximab is administered following the RA protocol, with an initial two doses of 1 g separated by 2 weeks, with each dose administered on an outpatient basis during a hour visit, with nursing support, the cost of a six-month trial of rituximab would be approximately $9,462.

**Gross direct cost of maintenance therapy**

If, at the end of six months, this treatment was judged to have been beneficial (improvement in function, reduction in relapses), we will assume that it would be followed by a maintenance dose of 1 g every 6 months for 2 years, for a total of 6 scheduled doses. With these assumptions the total cost (trial plus maintenance) would be approximately $28,986.

**Net Cost of maintenance therapy**

Without attempting any general estimation of the net cost of such therapy, it should be noted that rituximab might in patients who are maintained on IVIg or PE, result in reduced net cost or even in net gain. In such patients the impact of use of rituximab on direct treatment costs of MG will depend on the extent to which use of IVIg and PE can be reduced or abolished. For MG patients who require frequent doses of IVIg or PE for maintenance, for whom rituximab completely abolishes the need for such treatments, we estimated a reduction in direct net treatment costs of $7,614 (monthly PE) to $167,134 (weekly IVIg) per patient over 2 years. A 50% reduction in total requirement for IVIg/PE would be associated with an increased cost of $10,386 (monthly PE) to a cost reduction of $69,374 (weekly IVIg) per patient over 2 years. The small numbers and varying clinical scenarios limited our cost calculations. The potential influence of successful use of rituximab on treatment costs is illustrated in Figure 3. The approach to estimating these costs is shown in Appendix 1.
9.1.1. **Impact on other costs of a good therapeutic response to rituximab**

Quantifying costs associated with clinical improvement is difficult, given the heterogeneity of clinical status and will not be attempted here. However, in some cases they might be considerable. Thus, analysis of costs based on insurance databases suggests that ICU and hospitalization are significant contributors to costs\(^{175,176}\).

In the MUHC series, 2/10 patients were able to discontinue ventilation after three and four months respectively. In the published case series (Section 4.2.1), 9/85 patients had disease serious enough to require intubation and/or ventilation (Class V). Of these, 2/9 had a complete stable remission and 4/9 improved.

Given the cost of ICU nursing at the MUHC of $759/day (2009 data supplied by Nicholas Robert, adjusted to Canadian Dollars in 2012), a 2-year course of rituximab ($28,386) is equivalent in cost to 38 days nursing care in ICU.

10. **DISCUSSION**

For the diseases considered above, the evidence-base is small, and with a single exception, confined to case reports, prospective and retrospective case series, and patients collected in registries. The single exception is a randomized placebo phase trial of rituximab in inflammatory muscle diseases including DM\(^{125}\).
However, since all four indications are rare diseases, with prevalence between 1 in 100,000 and 5 in 10,000 people, higher quality data may not be available in a reasonable time.

In the MG case series, the majority of patients improved after rituximab treatment. While the characteristic course of MG is fluctuating, the selected patients either had poor response to multiple therapies or had been unable to tolerate standard treatments, and generally had severe disease with marked impairment (Class IVb or V). All patients with MuSK antibody, historically a marker for refractory disease, improved. Thus it seems probable that some MG patients will derive benefit from use of rituximab, although the proportion who might benefit may be exaggerated in these data based on case series and case reports alone.

A simple cost calculation indicated that for patients requiring frequent IVIg/PE for maintenance, rituximab could be cost-saving. Although the impact of rituximab on need for IVIg and PE was documented in only a minority of the observational studies, these consistently reported a reduction in use. Of ten patients treated at the MUHC, seven could discontinue IVIg or PE. One aspect that the cost calculation did not capture is that for patients who depend on frequent IVIg/PE for maintenance, delay in accessing treatment may result in myasthenic crisis and hospital admission. Rituximab has an advantage in ease and schedule of administration.

In the NMO case series, the majority of patients also improved, when improvement was measured as frequency of relapses, as defined by the authors. Most patients had no relapses during follow-up, although follow-up was in many cases short. Complicating the assessment is the observation that frequency of relapses generally declines over time, and that the damage done by previous relapses limits recovery, particularly in patients who have had a history of refractory disease treated by multiple modalities. More recent practice suggests use of rituximab earlier in the course of the disease to prevent accumulation and disability. A 2010 EFNS guideline recommends rituximab as first-line therapy for prevention of relapse.

In the Rituximab in Myositis (RIM trial) of rituximab in DM (adult and juvenile) and PM both treatment arms received rituximab but at different times, there was no difference between groups in the primary endpoint of time to improvement, either for all patients or the DM subgroup. The median time to response was overestimated in the power calculation and the overall response rate of patients who received placebo first was underestimated. The majority of patients (>80%) met the study definition for improvement by the end of the 44-week study. In the case series, patient response to rituximab was variable, reflecting in part the varied endpoint definitions, since efforts at standardization of outcomes tended to be less advanced in DM than in MG or NMO. Complete remissions were rarer.

The evidence base for CIDP was the smallest of four diseases, with two small and possibly overlapping case series and an email survey, and a dozen patients
described in case reports. Patients generally showed improvement in muscle strength, pain, paraesthesia, and others symptom of CIDP.

The US drug label for rituximab includes black box warnings for infusion reactions, tumour lysis syndrome (in patients with malignancies), severe mucocutaneous reactions, and progressive multifocal leucoencephalopathy, all of which have resulted in deaths\(^2\). These have not been reported in patients treated with rituximab in the four indications described here, with the exception of PML in a patient with DM. Additional warnings and precautions include hepatitis B reactivation with fulminant hepatitis, serious infections, cardiac arrhythmias and angina, bowel obstruction and perforation, and severe cytopenias\(^2\). These warnings are based on the cumulative experience in the development programs for B-cell lymphoma, RA, Wegener's granulomatosis, and microscopic polyangiitis, and on the off-label use in other indications. Safety reports for the four indications described in this report generally confined themselves to deaths, serious adverse events, and expected infections; other adverse events were probably underreported. There were no unexpected adverse events compared with the established safety profile and the severity and known complications of the diseases themselves, however, the numbers are too few to reliably detect an elevation of risk associated with rituximab.

11. CONCLUSIONS

The available evidence is based on case series and case reports involving small numbers of subjects, and therefore should be interpreted with caution. However, the rarity of these disorders means that higher quality data may never be obtained.

**Efficacy**

*Myasthenia gravis*

- There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with severe MG that is refractory to standard treatment, or who cannot tolerate standard treatment, may respond to rituximab, with in some cases marked clinical improvement to the point of remission.

- There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with MG who require very frequent dosing (eg, weekly) with IVIg and/or PE to avoid deterioration may be able to abolish or reduce their dependence. In such cases, use of rituximab may result in savings in cost and reduction in need for resources.
Neuromyelitis optica

- NMO is a distinct disease entity with a more severe prognosis than multiple sclerosis. Recurrent relapses early in the disease result in rapid accumulation of disability.
- There is a small but consistent body of evidence from uncontrolled studies that patients with NMO experience less frequent relapses following rituximab treatment (although a few may suffer exacerbations). On the basis of this evidence, rituximab with corticosteroids has entered guidelines and practice as first-line treatment.

Dermatomyositis

- In a randomized placebo-phase trial of rituximab in dermatomyositis (adult and juvenile) and polymyositis there was no difference between groups in the primary endpoint of time to improvement. By the end of the 44-week trial, most patients in both groups had reached the pre-defined measure of improvement. The evidence from a small number of case series for improvement is inconsistent. Some patients have experienced a modest improvement.

Chronic inflammatory demyelinating polyneuropathy

- There is an extremely small body of evidence from uncontrolled studies that suggests rituximab can produce improvement in patients with CIDP, with results ranging from modest improvement to remission.

Safety

Adverse events were reported for all the MG, DM and CIDP case series, and all the full-length reports of NMO case series. On-treatment deaths were reported for patients with NMO and DM, and hospitalizations due to infection were reported for patients with MG, NMO, and DM. The small size of the dataset means that it is difficult to assess increased risk of adverse events due to rituximab.

12. RECOMMENDATIONS

The data are of insufficient quantity and quality to support a recommendation for the routine use of rituximab in any of these four conditions.

There is sufficient evidence to support the use of rituximab in the treatment of a limited number of patients, as described below.
**Myasthenia gravis**

There is sufficient evidence to support temporary and conditional approval of rituximab in the treatment of patients with myasthenia gravis under the conditions outlined below:

- Hospitalized patients whose disease is refractory to other therapies
- Hospitalized patients whose treatment options are limited due to intolerance or contraindications to more accepted therapies.
- Patients who require very frequent use (more frequently than 10 days) of IVlg or PE
- The number of new patients treated per year be limited to 10.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a regularly updated registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of permanent approval should be considered.

**Neuromyelitis optica**

There is sufficient evidence to support temporary and conditional approval of rituximab in the treatment of patients with neuromyelitis optica under the conditions outlined below.

- Patients diagnosed with NMO who have positive NMO-IgG and have experienced one or more severe relapses.
- The number of new patients treated per year be limited to a maximum of three.

Since the present evidence concerning the use of rituximab is sparse, all relevant patient data should be collected and maintained in a regularly updated registry. In particular this should contain: Diagnostic data, reason for treatment, symptomatic status before and after treatment, dosage, adverse events.

The registry should be examined whenever appropriate, and at the latest in two years, at which time the question of continued/permanent approval should be considered.

**Dermatomyositis**

There is insufficient evidence to justify the use of rituximab in dermatomyositis other than in the context of a formal research study.

**Chronic inflammatory demyelinating polyneuropathy**
There is insufficient evidence to justify use of rituximab in CIDP other than in the context of a formal research study.

**General Recommendation**

To treat patients with rare diseases such as MG and NMO without collecting, coordinating, and publishing the results would constitute a serious waste of opportunity and resources. Accordingly, every effort should be made to enlist colleagues at associated institutions to share in a treatment and reporting protocol that would allow significant information concerning the benefits and indications for the use of rituximab to be accumulated and published.
### TABLE 1  Case series of rituximab in myasthenia gravis: study information

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Site, time</th>
<th>Design. Criteria for Rituximab treatment</th>
<th>Definition refractory MG</th>
<th>Rituximab dosing</th>
<th>Indication for retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collongues, 2012&quot;13</td>
<td>20</td>
<td>France, 4 sites, data collected 2010-2011</td>
<td>Retrospective. Refractory (n=13) and non-refractory (n=7).</td>
<td>No response to Tx, ≥ 2 immunosuppressants (including corticosteroids) (n=13)</td>
<td>(a) 375 mg/m² weekly x 4 weeks (n=14) OR (b) 1000 mg x 2 (n=6)</td>
<td>(a) Schedule: 375 mg/m² every 3 months OR (b) Clinical: 1000 mg with worsening symptoms.</td>
</tr>
<tr>
<td>Diaz-Manera, 2012&quot;15</td>
<td>17</td>
<td>Barcelona, Spain, 1 site</td>
<td>Retrospective. Refractory.</td>
<td>No significant clinical improvement after prednisone plus ≥ 3 immunosuppressants (AZA → CPA → MMF/TAC/ MTX)</td>
<td>375 mg/m² weekly x 4 weeks, then 375 mg/m² monthly x 2.</td>
<td>Clinical: Retreat with worsening symptoms interfering with activities of daily living.</td>
</tr>
<tr>
<td>Blum, 2011&quot;11</td>
<td>14</td>
<td>Brisbane, Australia, 3 sites. 2006-2010</td>
<td>Retrospective. Inadequate response (10 pts), contraindications to immunosuppressants (4 pts)</td>
<td>Not described</td>
<td>0.5 g x 2 within 2 weeks (one pt 4 doses, 1 pt 1 dose).</td>
<td>Laboratory/clinical: retreat if B-cell recovery with clinical relapse.</td>
</tr>
<tr>
<td>Guptill, 2011&quot;18</td>
<td>6</td>
<td>Durham US, Rome, Italy, 2 centers. Anti-MuSK.</td>
<td>Retrospective. Refractory.</td>
<td>No response to prednisone plus at least 1 immunosuppressant.</td>
<td>375 mg/m² weekly x 4 weeks, then monthly x 0-2</td>
<td>Clinical: Relapse</td>
</tr>
<tr>
<td>Maddison, 2011&quot;23</td>
<td>9</td>
<td>All UK, 8 centres</td>
<td>Retrospective. Not defined.</td>
<td>Not described</td>
<td>375 mg/m² weekly x 4 weeks, with repeat monthly dose in 3 pts.</td>
<td>Clinical: 375 mg/m² every 4 weeks</td>
</tr>
<tr>
<td>Nowak, 2011&quot;28 updated in Nowak, 2012 (abstract)&quot;29</td>
<td>14 (9)</td>
<td>Newhaven CT, USA, 1 centre.</td>
<td>Retrospective. Refractory.</td>
<td>Not controlled on immunotherapy, could not lower doses w/o relapse, severe side effects.</td>
<td>375 mg/m² weekly x 4 weeks, repeat every 6 months.</td>
<td>Schedule: Repeat 375 mg/m² x 4 every 6 months.</td>
</tr>
</tbody>
</table>
### Authors

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Site, time</th>
<th>Design. Criteria for Rituximab treatment</th>
<th>Definition refractory MG</th>
<th>Rituximab dosing</th>
<th>Indication for retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindburg, 2010&lt;sup&gt;22&lt;/sup&gt; 5 Goteborg, Sweden, 1 centre</td>
<td>Retrospective. Not defined.</td>
<td>Not described</td>
<td>375 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 4 weeks, then 375 mg/m&lt;sup&gt;2&lt;/sup&gt; every 3 months</td>
<td>Clinical: If clinical deterioration, 1000 mg x 2.</td>
<td></td>
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<tr>
<td>Desnuelle, 2011&lt;sup&gt;14&lt;/sup&gt; 13 Nice, France</td>
<td>Prospective. Refractory.</td>
<td>Worsening after 3 lines conventional therapy including prednisone, IVlg, PE, immunosuppressants</td>
<td>375 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 4 weeks, then 375 mg/m&lt;sup&gt;2&lt;/sup&gt; x 2 at 6 months.</td>
<td>Indication not specified.</td>
<td></td>
<td></td>
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<tr>
<td>Di Virgillo, 2011&lt;sup&gt;29&lt;/sup&gt; 8 Lausanne, Switzerland. 2009-2010</td>
<td>Prospective. Treatment failure or serious side effects. Need for frequent PE.</td>
<td>Not described</td>
<td>1000 mg x 2 within 15 days</td>
<td>Clinical: repeat if clinically indicated.</td>
<td></td>
<td></td>
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<tr>
<td>Tandan, 2008&lt;sup&gt;24&lt;/sup&gt; 6 Burlington, VT, Syracuse, NY.</td>
<td>Open label, Phase I prospective, 35-week. Active, symptomatic, refractory, moderate to severe MG.</td>
<td>Not described</td>
<td>375 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 4 weeks</td>
<td>Not retreated.</td>
<td></td>
<td></td>
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</tbody>
</table>

F, female; M, male.

AZA, azathioprine; CPA, cyclosporine A; CYC, cyclophosphamide; IVlg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; P, prednisone; PE, plasmapheresis; TAC, tacrolimus; Tx, thymectomy.
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Age at treatment (median), sex</th>
<th>Antibody</th>
<th>Disease duration (median)</th>
<th>Prior treatments</th>
<th>Status start</th>
<th>Status end</th>
<th>Change medications</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full report</td>
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<tr>
<td>Collongues, 2012</td>
<td>20</td>
<td>55 years; 11F 9M</td>
<td>AChR 12, MuSK 4, both 1, none 3</td>
<td>3.7 years</td>
<td>Tx 18, P 20, AZA 11, CYC 7, MMF 12, CPA 1</td>
<td>MGFA-cc Iib 2, IIIb 9, IVb 8, V 1</td>
<td>MGFA-cc I, IIa 6, IIIa 3, IIb 1, IVb 1, NA 2</td>
<td>Prednisone stopped in NRM, ↓ 86% RM</td>
<td>27.9 months</td>
</tr>
<tr>
<td>Diaz-Manera, 2012</td>
<td>17</td>
<td>50 years; 15F 2M</td>
<td>AChR 11, MuSK 6</td>
<td>7 years</td>
<td>Tx 3/6, P 14, AZA 5, CPA 4, CYC 1/3, MTX 1, TAC 1, MMF 3, IVIg 6</td>
<td>MGFA-cc IIIa 2, IIIb 2, IVb 11, V 2</td>
<td>MGFA-ps CSR 2, I 10, MM1 2, PR 2, U 1</td>
<td>Immunosupp. ↓ 12/14; P dose ↓ 52%. IVIg -50% 6/9, +100% 1/9.</td>
<td>31.1 months</td>
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<tr>
<td>Blum, 2011</td>
<td>14</td>
<td>53 years; 9F 5M</td>
<td>AChR 11, MuSK 3</td>
<td>5.5 years</td>
<td>Tx 8, P 13, AZA 9, CPA 5, TAC 3, CYC 1, TAC 3, MTX 5, MMF 1, PE 2, IVIg 9</td>
<td>MGFA-cc Ila 1, IIIb, IVa 1, IVb 9, V 2</td>
<td>MGFA-ps CSR 1, I 5, MM 3, PR 3, U 2</td>
<td></td>
<td>14.3 months</td>
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<tr>
<td>Guptill, 2011</td>
<td>6</td>
<td>46.5 years; 6F</td>
<td>MuSK 6</td>
<td>8.00 years</td>
<td>Tx 2, P 6, CPA 4, MMF 5, PE 4, IVIg 3</td>
<td>Not reported</td>
<td>MGFA-ps I2, MM 3, PR 1</td>
<td></td>
<td>21.8 months</td>
</tr>
<tr>
<td>Maddison, 201123</td>
<td>9</td>
<td>35 years; 9F</td>
<td>AChR 6, MuSK 3</td>
<td>6.0 years</td>
<td>Thx 6, P 9, CPA 2, CYC 1, MTX 2, MMF 4, PE 6, IVIg 8</td>
<td>MGFA-cc IIIb 2, IVb3, V 4</td>
<td>MGFA-ps CSR 1, I 3, PR 1, U 3, W 1</td>
<td></td>
<td>4-18 months</td>
</tr>
<tr>
<td>Nowak, 2011 with follow-up in Nowak, 2012 (abstract)29</td>
<td>14 (9)</td>
<td>38.5 years; 11F 3M</td>
<td>AChR 6, MuSK 8</td>
<td>Not reported</td>
<td>Thx 8, P 14, AZA 8, CPA 1, MMF 1, PE 12, IVIg 1</td>
<td>Individual symptoms only.‡</td>
<td>Not reported.‡ In update (n=9), all patients in clinical remission.‡</td>
<td>12/12 stopped PE after 3 cycles ritux. Median cycles PE 0 (0-34)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
### Abstract

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Age at treatment (median), sex</th>
<th>Antibody</th>
<th>Disease duration (median)</th>
<th>Prior treatments</th>
<th>Status start</th>
<th>Status end</th>
<th>Change medications</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindburg, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>5</td>
<td>57 years; 2M 3F</td>
<td>AChR 5</td>
<td>26 years</td>
<td>Tx 3, P 5, CPA 3, AZA 3, MMF 3, IVIg 3</td>
<td>QMG mean 17.8&lt;sup&gt;†&lt;/sup&gt;</td>
<td>QMG mean 6.2 [MGFA-ps CSR 1, I 3, D 1]&lt;sup&gt;10&lt;/sup&gt;</td>
<td>33.4 months</td>
<td></td>
</tr>
<tr>
<td>Desnuelle, 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>13</td>
<td>63 years (mean)</td>
<td>AChR 10, MuSK 1</td>
<td>Not reported</td>
<td>≥3 lines conventional therapy including prednisone, IVIg, PE, IS</td>
<td>MGFA-cc IV-V 5, II-III 8</td>
<td>MGFA-cc I-II 13</td>
<td>Prednisone ↓ 42%</td>
<td>6 months (13 pts), 12 months (8)</td>
</tr>
<tr>
<td>Di Virgillo, 2011&lt;sup&gt;29&lt;/sup&gt;</td>
<td>8</td>
<td>41 years (mean); 6 F</td>
<td>MuSK 2</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>6/8 clinical response</td>
<td>Prednisone ↓ 75%; Other medications ↓ 35%</td>
<td>4-24 months</td>
</tr>
<tr>
<td>Tandan, 2008&lt;sup&gt;24&lt;/sup&gt;</td>
<td>6</td>
<td>41 years; 6F</td>
<td>Not reported</td>
<td>11 years</td>
<td>Not reported</td>
<td>MGFA-cc not reported. QMG 16.2</td>
<td>MGFA-ps not reported. QMG 12.8±9.6</td>
<td>Not reported</td>
<td>7 months</td>
</tr>
</tbody>
</table>

<sup>†</sup> MGFA-cc at start for 6 patients (previously reported) estimated by Benveniste and Hilton, 2010<sup>10</sup> as IVb 2 patients, IIIb 2, and IIIa 2. MGFA-ps was estimated as MM 4 and I 2.

<sup>‡</sup> MGFA-cc at start estimated by Benveniste and Hilton, 2010<sup>10</sup> as IVb for all 5 patients. MGFA-ps was estimated as CSR 1 patient, I 3, and D (died) 1.

F, female; M, male.

AChR, acetylcholinesterase receptor; AZA, azathioprine; CPA, cyclosporine A; CYC, cyclophosphamide; IVIg, intravenous immunoglobulin; MuSK, muscle specific receptor kinase; MGFA-cc, Myasthenia Gravis Foundation of America Clinical Classification (scored as I through V, with a and b classification indicating absence and presence of bulbar symptoms); MGFA-ps, Myasthenia Gravis Foundation of America Postintervention Status (CSR, complete stable remission; I, improved; MM, MM1, MM2, and MM3, minimal manifestations; PR, pharmacologic remission; U, unchanged; W, worsened; D, died); MMF, mycophenolate mofetil; MTX, methotrexate; P, prednisone; PE, plasmapheresis; QMG, Quantitative Myasthenia Gravis Score; TAC, tacrolimus; Tx, thymectomy.
Table 3  Safety of rituximab in myasthenia gravis
Case reports that did not include safety information have been omitted to conserve space

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age, sex</th>
<th>Follow-up</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collongues, 2012</td>
<td>20</td>
<td>56 years; 11F 9M</td>
<td>27.9 months</td>
<td>Spondylodiscitis, 1 (1 year post rituximab).</td>
</tr>
<tr>
<td>Diaz-Manera, 2012</td>
<td>17</td>
<td>50 years; 15F 2M</td>
<td>31 months</td>
<td>Mild infusion reaction, 2.</td>
</tr>
<tr>
<td>Blum, 2011</td>
<td>14</td>
<td>53 years; 9F 5M</td>
<td>14.3 months</td>
<td>Mild infusion reaction, 2 patients. Altered sense of taste and eosinophilia (presumed reactivation of giardiasis), 1. Reactivation oral herpes, 1.</td>
</tr>
<tr>
<td>Desnuelle, 2011</td>
<td>13</td>
<td>63 years</td>
<td>6 months (13 pts), 12 months (8)</td>
<td>“No serious adverse events”</td>
</tr>
<tr>
<td>Di Virgillo, 2011</td>
<td>8</td>
<td>41 years; 5 F 3M</td>
<td>4-24 months</td>
<td>“No adverse events were observed”.</td>
</tr>
<tr>
<td>Guptill, 2011</td>
<td>6</td>
<td>46.5 years; 6F</td>
<td>21.8 months</td>
<td>“No significant adverse events”.</td>
</tr>
<tr>
<td>Maddison, 2011</td>
<td>9</td>
<td>35 years; 9F</td>
<td>Not reported</td>
<td>“No serious or significant AEs”. Fever and rigors, 1.</td>
</tr>
<tr>
<td>Nowak, 2011</td>
<td>14</td>
<td>38.5 years; 11F 3M</td>
<td>Not reported</td>
<td>Infusion reactions (flushing and chill/rigors), 1.</td>
</tr>
<tr>
<td>Lindburg, 2010</td>
<td>5</td>
<td>57 years; 2M 3F</td>
<td>39.5 months</td>
<td>Deaths, 1: Heart failure, 2 mos post rituximab (history of aortic valve disease, hypertension). SAEs, 1: Pneumonia and agranulocytosis, 1 month post infusion.</td>
</tr>
<tr>
<td>Tandan, 2009</td>
<td>6</td>
<td>41 years; 6F</td>
<td>7 months</td>
<td>Hypotension during infusion, 2.</td>
</tr>
<tr>
<td>Menge, 2012</td>
<td>3</td>
<td>2 F, 1 M, 39 years (mean).</td>
<td>11 (5-36) months</td>
<td>Adverse events (unspecified), 1.</td>
</tr>
<tr>
<td>Kundi, 2010</td>
<td>3</td>
<td>2 F, 1 M, 56 years (mean).</td>
<td>Not reported</td>
<td>&quot;None . . . any serious adverse events&quot;</td>
</tr>
<tr>
<td>Michaels, 2009</td>
<td>3</td>
<td>Not reported.</td>
<td>22-35 months</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Butterly, 2010</td>
<td>2</td>
<td>[1] 75 years M AChR [2] 62 years M, MuSK</td>
<td>18 months</td>
<td>No reports of notable AEs or SAEs</td>
</tr>
<tr>
<td>Gardner, 2008</td>
<td>2</td>
<td>[1] 30 years F, MuSK [2] 40 years F AChR</td>
<td>&gt;1 year</td>
<td>&quot;. . . have not had side effects attributable to rituximab&quot;</td>
</tr>
<tr>
<td>Author</td>
<td>N</td>
<td>Age, sex</td>
<td>Follow-up</td>
<td>Adverse events</td>
</tr>
<tr>
<td>---------------------</td>
<td>----</td>
<td>----------------------</td>
<td>-----------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Jordan, 2007\cite{45} (abstract)</td>
<td>1</td>
<td>56 years F, MuSK</td>
<td>34 months</td>
<td>&quot;No therapy-associated side-effects&quot; especially no severe infections</td>
</tr>
<tr>
<td>Hain, 2006\cite{32}</td>
<td>1</td>
<td>58 years F, MuSK</td>
<td>12 months</td>
<td>&quot;No side effects&quot;</td>
</tr>
<tr>
<td>Zaja, 2000\cite{67}</td>
<td>1</td>
<td>~42 years M, MG 4 years post BMT for AML</td>
<td>6 months</td>
<td>No complications or toxic effects.</td>
</tr>
</tbody>
</table>

F, female; M, male.
AML, acute myeloid leukemia; AChR, acetylcholinesterase receptor; LPL, lymphoplasmacytic lymphoma; MuSK, muscle specific receptor kinase
### Table 4  Case series of rituximab in neuromyelitis optica: study information

<table>
<thead>
<tr>
<th>Author</th>
<th>Site, time</th>
<th>Design. Criteria for ritux</th>
<th>Ritux dosing</th>
<th>Retreatment</th>
<th>Definition attack/relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full report</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenberg, 2012</td>
<td>Dallas TX, US</td>
<td>Retrospective.</td>
<td>100 mg or 1000 mg. Average number doses 4.9 (SD 3.0)</td>
<td>Not described.</td>
<td>Not defined.</td>
</tr>
<tr>
<td>Ip, 2012</td>
<td>Hong Kong</td>
<td>Retrospective registry. NMO or NMOSD</td>
<td>(a) 375 mg/m² weekly x 4 or (b) 1000 mg x 2</td>
<td>q 6-9 months, scheduled maintenance</td>
<td>Not defined</td>
</tr>
<tr>
<td>Lindsay, 2012</td>
<td>Dallas TX, US</td>
<td>Retrospective. All pts meeting 2006 diagnostic criteria, treated with rituximab</td>
<td>(a) 375 mg/m² weekly x 4 weeks or (b) 1000 mg x 2</td>
<td>Repeat on relapse</td>
<td>Not defined</td>
</tr>
<tr>
<td>Bedi, 2011</td>
<td>Florida, 2 centres, 1990-2010</td>
<td>Retrospective. All pts meeting 2006 diagnostic criteria, treated with rituximab</td>
<td>(a) 375 mg/m² weekly x 4 (n=4) or (b) 1000 mg q 2 weeks x 2 (n=17)</td>
<td>Schedule: (a) 375 mg/m² weekly x 2 q 12 months (b) repeat q 6 months</td>
<td>Acute/subacute appearance of new neurological signs/sx or worsening of deficits lasting &gt;24 hours, &gt;1 month post previous relapse</td>
</tr>
<tr>
<td>Kim, 2011</td>
<td>Goyang, Korea.</td>
<td>Prospective. Patients with relapsing NMO per 2006 criteria, with ≥1 relapse in the previous 12 months</td>
<td>(a) 375 mg/m² qw x 4 weeks (n=16), (b) 1000 mg q 2 weeks x 2 (n=14)</td>
<td>Repeat 1 infusion when memory B-cells ≥0.05% PBMCs.</td>
<td>Objective worsening new neurological symptoms lasting &gt;24 hours, increasing EDSS overall by 0.5, or by 1 on 2 functional subscales or by 2 on 1 subscale.</td>
</tr>
<tr>
<td>Pellkofer, 2011</td>
<td>Munich, Germany</td>
<td>Prospective. NMO not responding to ≥1 standard rx</td>
<td>1000 mg q 2 weeks x 2</td>
<td>Initially retreatment when B-cells recover, later on schedule q 6-9 mos</td>
<td>Not defined</td>
</tr>
<tr>
<td>Author</td>
<td>Site, time</td>
<td>Design. Criteria for ritux</td>
<td>Ritux dosing</td>
<td>Retreatment</td>
<td>Definition attack/relapse</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Jacob, 2008</td>
<td>6 US centres, 1 UK</td>
<td>Retrospective. All pts with relapsing NMO or longitudinally extensive transverse myelitis with ≥1 dose rituximab and ≥6 months follow-up</td>
<td>(a) 375 mg/m² weekly x 4 (n=18), (b) 1000 mg q2 weeks x 2 (n=4), (c) not available (n=3)</td>
<td>Schedule: repeat q6 months or q12 months, or when B-cells recovered</td>
<td>Not defined</td>
</tr>
<tr>
<td>Flores, 2012</td>
<td>Mexico City, Mexico. 2007-2011</td>
<td>Retrospective. Patients with NMO treated with immunotherapies.</td>
<td>1500 mg (frequency or divided dose not indicated)</td>
<td>500 mg q6 months</td>
<td>Not defined</td>
</tr>
<tr>
<td>Aboul-Enein, 2011</td>
<td>Vienna &amp; Innsbruck, Austria</td>
<td>Patients with antibody-positive NMO with &gt;5 cycles rituximab</td>
<td>375 mg/m² qw x 4 weeks</td>
<td>1000 mg or 375 mg/m² q 6 months</td>
<td>Not defined</td>
</tr>
<tr>
<td>Hernandez, 2011</td>
<td>Mexico City, Mexico</td>
<td>Retrospective. Patients with NMO treated with immunotherapies.</td>
<td>(a) 1000 mg q2w (n=5) or (b) 500 mg q2w</td>
<td>Not described.</td>
<td>Not defined</td>
</tr>
<tr>
<td>Radaelli, 2011</td>
<td>Milan, Italy</td>
<td>Retrospective. NMO spectrum with ≥1 dose rituximab and ≥6 months follow-up</td>
<td>Not detailed.</td>
<td>Not described.</td>
<td>Not defined</td>
</tr>
<tr>
<td>Genain, 2007</td>
<td>San Francisco, US</td>
<td>Retrospective. Patients from an ITT open label trial.</td>
<td>1000 mg q 2 weeks x 2</td>
<td>Schedule: repeat at 9 months, or when B-cells recovered (n=4)</td>
<td>Not defined.</td>
</tr>
</tbody>
</table>

PBMC, peripheral blood mononuclear cell; EDSS, Extended Disability Status Scale; NMOSD, neuromyelitis optica syndrome disorder

† The abstract by Kim et al, 2012, is by the same authors and institution as the article by Kim et al, 2011. Both are included, as the abstract adds an additional 51 patients.
### Table 5  Case series of rituximab in neuromyelitis optica: patient information

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Age at treatment, sex</th>
<th>Disease duration (median)</th>
<th>Prior treatments</th>
<th>Status start (median, unless otherwise indicated)</th>
<th>Status end (median, unless otherwise indicated)</th>
<th>Follow-up (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenberg, 2012&lt;sup&gt;76&lt;/sup&gt;</td>
<td>21</td>
<td>45 y (mean). 18 F 3 M</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Relapses 6/21 patients.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ip, 2012&lt;sup&gt;53&lt;/sup&gt;</td>
<td>7</td>
<td>52 years. 6 F 1 M</td>
<td>39 months (range, 2-260)</td>
<td>Not reported</td>
<td>ARR 1.36 (0.5-12). EDSS 8 (6-9.5)</td>
<td>ARR 0 (0-0.5). EDSS 7 (3-9.5)</td>
<td>24 months</td>
</tr>
<tr>
<td>Lindsay, 2012&lt;sup&gt;64&lt;/sup&gt;</td>
<td>9</td>
<td>39.7 years (mean). 9 F 1 M</td>
<td>26 months (range, 15-148)</td>
<td>P 9, PE 4, AZA 3, IVlg 2, IFNB 1, GLA 1</td>
<td>EDSS 3.5 (range, 0-8)</td>
<td>EDSS 4 (range, 2-10)</td>
<td>24 months</td>
</tr>
<tr>
<td>Bedi, 2011&lt;sup&gt;74&lt;/sup&gt;</td>
<td>23</td>
<td>37.1 y (mean, SD 14.6). 21 F 2 M</td>
<td>114 months (range, 13-266)</td>
<td>None, 8; IMS 8; IM 3; both 4</td>
<td>ARR 1.9 (0.3-5.1). EDSS 7.0 (3-9)</td>
<td>ARR 0.0 (0 - 1.3). EDSS 5.5 (0-8); EDSS decreased ≥1.0, 10/23.</td>
<td>32.5 months</td>
</tr>
<tr>
<td>Bomprezzi, 2011&lt;sup&gt;84&lt;/sup&gt;</td>
<td>18</td>
<td>46 y (mean). 15 F 3 M</td>
<td>41 months (range, 8-88)</td>
<td>MIT or CYC 12, PE 12, INF 7, GLA 1</td>
<td>ARR 1.6 (0.5-3.4) (13/18 patients)</td>
<td>ARR 0.55 (0-15.6) (13/18 patients)</td>
<td>16.9 months</td>
</tr>
<tr>
<td>Kim, 2011&lt;sup&gt;76&lt;/sup&gt; †</td>
<td>30</td>
<td>34.8 y (mean, SD 10.5). 27 M 3.</td>
<td>4.5 years (mean, SD 3.8)</td>
<td>IFNB 16, AZA 6, P 4, Others 3</td>
<td>ARR 1.9 (0.4-10.0). EDSS 4.4 (mean, range 1-8.5)</td>
<td>ARR 0 (0-6.3). EDSS 3.0 (mean, range 1-7.5)</td>
<td>24 months</td>
</tr>
<tr>
<td>Pellkofer, 2011&lt;sup&gt;80&lt;/sup&gt;</td>
<td>10</td>
<td>49.0 (range 24-68). 9 F, 1 M</td>
<td>35.3 months (range, 13.1-45.0)</td>
<td>INF 4, AZA 4, IVlg 2, CYC 1, Others 5</td>
<td>ARR 1.8 (range, 1.3-4.6)</td>
<td>ARR 0.3 (range, 0-5.3)</td>
<td>27 months</td>
</tr>
<tr>
<td>updated in Kumpfel, 2012 (abstract)&lt;sup&gt;89&lt;/sup&gt;</td>
<td>10</td>
<td>49.0 (range 24-68). 9 F, 1 M</td>
<td>35.3 months (range, 13.1-45.0)</td>
<td>INF 4, AZA 4, IVlg 2, CYC 1, Others 5</td>
<td>ARR 1.8 (range, 1.3-4.6)</td>
<td>ARR 0.3 (range, 0-5.3)</td>
<td>27 months</td>
</tr>
<tr>
<td>Jacob, 2008&lt;sup&gt;77&lt;/sup&gt;</td>
<td>25*</td>
<td>38 years (median, range 7-65). 22 F 3 M</td>
<td>4.5 years (0.8 to 17 years)</td>
<td>AZA 14, IFNB 12, P 10, IVlg 7, MIT 7, GLA 4, CYP 3</td>
<td>ARR 1.7 (0.5-5.0). EDSS 7 (range 3-9.5)</td>
<td>ARR 0.0 (0 - 3.2). EDSS 5 (3-10); EDSS improved 11/25, worsened 5/25.</td>
<td>19 months</td>
</tr>
</tbody>
</table>
**Rituximab in neurological diseases**

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Age at treatment, sex</th>
<th>Disease duration (median)</th>
<th>Prior treatments</th>
<th>Status start (median, unless otherwise indicated)</th>
<th>Status end (median, unless otherwise indicated)</th>
<th>Follow-up (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flores, 2012⁹¹</td>
<td>13</td>
<td>33.3 years (mean). 12 F</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Annualized Relapse Rate (ARR) 1.0. EDSS (med) 4.8</td>
<td>ARR 0.1. EDSS 2.</td>
<td>24 months</td>
</tr>
<tr>
<td>Kim, 2012⁹⁰ †</td>
<td>81</td>
<td>35 years</td>
<td>52 months</td>
<td>Previous treatment 33, treatment naive 48</td>
<td>ARR 1.9 (0.4 - 12.0).</td>
<td>ARR 0 (0-53). Disability improved or stabilized in 96%.</td>
<td>41 months</td>
</tr>
<tr>
<td>Menge, 2012⁵⁴</td>
<td>6</td>
<td>42 y (mean, SD 19)</td>
<td>11 months (range, 1-84)</td>
<td>Mean number 2.5 (range 0-3)</td>
<td>Not reported</td>
<td>6/6 improved; criteria not specified</td>
<td>14 (range, 0-52 months)</td>
</tr>
<tr>
<td>Aboul-Enein, 2011⁷⁵</td>
<td>5</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>RR 0.58-2.77</td>
<td>RR 0-0.67</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hernandez, 2011⁹²</td>
<td>9</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>ARR 1.8</td>
<td>ARR 0 (1 g), 1 (500 mg)</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Radaelli, 2011⁷⁹</td>
<td>17</td>
<td>14 F 3 M.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Mean ARR 2.6. EDSS 5.5.</td>
<td>Mean ARR 0.5. EDSS stable/improved 14.</td>
<td>28 months (mean)</td>
</tr>
<tr>
<td>Genain, 2007¹⁰⁶</td>
<td>10</td>
<td>40.2 years (mean). 7 F 3 M.</td>
<td>4.7 years</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Relapse rate 0.32 times pre-treatment relapse rate</td>
<td>3-12 months</td>
</tr>
</tbody>
</table>

* Including one pediatric patient, and two with relapsing myelitis.

† The abstract by Kim et al, 2012⁹⁰, is by the same authors and institution as the article by Kim et al, 2011⁷⁶. Both are included, as the abstract adds an additional 51 patients.

ARR, Annualized Relapse Rate; F, female; M, male.
AZA, azathioprine; CPA, cyclosporine A; CYC, cyclophosphamide; EDSS, Extended Disability Status Scale; GLA, glatimer acetate; IFNB, interferon B; IVIg, intravenous immunoglobulin; IMM, immunomodulator; IMS, immunosuppressant; MIT, mitoxantrone; MMF, mycophenolate mofetil; MTX, methotrexate; P, prednisone; PE, plasmapheresis; TAC, tacrolimus.
Table 6  Safety of rituximab in neuromyelitis optica

Case reports that did not include safety information have been omitted to conserve space

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Patient(s) age, sex</th>
<th>Follow-up</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg, 2012</td>
<td>21</td>
<td>45 y (mean). 18F</td>
<td>Not reported</td>
<td>Death 1: NMO (15 months post start rituximab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindsey, 2012</td>
<td>9</td>
<td>39.7 years (mean). 8F</td>
<td>24 months</td>
<td>Adverse events indicated as none.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menge, 2012 (abstract, poster)</td>
<td>6</td>
<td>42 (mean)</td>
<td>14 mo (0-52)</td>
<td></td>
</tr>
<tr>
<td>Bedi, 2011</td>
<td>23</td>
<td>37.1 (mean), 21F</td>
<td>32.5 (7-63)</td>
<td>Recurrent HZ infection 1, UTI 1, mild respiratory infection 2, fatigue 1, leukopenia 1, LFTs 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, 2011</td>
<td>30</td>
<td>34.8 (mean). 27F</td>
<td>24 mos</td>
<td>AEs: infusion reaction, 12; infections, 12 (nasopharyngitis, URTI, LRTI, UTI). Discontinuations none.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellkofer, 2011</td>
<td>10</td>
<td>49.0 (mean, range 24-68)</td>
<td>30 mo</td>
<td>Death: cardiovascular failure, 1 (3 days post rituximab). AEs: urogenital infection, thrombosis and cardiovascular failure, 1 (fatal); urosepsis 1; HZ urogenital infection 1; urogenital infection 1; adenexitis 1, pneumonia, 1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genain, 2007 (abstract)</td>
<td>10</td>
<td>40.2 y (mean). 7F</td>
<td>3-12 months</td>
<td>No serious infections.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matiello, 2011</td>
<td>1</td>
<td>64 years F, NMO 4 years, Hodgkin lymphoma treated with SCT, then NMO relapse</td>
<td>ca 24 months</td>
<td>Recurrence of pelvic lymphoma 1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurup, 2009 (abstract)</td>
<td>1</td>
<td>32 years M, treated for lymphoma with rituximab, developed NMO</td>
<td>Not specified</td>
<td>Report of NMO developing after rituximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellkofer,</td>
<td>1</td>
<td>19 years F, NMO 6</td>
<td>ca 2</td>
<td>Inadvertent pregnancy. Baby developing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rituximab in neurological diseases

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Patient(s) age, sex</th>
<th>Follow-up</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009\textsuperscript{174}</td>
<td>years</td>
<td>years</td>
<td>normally.</td>
<td></td>
</tr>
<tr>
<td>Karantoni, 2008\textsuperscript{108} (abstract)</td>
<td>1</td>
<td>51 years F, 15 y hx, treated for MS</td>
<td>&gt;1 year</td>
<td>&quot;No significant side effects*</td>
</tr>
</tbody>
</table>

C diff, *Clostridium difficile*; HSV, herpes simplex virus; HZ, herpes zoster; LRTI, lower respiratory tract infection; MS, multiple sclerosis; SCT, stem cell transplant; TB, tuberculosis; URTI, upper respiratory tract infection;
### Table 7  Case series of rituximab in dermatomyositis: study information

<table>
<thead>
<tr>
<th>Author</th>
<th>Site, time</th>
<th>Design. Criteria for ritux</th>
<th>Ritux dosing</th>
<th>Retreatment</th>
<th>Definition response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahler, 2011</td>
<td>Nijmegen, the Netherlands. August 2005-January 2009</td>
<td>Prospective. DM or PM by standard criteria with positive biopsy findings. Refractory disease with poor response to prednisone and ≥1 immunosuppressant.</td>
<td>1000 mg q 2 weeks x 2</td>
<td>With increased disease activity</td>
<td>Significant changes in muscle enzyme levels and increase in muscle strength (handheld dynamometry, MMT)</td>
</tr>
<tr>
<td>Sultan, 2008</td>
<td>London, UK</td>
<td>Prospective. DM or PM by standard criteria, with muscle weakness of at least 2 muscle groups. Refractory disease. Open-label single arm (n=5). Clinical need (n=3).</td>
<td>1000 mg q 2 weeks x 2</td>
<td>None</td>
<td>≥15% improvement in muscle strength by myometry, 30% reduction CPK at 6 months.</td>
</tr>
<tr>
<td>Chung, 2007</td>
<td>Stanford, CA. Dec 2004 - July 2005</td>
<td>Prospective. Open-label single arm. Probable or definite DM with 2 of symmetrical muscle weakness, positive muscle biopsy, raised enzymes, electromyographic abnormality, plus skin disease.</td>
<td>1000 mg q 2 weeks x 2</td>
<td>None</td>
<td>Primary endpoint: % with PR at week 24. PR ≥50% reduction CPK if baseline &gt;2X ULN, &gt;50% reduction in muscle strength deficit; at least &gt;75% improvement in DSSI.</td>
</tr>
<tr>
<td>Levine, 2005</td>
<td>Phoenix, AZ</td>
<td>Prospective. Open-label pilot. DM with no response to ≥1 previous standard treatment, or muscle strength &lt;75% normal</td>
<td>100 mg/m² (n=3), 375 mg/m² (n=4) weekly x 4</td>
<td>None</td>
<td>Primary endpoint: Improvement ≥12% in muscle strength by quantitative muscle testing at one year on stable medication.</td>
</tr>
</tbody>
</table>

CPK, creatine phosphokinase; MMT, manual muscle testing; ULN, upper limit of normal.
Table 8  Case series of rituximab in dermatomyositis: patient information

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age at treatment, sex</th>
<th>Disease duration</th>
<th>Prior treatments</th>
<th>Status start</th>
<th>Status end</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahler, 2011</td>
<td>13 (8 DM)</td>
<td>44.4 (mean) 7F 6M</td>
<td>Median 4 years (IQR 2.5-6.5)</td>
<td>MTX 10, AZA 8, P 4, IMA 3, ETA 3, CPA 2, ADA 1, CYC 1, IVlg 1</td>
<td>CPK 235-2139 U/L, LDH 502-884 U/L, MMT 52-63.</td>
<td>Median CPK reduced by 93.2%; median LDH reduced by 40%. MMT increased 7%</td>
<td>Median 27.1 mos</td>
</tr>
<tr>
<td>Sultan, 2008</td>
<td>8 (5 DM)</td>
<td>56-63 years, 4F 1M (DM)</td>
<td>7-20 years</td>
<td>P5, CPA 4, MTX 4, IVlg 3, AZA 3, LEF 1, PEN 1, CYP 4, THA 1, ETA 1.</td>
<td>CPK 292-1571 U/L</td>
<td>2/5 DM pts clinical response.</td>
<td>6 months to outcome</td>
</tr>
<tr>
<td>Chung, 2007</td>
<td>8</td>
<td>38-76 years 1F 7M</td>
<td>Median 3.5 years (1-24)</td>
<td>P 6, AZA 5, MTX 5, HCO 3, IVlg 3, CPA 3, Topical agents 3, MMF 2, TAC 1, ETA 1</td>
<td>CPK 16-2045 U/L, MMT 78-90; DSSI 2.5-15.3</td>
<td>Partial remission (endpoint) 3 patients; 3 improved MMT without PR; 3 stable CPK values; DSSI generally unchanged</td>
<td>Planned 6 months</td>
</tr>
<tr>
<td>Levine, 2005</td>
<td>7 (6 evaluated)</td>
<td>21-64 years, 5F 2M</td>
<td>0.3-15 years</td>
<td>P 6, MTX 4, AZA 3, ETA 3, CYP 1, CPA 1, HCQ 1, IVlg 1</td>
<td>Strength 39-60% normal; CPK 128-5600 U/L; FVC 45-57% predicted (n=3)</td>
<td>Improved strength, 6 patients (best measure) 68-102% normal; CPK 57-1168 U/L; FVC 65-82% predicted (n=3)</td>
<td>6-13 months (1 lost to follow-up)</td>
</tr>
</tbody>
</table>

ADA, adalimumab; AZA, azathioprine; CPA, cyclosporine; CPK, creatinine phosphokinase; CYP, cyclophosphamide; FVC, forced vital capacity; DSSI, Dermatomyositis Skin Severity Index; ETA, etanercept; HCO, hydroxychloroquine; IMA, infliximab; LDH, lactate dehydrogenase; LEF, leflunomide; MMT, manual muscle testing; MMF, mycophenolate mofetil; MTX, methotrexate; P, prednisone; TAC, tacrolimus; THA, thalidomide.
Table 9  Safety of rituximab in dermatomyositis

Case reports that did not include safety information have been omitted to conserve space

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Age, sex</th>
<th>Follow-up</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oddis, 2010,</td>
<td>200</td>
<td>Early rituximab 43, 71% F; late rituximab 40, 75% F.</td>
<td>Early rituximab 44 weeks (planned); late rituximab 36 weeks.</td>
<td>(AEs for all patients) Death: 74 years F, possible malignancy, stroke, 1. Withdrawal: 1. SAEs 67 (events), 26 related: pneumonia 6, cellulitis 6, urosepsis 2, herpes zoster 2, septic arthritis 1, histoplasmosis 1, UTI 1, RTI 1, heart failure 1, dysrhythmia 1, venous thrombosis 1, syncope 1, rash 1, neurologic symptoms 1 (no PML). Infusion reactions: with rituximab 60/389, with placebo 21/393.</td>
</tr>
<tr>
<td>2012 [128,127]</td>
<td>(RCT)</td>
<td>DM</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Mahler, 2011</td>
<td>13</td>
<td>44.4 (mean) 7F 6M</td>
<td>Median 27.1 mos</td>
<td>SAEs, 3: Hospitalizations for gastroenteritis, fever, heart failure (1 each)</td>
</tr>
<tr>
<td>(abstract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sultan, 2008</td>
<td>5</td>
<td>DM 56-63 years, 4F 1M</td>
<td>&gt;6 months</td>
<td>Death, 1: 58 years F, non-responder on high prednisone, diverticular perforation, massive GI hemorrhage, multiorgan failure (1 month after rituximab). AEs, 2: allergic response to rituximab 1, nodular sclerosing lymphoma 1 (time unknown).</td>
</tr>
<tr>
<td>Chung, 2007</td>
<td>8</td>
<td>38-76 years 1F 7M</td>
<td>Planned 6 months</td>
<td>Death: cancer, 1, 9 mos post infusion. AEs, 13: Infusion reaction 3; ↑LFTs 1 (resolved with d/c AZA). Infections, 9: skin 2, bronchitis 3, sinusitis 2, UTI 1, otitis media 1.</td>
</tr>
<tr>
<td>Levine, 2005</td>
<td>7</td>
<td>21-64 years, 5F 2M</td>
<td>6-13 months</td>
<td>Cellulitis when calcinosis broke skin, 1; shortness of breath, hypertension with infusion, 1.</td>
</tr>
<tr>
<td>Canto-Mangana,</td>
<td>1</td>
<td>31 years F</td>
<td>&gt;18 months</td>
<td>AEs, 2: Bacterial pharyngitis, oropharyngeal candidiasis</td>
</tr>
<tr>
<td>2012 [135]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanchez-Ramon,</td>
<td>1</td>
<td>44 years F, 3 y DM/PM. Intolerant to P, AZA, MTX.</td>
<td>6 mos</td>
<td>AEs, 1: Hypogammaglobulinemia requiring ongoing IVIg</td>
</tr>
<tr>
<td>2010 [145]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feist, 2008</td>
<td>1</td>
<td>55 years M, &lt;1 year</td>
<td>&gt;4 years</td>
<td>&quot;No serious adverse events or infections&quot;</td>
</tr>
<tr>
<td>Touma, 2008</td>
<td>1</td>
<td>25 years F, 2 mos</td>
<td>8 mos.</td>
<td>&quot;No side effects were reported&quot;</td>
</tr>
</tbody>
</table>

AZA, azathioprine; GI, gastrointestinal; JDM, juvenile dermatomyositis; PM, polymyositis; RTI, respiratory tract infection; UTI, urinary tract infection.
REFERENCES


Rituximab in neurological diseases

APPENDICES

Appendix 1 Details of cost estimates

IVIg therapy. Each IVIg treatment requires 3-4 vials of IVIg. The initial IVIg treatment is given daily for 3 days, followed by single maintenance treatments. Each dose is administered on an outpatient basis over 4 hours, and requires nursing support estimated at around $50 per hour (Dr Genge, personal communication). Patients with severe disease may need retreatment every week to every three weeks to avoid a crisis and hospitalization, thus such patients may require 37 to 104 treatments over 2 years (Dr Genge, personal communication). This is consistent with the analysis by Guptill et al, 2011 and 2012. In their overall cohort of 1288 patients (out of 6 million in the insurance database), 12% received IVIg 5 to >100 times over two years. In a matched study comparing costs of 113 patients with MG and patients without MG, the 6 (5.3%) patients who received MG had a total of 136 IVIg treatments over one year, an average of 23 treatments per patient. For our cost estimates we would assume that such patients will receive 46 treatments over 2 years.

Reports on costs of MG management indicate that hospitalization (ICU and non-ICU) and the cost of IVIg were major contributors to the cost of treatment of MG. In the analysis by Guptill et al, of a US insurance database, IVIg administration contributed 85% of MG-related pharmacy costs, and a subset of approximately 55 patients (of 1288 patients total) who received more than 20 infusions over the study period of 2 years contributed 62% of all pharmacy costs.

Plasmapheresis. The minimum number of plasmapheresis treatments is 6, with some patients requiring additional weekly to monthly PE. Each treatment is administered on an outpatient basis over several hours and requires blood-bank nursing support. Patients with severe disease may need retreatment every week to every month, resulting in 24 to 104 treatments over 2 years (Dr. Genge, personal communication). This is consistent with the most informative case series by Nowak et al (14 patients), in which the median number of cycles of PE in the 12 months prior to rituximab was 7.5 (range, 0 to 34). For present purposes this equates to an estimate of 0 to 68 over two years.

These estimates assume that patients are maintained on one treatment or another over time, and disregard the minority who receive both. In the insurance database of hospital admissions for MG or MG crisis analysed by Mandawat et al, 31.3% of patients received IVIg or PE, and 0.5% patients received both.

Rituximab therapy. Rituximab is administered following the RA protocol, with an initial two doses of 1 g separated by 2 weeks, and a maintenance dose of 1 g administered every 6 months for 2 years, for a total of 6 scheduled doses. Each dose is administered on an outpatient basis at a 90 minute to 2 hour visit, and requires nursing support.
**Impact on costs of replacement of IVIg or PE by rituximab.** The cost of the three treatment modalities are compared in Table 10. The impact of the use of rituximab on direct treatment costs of MG will depend on the extent to which use of IVIg and PE can be reduced or abolished.

**Table 10 Estimate of the average cost per patient for 2 years of treatment (initiation and ongoing) with rituximab, IVIg, and PE.**

<table>
<thead>
<tr>
<th>Resource use (unit)</th>
<th>Unit price</th>
<th>Estimate cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab therapy in 2 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (1 g)</td>
<td>2 (two doses)</td>
<td>$4,631</td>
</tr>
<tr>
<td>Nursing (hour)</td>
<td>4 (2*2 hours)</td>
<td>$50</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (1 g)</td>
<td>4 (1 dose per 6 month)</td>
<td>$4,631</td>
</tr>
<tr>
<td>Nursing (hour)</td>
<td>8 (2*4 hours)</td>
<td>$50</td>
</tr>
<tr>
<td>Total (trial plus maintenance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IVIg maintenance therapy in 2 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIg (3 vials per week)</td>
<td>312 (3*104 vials)</td>
<td>$560</td>
</tr>
<tr>
<td>IVIg (3 vials per 3 week)</td>
<td>105 (3*35 vials)</td>
<td>$560</td>
</tr>
<tr>
<td>Nursing (1 therapy per week) (hour)</td>
<td>416 (4*104 hours)</td>
<td>$50</td>
</tr>
<tr>
<td>Nursing (1 therapy per 3 week) (hour)</td>
<td>140 (4*35 hours)</td>
<td>$50</td>
</tr>
<tr>
<td>Total (1 therapy per week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (1 therapy per 3 week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasmapheresis maintenance therapy in 2 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: Plasmapheresis (1 session per week)</td>
<td>104 sessions</td>
<td>$1,500*</td>
</tr>
<tr>
<td>Total: Plasmapheresis (1 session per month)</td>
<td>24 sessions</td>
<td>$1,500*</td>
</tr>
</tbody>
</table>

* Nursing costs included in the estimate.

If rituximab were to eliminate completely the need for IVIg for maintenance, assuming no offsetting change in disease status or adverse effects, over two years there would be cost savings of $37,414 to $167,134 per patient. Four of five patients in the MUHC series and 6/6 patients described by Lebrun et al\textsuperscript{20} (part of the Collongues series) were able to discontinue IVIg. Those who could not reduce their IVIg at all would not continue on rituximab, therefore would not contribute to rituximab costs. The case series published by Blum et al\textsuperscript{11} showed a lesser but still cost-significant dose reduction, 6/9 patients had an IVIg dose reduction of 50%
(calculated cost savings of $4,514 to $69,374; Figure 3), 2/9 had no change, and one had an exacerbation that required a course of IVIg to treat.

Similarly if rituximab were to eliminate completely the need for PE for maintenance, assuming no offsetting change in the patient’s disease status or adverse effects, over two years there would be cost savings of $7,614 to $127,614 per patient. In the MUHC series, four patients were able to stop PE, and one could reduce the frequency, while in the Nowak series, the median number of PE cycles over 12 months was reduced from 7.5 to 0, and the upper limit was reduced by approximately 50% (34 versus 19 cycles over 12 months)\textsuperscript{28}, which would represent a cost impact ranging from an additional expense of $10,386 to a cost savings of $49,614 per patient. After the third cycle (18 months after initiation of rituximab), all the patients described by Nowak et al were able to stop PE.