A Review: The Use of Rituximab in Neuromuscular Diseases

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Abstract
Autoimmunity plays a major role in the pathogenesis of many neuromuscular disorders such as chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, polymyositis, dermatomyositis, myasthenia gravis, Lambert Eaton syndrome, and stiff person syndrome. Although most of these disorders respond favorably to the commonly used immunomodulatory agents such as steroids, intravenous gamma globulin, plasmapheresis, and chemotherapy, some are initially refractory, whereas others gradually lose responsiveness. Therefore, alternative, selective, and novel immunosuppressive agents are used to treat these cases. Among these agents, rituximab has shown promise in some of the neuromuscular disorders with minimal side effects. Rituximab is a genetically engineered antibody that depletes CD20+ B-cells and is Food and Drug Administration-approved for treatment of non-Hodgkin lymphoma, CD20+ CLL, and rheumatoid arthritis. It carries a favorable side effects profile. However, evidence of efficacy is limited to case series and large prospective randomized controlled trials are lacking. In this article, we review and discuss the available literature on rituximab in treatment of various autoimmune neuromuscular diseases.

Key Words: rituximab, neuromuscular disease, novel treatments in autoimmune diseases, multifocal motor neuropathy, neuropathy with anti-MAG antibodies, polymyositis, dermatomyositis, myasthenia gravis

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RITUXIMAB

Mechanism of Action
Rituximab is a genetically-engineered mouse-human chimeric monoclonal antibody. Rituximab specifically eliminates B-cells and B-cell precursors by binding to CD20 antigen inducing their lysis. Figures 1 to 3 summarize the suggested mechanism by which rituximab depletes CD20+ B-cells. This is thought to be through a combination of antibody-dependent cellular cytoxicity involving macrophages (Fig. 1), complement-dependent cytotoxic effects (Fig. 2), and the promotion of apoptosis (Fig. 3). Although the role of CD 20 is not fully understood in B-cell homeostasis, it is thought to affect the Ca++ influx to the cell, thus activating B-cell lymphocytes.

Rituximab is Food and Drug Administration-approved for treatment of CD 20-positive lymphomas and rheumatoid arthritis and is reported to be beneficial in multiple autoimmune disorders. Rituximab reduces peripheral B-lymphocyte counts by 90% within 3 days. B-cell depletion influences cytokine networks, B-cell-mediated antigen presentation, and activation of T-cells and macrophages.

Total antibody levels are not significantly reduced after a single treatment course because plasma cells are not targeted as a result of their lack of CD 20; thus, the rapid onset of action is unlikely to be explained by a reduction in pathogenic autoantibodies. A more likely explanation is that the effects of rituximab on radiologic and clinical outcomes observed in clinical trials resulted from lysis of memory B-cells located in the peripheral blood, lymphoid tissues, and perhaps in the central nervous system. Interference with antigen presentation by B-cells, or with activation of T-cells or macrophages by proinflammatory B-cell cytokines such as interferon-γ and interleukin-12, may also play a role.

Dose and Administration
The standard dose of rituximab is 375 mg/m² weekly for 4 weeks. This is derived from the original pivotal Phase III clinical trial...
of rituximab for indolent lymphoma. However, recently a dose of 750 mg/m² (up to 1.0 g total dose) on Days 1 and 15 is more frequently used following a double-blinded clinical trial of rituximab in rheumatoid arthritis. Both doses were tolerated very well and the majority of adverse events were associated with the first rituximab infusion; therefore, it is recommended that the first infusion is administered in an inpatient setting; subsequent infusions can be given as an outpatient with 1 to 2 hours monitoring after the infusion.

**Side Effects**

Information about side effects is mostly derived from studies on immunosuppressed hosts who were on multiple chemotherapeutic agents. Complications such as tumor lysis syndrome are not expected in neuromuscular patients.

Most side effects are mild and transient such as fever, chills, headache, and asthenia. Hypotension, bronchospasm, urticaria, leukopenia, progressive multifocal leukoencephalopathy, and reactivation of viral infections are rare but serious potential adverse events.
The long-term hematologic side effects are uncertain.

**Review of Neuromuscular Disorders Treated With Rituximab**

**Strategy of Search**

We conducted a full search using MEDLINE (January 1995 to June 2010) and MEDLINK search engines for all randomized controlled trials (RCTs) of rituximab in autoimmune neuromuscular diseases published in English. We also searched for controlled quasirandomized trials in which treatment allocation was intended to be random but might have been biased as a result of alternate allocation or allocation according to the day of the week. We evaluated historically controlled trials, uncontrolled prospective and retrospective comparative cohort studies, case-control studies, and case series. Our key words were: rituximab, neuromuscular disease, novel treatments in autoimmune diseases as well as specific names of the neuromuscular disorders of interest (ie, multifocal motor neuropathy, neuropathy with antemyelin-associated glycoprotein antibodies, chronic inflammatory demyelinating polyneuropathy, polymyositis, dermatomyositis, and myasthenia gravis).

**Inclusion Criteria of the Studies**

Because rituximab is a fairly new medication in neuromuscular diseases, all case series, case reports as well as controlled studies were included for review.

**Strength of Evidence**

The GRADE approach is a structured system for rating quality of evidence and grading strength of recommendation in clinical practice.\(^6,7\) This system classifies quality of evidence as high (Grade A), moderate (Grade B), low (Grade C), or very low (Grade D). Randomized trials begin as high-quality evidence (Grade A) but may be downgraded to moderate (Grade B) as a result of limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias. In high-quality evidence, further research is very unlikely to change our confidence in the estimate of effect. In moderate-quality evidence, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Well-done observational studies are considered moderate (Grade B) evidence, leaving large case series as low (Grade C) and small case series with expert opinion as very low (Grade D) evidence. In low-quality evidence, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Finally, in small case series, the quality of the evidence is very low, making the estimate uncertain.

**Multifocal Motor Neuropathy**

Multifocal motor neuropathy (MMN) is a rare, almost always asymmetric, demyelinating,
purely motor neuropathy mainly starting between ages 20 to 50 years with slow and often stepwise progression. Intravenous immunoglobulin (IVIg) is usually effective and well tolerated when applied properly. However, some patients experience decreased efficacy of IVIg over time. Cyclophosphamide is also commonly used but is poorly tolerated.

Uncontrolled studies indicate that rituximab may be effective in the majority of the treated patients (Table 1). The first report was in four declining MMN cases despite treatment 3 to 5 years earlier with plasma exchange and cyclophosphamide. One had received IVIg 1 year earlier with transient response. Four weekly intravenous infusions of rituximab (375 mg/m²) significantly improved the function, increased quantitative strength measurements, and reduced titers of serum autoantibodies in all four cases at 3 to 6 months after the initial treatment.

The largest published case series was a 2-year open-label study of rituximab at a similar dose in 21 cases of IgM-associated polyneuropathies, some of whom received maintenance therapy. This included 14 patients with MMN with positive IgM antiganglioside antibodies; 11 of those patients had conduction block. The control group consisted of 13 cases that were not treated as a result of patient choice, lack of insurance coverage, or evaluation and follow-up before rituximab. Quantitative strength measures improved by 13% to 22% in the rituximab group at 1 and 2 years and remained essentially unchanged in the control subjects. This corresponded to a 45% reduction in GM1 titers at 2 years. However, most patients with initial benefit developed recurrent weakness beginning from 3 to 9 months after treatment. Hence, 8 to 15 months after the initial course of rituximab, those patients received a second set of treatment (375 mg/m² every week for 2 weeks and then one infusion every 10 weeks). Over the 2 years of the study, those patients showed improved strength, averaged at 23% of their normal strength. The authors concluded that continued treatment might often be necessary to optimize clinical improvement.

### TABLE 1. Rituximab in Refractory Multifocal Motor Neuropathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Grade of Evidence</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine and Pestronk¹⁰</td>
<td>1999</td>
<td>5 (4 with MMN, one with anti-MAG)</td>
<td>D</td>
<td>Patients showed increased strength and a progressive decline in their serum antibody titers to GM1 ganglioside or MAG</td>
</tr>
<tr>
<td>Pestronk et al¹¹</td>
<td>2003</td>
<td>21 patients (14 with MMN)</td>
<td>C</td>
<td>rituximab significantly improved strength and effectively reduced IgM titers, 16 of the 21 patients received a second set of treatment</td>
</tr>
<tr>
<td>Gorson et al¹²</td>
<td>2007</td>
<td>2 with MMN</td>
<td>D</td>
<td>One patient reduced IVIg by 43%, whereas the other patient required increased IVIg</td>
</tr>
<tr>
<td>Stieggbauer et al¹³</td>
<td>2009</td>
<td>3</td>
<td>D</td>
<td>Sustained clinical improvement</td>
</tr>
</tbody>
</table>

MMN, multifocal motor neuropathy; MAG, myelin-associated glycoprotein; IVIg, intravenous immunoglobulin.
Gorson et al reported a prospective, uncontrolled, 12-month pilot trial of six patients, two of whom had MMN. Patients were treated with rituximab (375 mg/m$^2$ every week for 4 consecutive weeks). One patient reached the arbitrary primary end point of a reduced cumulative IVIg dosage by at least 25% at 1 year after rituximab therapy compared with the previous year, whereas the other patient with MMN required increased IVIg. The authors hypothesized that none of their patients achieved prolonged B-cell suppression with this regimen.

Lately, Stieglbauer et al reported a series of three patients with MMN and declining response to IVIg. Monotherapy with rituximab (375 mg/m$^2$ every week for 2 consecutive weeks) was followed by sustained clinical improvement. The authors attributed the observed improvement to rituximab alone, because all patients discontinued IVIg at least 1 month before initiation of rituximab therapy. All are noncontrolled studies and used a dose of 375 mg/m$^2$ every week for 4 consecutive weeks.

Although three of these limited case series suggest a clinical benefit of rituximab in MMN, this estimate is uncertain. This is the result of the low grade and mostly very low grade of the evidence at hand. RCTs are lacking.

**Neuropathy With Antimyelin-Associated Glycoprotein Antibodies**

Demylinating polyneuropathy associated with IgM monoclonal gamopathy and antibodies against myelin-associated glycoprotein (MAG) is a distinct entity that presents with progressive sensory ataxia or sensorimotor deficits. Despite the obvious autoimmune mechanisms underlying this illness, cyclophosphamide, IVIg, prednisone, and other immunosuppressants offer only minimal and transient benefit to a small number of those patients. Of the 21 rituximab-treated cases, from Pestronk et al’s report, seven had neuropathy with MAG antibodies and all improved.

Rojas et al administered rituximab to two patients with chronic motor neuropathy with IgM-antibodies received IVIg at progressively reduced intervals. One case remained stable at 2 months then required IVIg at Month 3 and the other case got worse after rituximab infusion.

In 2005, Renaud et al reported a case series of nine patients with anti-MAG neuropathy treated with rituximab (375 mg/m$^2$ weekly for 4 weeks). Six patients improved clinically as reflected by the Neurologic Disability Score at 12 months; however, two patients remained the same and one deteriorated. This was followed in 2006 by a study of high-dose rituximab, 750 mg/m$^2$ administered weekly for 4 weeks, in patients who had not received the lower-dose rituximab for at least 17 months. They treated eight patients from the prior study, one of whom died months later of unrelated causes. Four of seven participants were noted to have improvement in the Neurologic Disability Score variables along with improvement of nerve conduction velocities and a reduction of anti-MAG antibody titers. Two had not responded to the lower dosage.

In an uncontrolled open-label study, eight of the 13 patients (62%) with anti-MAG polyneuropathy improved at 1 year after rituximab treatment. The eight responders improved in their inflammatory neuropathy cause and treatment (INCAT), sensory sum score, and the Medical Research Council sum score for muscle strength. Seven also improved in the INCAT disability score.

The randomized double-blind placebo-controlled trial of rituximab (four weekly infusions, each 375 mg/m$^2$) in patients with anti-MAG demyelinating neuropathy included 13 rituximab and 13 control cases. Although the process of randomization is not fully described, it was balanced for age, duration of the disease, and other significant parameters but not for gender. The primary outcome measure was a change of 1 point in INCAT disability scale score in the lower extremities at Month 8. Although four of 13 rituximab-treated patients met the primary outcome
measure compared with none of the placebo recipients, the difference was not statistically different ($P = 0.096$) and one patient got worse. One patient, randomized to rituximab and properly rated at screening as having an INCAT score of 1, was discovered in retrospect that he had been entered as having a normal (0) INCAT leg score. Reanalysis with exclusion of this case yielded a statistically significant difference between drug and placebo. Although the onset and peak of improvement coincided with B-cell depletion, it is unclear whether the described improvement was the result of depletion of B-cells or to reduction of autoantibodies.  

**Myasthenia Gravis**

Myasthenia gravis (MG) is an autoimmune disease caused by failure of neuromuscular transmission as a result of decreased sensitivity of the postsynaptic membrane to the neurotransmitter acetylcholine. The anti-acetylcholine receptor (AChR) antibodies (Ab) and complement cascade are implicated in the autoimmune attack against the AChR, which leads to a loss of these receptors and ultimately degeneration of the post synaptic membrane. Eighty percent of generalized MG cases are seropositive for the AChR Ab. Thirty percent to 50% of the seronegative cases harbor muscle-specific tyrosine kinase (MuSK) antibodies. The remaining double-seronegative generalized MG patients have IgG1 AChR antibodies to rapsyn-clustered AChR in 60% of cases.

The first reports on the use of rituximab in MG were in patients treated for lymphoma. In three of these patients, rituximab was administered at 375 mg/m$^2$ weekly for 4 weeks, and in one, the dose was 260 mg/m$^2$ weekly for 4 weeks. Clinical symptoms of MG such as diplopia and muscle fatigability as well as pulmonary function tests showed improvement with a decrease in the serum AChR Ab levels.

This was followed by the publication of several small and one large uncontrolled case series. In 2008, Illa et al reported treating six severe refractory myasthenics (three AChR Ab-positive and three MuSK-positive) with rituximab at 375 mg/m$^2$ weekly for 4 weeks. All six cases (five MGFA Grade IVb and one Grade V) clinically improved dramatically. Although there was a decline in serum antibody titers in the AchRc Ab group, this was significantly better at 9 months in the MuSK-positive group and correlated with a more sustained clinical improvement. No severe adverse events were reported.

Lindberg et al reported their retrospective review of five patients with AChR Ab-positive MG resistant to conventional immunosuppression including three with thymoma. Rituximab treatment was initially with four weekly infusions of 375 mg/m$^2$. Quantitative MG score was overall markedly lower after rituximab, and in the three patients with respiratory muscle involvement, the forced vital capacity was increased. Three patients relapsed 12 to 23 months after the initial response and one had an incomplete response. Therefore, these four cases received a second treatment with 1000 mg infusions in biweekly interval and this was repeated again in two cases. All four patients responded to rituximab with a remarkable reduction of MG symptoms, although the onset of improvement was slow and gradual, which could be explained by the MG severity or duration.

Maddison et al reported data obtained from a nationwide survey of physicians treating MG in the United Kingdom. They identified 10 patients diagnosed with generalized MG (seven AChR Ab-positive and three MuSK-positive) and two with Lambert-Eaton myasthenic syndrome. Rituximab was administered in standard doses in eight cases, whereas the rest received one or two infusions at 375 mg/m$^2$. Over the 4- to 48-month follow-up period, three of seven AChR Ab-positive MG cases improved on their MGFA postintervention status, whereas all MuSK-positive cases improved. Both Lambert-Eaton myasthenic syndrome cases improved but did not achieve remission. However, four patients did not have significant benefit from rituximab and three of those received fewer than four infusions.
There are other small case series that have suggested similar efficacy of rituximab in generalized MG. The report by Lebrun et al included six bedridden MG cases; one was AchRc Ab-positive, three had MuSK Ab, and two were double-seronegative cases. Rituximab was administered at 375 mg/m² on Days 1, 8, 15, and 21 during the first month and then one dose every 2 months. All cases responded very well to rituximab with significant clinical improvement allowing for the tapering of prednisone and pyridostigmine bromide. Nelson et al reported response in three patients with MG with thymoma after treatment with rituximab.

Tandan is leading an ongoing open-label Phase I to II pilot trial of rituximab in refractory MG. This study is closed to enrollment. The primary outcome measure is to examine the effects of rituximab on disease activity in patients with MG with refractory disease. The secondary outcome measure is the safety and tolerability of rituximab in patients with MG with refractory disease. The investigator's plan is to follow all 10 patients for 1 year (ClinicalTrials.gov NCT00619671).

To date, more than 30 cases have been reported of patients with MG treated with rituximab (Table 3). Only seven did not have significant improvement in their symptoms. However, given the bias of reporting positive studies and the low grade of evidence, it is difficult at this time to derive any firm conclusions about the role of rituximab in MG beyond the prevailing excitement.

**Dermatomyositis**

Dermatomyositis (DM) is an inflammatory muscle disease caused by a humeral response directed against the intramuscular vascular endothelium. Most cases respond to corticosteroids. Methotrexate, azathioprine, mycophenolate, and IVIg are also effective second-line therapies. However, refractory cases are also reported, especially in children.

Levine reported a small open-label uncontrolled pilot trial in seven adult DM cases, six of whom were responding inadequately to established immunosuppressive agents. Subjects received four intravenous infusions of rituximab at 100 to 375 mg/m² given at weekly intervals. The primary efficacy outcome parameter was the maximal muscle strength measured by quantitative dynamometry in 18 different muscle groups. Treatment was considered to be effective if muscle strength was improved by 12% at 24 and 52 weeks. One patient was lost to follow-up, whereas two patients were followed up for a minimum of 24 weeks, two patients for 36 weeks, and two patients for at least 52 weeks. At baseline, patients muscle strength ranged from 39% to 60% of normal. Improvements were evident as early as 4 weeks after initial infusion and were maximal at 12 weeks in two patients and at 24 weeks in two patients. Thereafter, muscle strength began to wane in these four patients. In the other two patients, maximal improvement was reached at 36 weeks and was sustained. Overall strength at the time of maximal improvement ranged from 68% to 102% of normal strength. Rituximab consistently depleted B-cell levels and notably, improvements in muscle strength, rash, vital capacity, and enzyme markers corresponded to B-cell depletion.

Cooper et al performed a retrospective chart review of four pediatric patients, ages 10 to 17 years, with juvenile DM refractory to methotrexate, prednisone, and IVIg. All patients tolerated rituximab well. The only case with antibodies to Mi-2 had a dramatic response in her muscle and cutaneous manifestations beginning 2 months after weekly rituximab infusions at a dose of 375 mg/m² for a total of four doses. She was retreated at 1 year for a relapse with good response. In two other cases, strength and rash started to improve at 2 months and near-normalized at 6 months after rituximab infusion. One of these two cases responded to rituximab administered 1 year later for a relapse. The fourth case improved in strength but not in rash at 2 months and was therefore treated with IVIg. One year later, Case 4 started cyclosporine for cutaneous vasculitis and interstitial lung disease.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Controlled</th>
<th>Grade of Evidence</th>
<th>Dose of Rituximab</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pestronk et al⁹</td>
<td>2003</td>
<td>7</td>
<td>Retrospective</td>
<td>C</td>
<td>375 mg/m² once weekly for 4 weeks</td>
<td>Significantly improved strength and effectively reduced IgM titers</td>
</tr>
<tr>
<td>Rojas-Garcia et al¹⁶</td>
<td>2003</td>
<td>2</td>
<td>No</td>
<td>D</td>
<td>Rituximab IV 375 mg/m² once weekly for 4 weeks after 1 month washout period from IVIg infusions</td>
<td>No improvement in either patient.</td>
</tr>
<tr>
<td>Renaud et al¹⁷</td>
<td>2003</td>
<td>9</td>
<td>No</td>
<td>D</td>
<td>375 mg/m² every week for 4 consecutive weeks</td>
<td>6 improved, 2 stabilized, one worsened</td>
</tr>
<tr>
<td>Renaud et al¹⁸</td>
<td>2006</td>
<td>8</td>
<td>No</td>
<td>D</td>
<td>750 mg/m² weekly for 4 weeks</td>
<td>Continuation of the previous set of patients, 4 patients improved in their NDS</td>
</tr>
<tr>
<td>Benedetti et al¹⁹</td>
<td>2007</td>
<td>13</td>
<td>No</td>
<td>C</td>
<td>375 mg/m² weekly for 4 weeks</td>
<td>8 patients improved in the ISS, 2 stabilized, and 3 worsened</td>
</tr>
<tr>
<td>Dalakas et al²⁰</td>
<td>2009</td>
<td>26 (13 on rituximab, 13 on placebo)</td>
<td>Yes</td>
<td>B</td>
<td>375 mg/m² weekly for 4 weeks</td>
<td>Placebo controlled trial, significant difference in favor of the rituximab arm after excluding 1 case</td>
</tr>
</tbody>
</table>

MAG, myelin-associated glycoprotein; IV, intravenous; IVIg, intravenous immunoglobulin; NDS, Neurologic Disability Score; ISS, sensory sum score.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Controlled</th>
<th>Grade of Evidence</th>
<th>Dose of Rituximab</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illa et al</td>
<td>2008</td>
<td>6</td>
<td>No</td>
<td>D</td>
<td>375 mg/m² every week for 4 consecutive weeks</td>
<td>Improvement of clinical and laboratory parameters, especially in the 3 MuSK cases Improved</td>
</tr>
<tr>
<td>Stiegler et al</td>
<td>2009</td>
<td>3</td>
<td>No</td>
<td>D</td>
<td>Guided by the total count of peripheral B lymphocytes</td>
<td>3 MuSK, 1 AChR Ab, and 2 double-seronegative improved</td>
</tr>
<tr>
<td>Lebrun et al</td>
<td>2009</td>
<td>6</td>
<td>No</td>
<td>D</td>
<td>375 mg/m² every week for 4 weeks then 2-monthly dose of 375 mg/m²</td>
<td>3 MG cases with thymoma responded with stabilization and reductions in immunosuppressive medications</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>2009</td>
<td>3</td>
<td>No</td>
<td>D</td>
<td>375 mg/m² every week for 4 consecutive weeks, one patient received only one dose</td>
<td>Slow but remarkable reduction in MG symptoms</td>
</tr>
<tr>
<td>Lindberg et al</td>
<td>2010</td>
<td>5</td>
<td>No</td>
<td>D</td>
<td>375 mg/m² every week for 4 consecutive weeks, retreatment with 1000 mg weekly × 2</td>
<td></td>
</tr>
<tr>
<td>Tandan et al</td>
<td>2010</td>
<td>10</td>
<td>No</td>
<td>C</td>
<td>Ongoing pilot study</td>
<td>Ongoing pilot study</td>
</tr>
<tr>
<td>Maddison et al</td>
<td>2010</td>
<td>12</td>
<td>No</td>
<td>C</td>
<td>375 mg/m² every week for 4 consecutive weeks</td>
<td>Ongoing pilot study</td>
</tr>
</tbody>
</table>

MuSK, muscle-specific tyrosine kinase; AChR Ab, antiacetylcholine receptor antibody; MG, myasthenia gravis.
In an open-label prospective trial of rituximab in eight patients with refractory DM, all subjects received two doses of 1 g rituximab 2 weeks apart. The primary end point measure was the percentage of patients with a partial remission at Week 24. This was defined as one of the following: at least 50% reduction in CPK levels (if the baseline values were greater than two times elevated); at least 50% reduction in muscle strength deficit (if the baseline manual muscle testing score was less than 85); or a 75% improvement in the DM skin severity index score. It is interesting that the baseline manual muscle testing score was normal in one case and that the lowest manual muscle testing score was 78 out of 90, indicating milder degrees of weakness. Rituximab infusions were well tolerated with complete peripheral B-cell depletion through Week 24. Of the eight subjects, three (38%) met predefined criteria for partial remission, showing improvement in muscle strength in each case. No significant changes in skin disease were observed through 24 weeks of follow-up. Muscle enzyme levels fluctuated throughout the study and did not reflect muscle strength.

A randomized controlled trial of rituximab in refractory juvenile and adult DM and in adult polymyositis is ongoing but closed to enrollment. This Phase II clinical trial is testing two hypotheses. The study hopes to demonstrate that the time to improvement in the group receiving rituximab first (Group A) will occur significantly earlier than in patients receiving rituximab later (Group B) and that the proportion of patients improved at Week 8 will be significantly greater in Group A than in Group B. Table 4 shows evidence grade on using rituximab in patients with dermatomyositis.

**CONCLUSION**

Although rituximab was suggested to be effective and relatively safe in several autoimmune neuromuscular disorders,
most of the published data are derived from small uncontrolled case series. Given the associated price tag of rituximab ($646.65 retail cost of 10-mL vial, 10 mg/mL) and the continuing economic pressure to reduce healthcare costs, large controlled trials of rituximab are critically important to the well-being of our neuromuscular patients. A large RCT of rituximab has completed recruitment and is ongoing in the idiopathic inflammatory myopathies. A small RCT of rituximab in MAG neuropathy recently reported modestly encouraging preliminary results. There is certainly a need for large RCTs in MG, both AChR-positive and especially MuSK cases. Perhaps a similar approach should be considered in MMN. Until then, the role of rituximab in autoimmune neuromuscular disorder remains experimental and uncertain.

REFERENCES


39. RIM Study: Phase II trial Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis (DM) and Adult Polymyositis (PM) (ClinicalTrials.gov NCT00106184).