Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

*Volume 15, Number 4*
*June 2014*



# Treatment-Refractory Myasthenia Gravis

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## Abstract

**Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission and is a prototypical autoimmune disorder. Most patients with MG are successfully treated with acetylcholinesterase inhibitors, corticosteroids, and/or steroid sparing agents such as azathioprine and mycophenolate mofetil. There is a small subset of patients, however, with treatment-refractory disease. In these cases, medications such as rituximab, high-dose cyclophosphamide, and eculizumab may be used. Thymectomy (in some cases repeat thymectomy) is another option in selected patients. Studies evaluating these and other forms of therapy in treatment-refractory MG are reviewed.**

**Key Words: myasthenia gravis, refractory, rituximab, cyclophosphamide, eculizumab, thymectomy**

(*J Clin Neuromusc Dis* 2014;15:167–178)

## INTRODUCTION

Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission with a world-wide prevalence estimated to be between 25 and 142 per million.[1] MG is a prototypical autoimmune disease. Approximately 85% of patients with generalized MG have antibodies to the acetylcholine receptor (AChRAb). Previous reports that examined the frequency of antibodies to muscle receptor tyrosine kinase (MuSK) have found a range from 0% to 49% with a mean frequency of about 35%.[2–6] Similarly, a small percentage of patients have antibodies to lipoprotein-related protein 4 (LRP4). Treatment of MG usually includes a combination of symptomatic therapy with acetylcholinesterase inhibitors (eg, pyridostigmine), immunosuppressive medications, and in selected patients thymectomy.[7] Myasthenic crisis is defined as ventilatory failure due to weakness of bulbar muscles and/or muscles of respiration, and occurs in 15%–20% of patients, usually earlier on in the disease course. It is more common in patients with MuSK antibodies (MuSK Ab).[5,8,9] Treatment is aimed at eliminating the cause for crisis, if any (eg, infection), and immunotherapy using either intravenous immunoglobulin (IVIg) or plasma exchange.

With adequate treatment, most MG patients are able to live productive lives with few or no symptoms. There is a distinct subset of patients, however, who have very difficult-to-control disease. These patients are often referred to as having treatment-refractory myasthenia. Despite there being no standard definition of refractory myasthenia, previous studies have generally used the following criteria: (1) failure to respond to otherwise adequate doses and durations of conventional immunosuppressive treatments, (2) unacceptable adverse reactions to conventional treatments, (3) requirement of excessive amounts of potentially harmful agents, (4) presence of comorbidities that preclude the use of conventional treatments, (5) requirement for repeated rescue treatment with short-term therapies such as IVIg and plasma exchange, and/or (6) frequent myasthenic crises.[10] Patients with MuSK Ab seem to have refractory disease more likely than those with other forms of MG.

The exact prevalence of refractory myasthenia is unknown, but it is estimated to occur in approximately 10% of patients with generalized disease.[11] Suh et al[12] performed a retrospective study of 128 sequential patients who were seen in their clinic in a large tertiary referral center. They defined refractory patients as those who could not lower their immunotherapy without clinical relapse, were not clinically controlled on their immunotherapy regimen, or experienced severe side

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The authors report no conflicts of interest.

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effects from immunotherapy. Based on this definition, 19 of 128 (14.8%) patients were found to be refractory. This is likely to be an overestimate because they conducted the study on a large tertiary clinic referral population that likely consisted of patients with less stable disease. The median age of the refractory group was 36 years versus 60 years in the nonrefractory group. Refractory patients were more likely to be female (14/19) and MuSK Ab positive [47% vs. 2% of nonrefractory group ($P < 0.001$)]. Patients in the refractory group were also more likely to have undergone thymectomy and to have had thymoma.

When patients are deemed to be refractory, more aggressive treatment is warranted to prevent life-threatening crises. Although there are no evidence-based guidelines, agents such as rituximab, high-dose cyclophosphamide, and more recently eculizumab have been used. Thymectomy (repeat thymectomy in some cases) is another option. In the following sections, we will review the application of these therapies in refractory MG.

## RITUXIMAB

Rituximab is a chimeric murine–human IgG1 kappa monoclonal antibody that depletes B cells by binding to their CD20 molecule and initiating complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity.[13] The drug does not impair B cell recovery or antibody production or secretion. Rituximab has been used successfully in a number of autoimmune diseases including systemic lupus erythematosus, autoimmune hemolytic anemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura, mixed cryoglobulinemia, and Wegener granulomatosis.[14] The benefits of rituximab in refractory myasthenia were first described by Zaja et al[15] in 2000 and in several case reports and small, mostly retrospective, series since then.[11,16–26]

Lebrun et al[21] prospectively followed 6 patients (3 MuSK Ab positive, 1 AChRAb positive, and 2 seronegative) with refractory myasthenia. All patients failed treatment with 2–3 standard agents and had previously undergone thymectomy. Patients received 375 mg/m$^2$ of rituximab weekly for 4 weeks, and then monthly for 2 months. After the initial phase, treatment was given based on the clinical status (patient-reported worsening or the need to increase acetylcholinesterase inhibitors). Two patients required repeat infusions for 1 year and 2 others for 2 years. Clinical improvement was noted in all patients within 1 month of treatment, defined by the investigators as their ability to perform clinical activities without weakness. All patients were eventually tapered from acetylcholinesterase inhibitors, prednisone, and/or other immunosuppressants. Rituximab was well tolerated in these patients without significant adverse effects or opportunistic infections.

Nowak et al[23] performed a retrospective study of 14 refractory patients (6 AChRAb positive and 8 MuSK Ab positive) who were successfully treated with rituximab. Patients were defined as refractory when they could not lower immunotherapy without clinical relapse, were not clinically controlled on their immunotherapy regimen, or had severe side effects from the therapy. Rituximab dosing was 375 mg/m$^2$ weekly for 4 weeks with a repeat cycle of 375 mg/m$^2$ weekly for 4 weeks repeated every 6 months. The mean prednisone dose decreased by 65.1%, 85.7%, and 93.8% after cycles 1, 2, and 3, respectively. There was a statistically significant reduction in the number of plasma exchange sessions after rituximab treatment. AChRAb titers also declined. A clinically evident improvement was sustained in all patients. There were few adverse effects of the drug in this study with 1 patient developing transient leukopenia. The same group also reported 6 patients (4 MuSK Ab positive and 2 AChRAb positive) treated with rituximab for refractory disease.[11] As in the larger study, all patients improved clinically and/or were able to reduce their doses of immunosuppressants.

A retrospective, observational study performed by Collongues et al[22] evaluated the effect of rituximab in both refractory patients (n = 13; 7 AChRAb positive, 3 MuSK Ab positive, 1 both AChRAb and MuSK Ab

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positive, and 2 seronegative) and nonrefractory patients dependent on corticosteroids (n = 7; 5 AChRAb positive, 1 MuSK Ab positive, and 1 seronegative). Patients in this study were considered refractory if they failed to respond to thymectomy and at least 2 successive immunosuppressive drugs, with or without corticosteroids. All immunosuppressive treatments were stopped before rituximab infusions except for corticosteroids. Rituximab was given according to 2 different protocols: (1) 375 mg/m$^2$ weekly for 4 weeks, and then 375 mg/m$^2$ every 3 months or (2) 2 infusions of 1 g each 2 weeks apart, and then 1 g as required if symptoms worsened. Patients were followed for 2 years. Relapses were treated with IVIg or plasma exchange. In the refractory patients, the annualized relapse rate decreased from 2.1 to 0.3 ($P < 0.001$) compared with the 2 years before rituximab induction. In the refractory group, Myasthenia Gravis Foundation of America (MGFA) classification dropped from a range of 3b-5 to 0-4b. Corticosteroids were withdrawn in 6 refractory patients after 6 months. After 1 year, the mean steroid dose in all patients decreased from 38.5 mg/d to 8.7 mg/d; and after 18 months, it had fallen further to 6 mg/d. No side effects of the treatment were seen in the refractory group; 1 patient in the nonrefractory group developed spondylodiscitis.

Diaz-Manera et al[27] reported on long-term follow-up of 17 drug-resistant patients (11 AChRAb positive and 6 MuSK Ab positive) treated with rituximab. They defined drug-resistant patients as those who failed at least 3 second-line agents (eg, azathioprine, mycophenolate). Rituximab was given at a dose of 375 mg/m$^2$ weekly for 4 weeks, then monthly for 2 months; reinfusions were given if symptoms worsened enough to interfere with activities of daily living. The MGFA post-intervention status was assessed every 3 months, and antibody titers were also measured. Treatment was generally well tolerated except for 2 patients who had either facial flushing or generalized rash. The mean duration of the follow-up was 31 (range, 4–60) months. All MuSK Ab–positive patients reached minimal manifestation status by 3 months after treatment, and all maintained this favorable status or were in remission at 35 months. The average prednisone dose in this group fell from 49 mg/d to 6.5 mg/d at 35 months. Ten of 11 AChRAb-positive patients improved at 3 months. The average dose of prednisone was reduced from 30.5 mg/d to 17.2 mg/d in this group. Six patients who required reinfusions did improve, but none reached minimal manifestations status or remission. There were no significant changes in second-line immunosuppressant dosing in the AChRAb-positive group, unlike the MuSK MG group. MuSK Ab titers declined significantly but the AChRAb titers did not. The authors highlighted the longer lasting treatment effect of rituximab in MuSK Ab–positive patients and hypothesized that this may be due to differences in the pathophysiology of this form of the disease, which is largely mediated by the IgG4 immunoglobulin subclass.

Finally, Illa et al[19] described a sustained response to rituximab in refractory MG. They reported 6 patients with severe disease (3 AChRAb positive and 3 MuSK Ab positive). Per MGFA classification, 5 patients were in stage IVB and 1 patient in stage V, and all were refractory to other treatments. Patients received 375 mg/m$^2$ of rituximab weekly for 4 weeks, and then a single dose monthly for 2 months. The infusions were well tolerated without any side effects being reported. All patients improved clinically; MGFA post-intervention status was minimal manifestations for the 3 MuSK MG patients. All MuSK patients achieved minimal manifestations status 3 months after the infusion, which persisted for 9–22 months. As in previous reports, the response was less robust in AChRAb-positive patients. The investigators were able to reduce immunosuppressive agents in all MuSK patients without clinical relapse.

In general, rituximab was well tolerated by all patients in these studies. The most common side effects were related to the infusions and included fever, chills, hypotension, and dyspnea. Although no reports of progressive multifocal leukoencephalopathy have been reported to date in MG patients

receiving rituximab, this CNS infection has developed in patients receiving the drug for other disease states.[28] Of note, there is no standard dosing regimen for rituximab in MG, although the B-cell lymphoma dosing of 375 mg/m$^2$ weekly for 4 weeks is most commonly used, followed by repeat infusions as clinically indicated. Table 1 lists the dosing regimens used in these studies and the effects of treatment. Studies also suggest that rituximab may have a more dramatic response in MuSK MG. An National Institute for Neurological Disorders and Stroke-funded study of rituximab is commencing in AChRAb-positive MG through the NeuroNEXT clinical trials network.

## CYCLOPHOSPHAMIDE

Several studies have demonstrated the benefit of pulsed cyclophosphamide in the treatment of refractory MG.[10,29–32] Cyclophosphamide is a pro-drug that is hepatically converted to the intermediates 4-hydroxycyclophosphamide and aldophosphamide; the intermediates are ultimately transformed to phosphoramide mustard. Cyclophosphamide targets only mature immune cells. Hematopoietic stem cells are resistant to its effects because they have high levels of cellular aldehyde dehydrogenase, which inactivates aldophosphamide to form inert carboxyphosphamide.[33]

Drachman et al[10] first proposed treating patients with refractory MG with high-dose cyclophosphamide in an attempt to "reboot the immune system" by eliminating the mature immune system while leaving hematopoietic stem cells intact. In their study, they treated 12 refractory patients with high-dose cyclophosphamide 50 mg/kg intravenously daily for 4 days (HiCy). All patients had severe disease before receiving HiCy in a hospital setting: 5 were MGFA class V, 6 were class IV, and 1 was class III. Patients were well hydrated and also treated with ondansetron and mesna to manage nausea and prevent hemorrhagic cystitis. After infusions, patients received red blood cell and platelet transfusions as needed. Granulocyte colony–stimulating factor (G-CSF) was given 6 days after the last infusion and continued until the absolute neutrophil count was above 1000 cells per microliter for 2 consecutive days. Patients also received prophylactic antibiotics while neutropenic. The study subjects were evaluated every 2 months for 12 months, and then for every 3 months. Patients tolerated the infusions fairly well, although 7 experienced neutropenic fever. All but 1 patient showed clinical benefit starting 3 weeks to 3 months after HiCy. More than half experienced prolonged remission. An earlier, smaller study performed by the same group demonstrated benefit in 3 patients who received HiCy that lasted at least 3.5 years.[30] Interestingly, one-quarter of patients in the larger study became responsive to immunosuppressive medications that previously were ineffective for them. The authors concluded that although this highly aggressive treatment approach did not universally cure MG, a "rebooted" immune system did allow for more effective responses to moderate doses of conventional immunosuppressants. This HiCy treatment has not received wide acceptance at MG centers, likely because of its aggressive nature and need for supportive care akin to bone marrow transplantation.

A prospective, double-blind placebo-controlled trial of cyclophosphamide was conducted by De Feo et al[31] involving 23 patients with severe, refractory, generalized, severe refractory MG. Subjects were eligible if they did not respond adequately to corticosteroids, remained to be dependent on corticosteroids for at least 6 months, failed previous attempts to reduce prednisone below 10 mg/d, or experienced significant steroid-related side effects. Poor disease control was defined as moderate or severe respiratory involvement (forced vital capacity less than 60% predicted), moderate or severe swallowing impairment, and moderate or severe limb involvement. Intravenous pulses of cyclophosphamide (initial dose 500 mg/m$^2$) or placebo were given monthly for 6 months, then every other month for 6 months for a total of 9 pulses. Cyclophosphamide doses were adjusted at each infusion based on the clinical response, presence of side

**TABLE 1.** Dosing Regimen and the Effects of Treatment

| Study | Patients | Rituximab Dosing | Repeat Dosing | Clinical Response |
|---|---|---|---|---|
| Lebrun et al[21] | 3 MuSK; 1 AChR; 2 seronegative | 375 mg/m$^2$ weekly $\times$4 weeks, then monthly for 2 months | 2 patients required repeat infusions for 1 year and 2 others for 2 years | Clinical improvement in all; all patients were eventually tapered from AChEI, prednisone, or other immunosuppressants |
| Nowak et al[23] | 6 AChR; 8 MuSK | 375 mg/m$^2$ weekly $\times$4 weeks, then 375 mg/m$^2$ weekly for 4 weeks for 6 months | Patients received 2–6 cycles based on the clinical response | Clinically evident improvement was sustained in all patients: 4/8 MuSK patients in remission at the last visit; 6/6 AChR patients in remission at the last visit |
| Zebardast et al[11] | 4 MuSK; 2 AChR | 375 mg/m$^2$ weekly $\times$4 or 6 weeks | 2 patients required 1 cycle, 1 patient required 2 cycles, 1 patient required 3 cycles, 2 patients required 4 cycles based on the response | 3/4 MuSK patients in remission, the other clinically improved; 1/2 AChR patients in remission, the other clinically improved |
| Collongues et al[22] | 7 AChR; 3 MuSK; 1 AChR + MuSK; 2 seronegative | (1) 375 mg/m$^2$ weekly $\times$4 weeks, then 375 mg/m$^2$ every 3 months or (2) 2 infusions of 1 g each 2 weeks apart | 1 g as required if symptoms worsened | Improved MGFA scores in all patients at 2 years |



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**TABLE 1** (*Continued*)

| Study | Patients | Rituximab Dosing | Repeat Dosing | Clinical Response |
|---|---|---|---|---|
| Diaz-Manera et al[27] | 11 AChR; 6 MuSK | 375 mg/m$^2$ weekly $\times$4 weeks, then monthly for 2 months | 6/11 AChR patients required reinfusions based on clinical symptoms; 0/6 MuSK patients required reinfusion | MuSK Patients<br>All MuSK Ab–positive patients reached minimal manifestation status by 3 months after treatment, and all maintained this favorable status or were in remission at 35 months<br>Significant reduction in second-line immunosuppressant dosing in all patients<br>MuSK Ab titers declined in all patients<br>AChR patients<br>10/11 AChRAb-positive patients improved at 3 months<br>No significant changes in second-line immunosuppressant dosing<br>AChRAb titers did not decline |

**TABLE 1** (*Continued*)

| Study | Patients | Rituximab Dosing | Repeat Dosing | Clinical Response |
|---|---|---|---|---|
| Illa et al[19] | 3 AChR; 3 MuSK | 375 mg/m$^2$ of rituximab weekly ×4 weeks, then a single dose monthly for 2 months | NA | MuSK patients<br>All MuSK patients achieved minimal manifestations status 3 months after infusion, which persisted for 9–22 months. Reduced immunosuppressive agents in all MuSK patients without clinical relapse<br>AChR patients<br>All patients improved but did not reach minimal manifestations status. Reduced dosages of medications in all patients |

| Study | Patients | Cyclophosphamide Dosing | Clinical Response |
|---|---|---|---|
| Drachman et al[10] | 8 AChRAb; 1 MuSK Ab; 3 seronegative | 50 mg/kg IV daily ×4 days | All but 1 patient showed clinical benefit starting 3 weeks to 3 months after HiCy. More than half of the patients experienced prolonged remission |
| Drachman et al[30] | 2 AchRAb; 1 MuSK Ab | 50 mg/kg IV daily ×4 days | Clinical improvement in all up to 3.5 years of follow-up |



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**TABLE 1** (*Continued*)

| Study | Patients | Cyclophosphamide Dosing | Clinical Response |
|---|---|---|---|
| De Feo et al[31] | 23 AChRAb | 500 mg/m$^2$ monthly ×6 months, then every other month ×6 months (doses adjusted based on clinical response, presence of side effects, and white blood cell count) | Statistically significant reduction in the mean daily doses of cyclophosphamide group at 12 months (14.4 mg/d vs. 32.5 mg/d) |
| Dezern et al[29] | Not reported | 50 mg/kg IV daily ×4 days | Complete remission lasting 29–108 months in 3 patients after 2 cycles each. One patient had no response to a third cycle |
| Gladstone et al[32] | 1 AChRAb; 2 seronegative | 50 mg/kg IV daily ×4 days | Complete remission in 1 patient, improved severity of disease in 2 other patients |
| **Study** | **Patients** | **Eculizumab Dosing** | **Clinical Response** |
| Howard et al[40] | 14 AChRAb | 600 mg IV every week for 4 weeks, 900 mg IV on week 5 followed by 900 mg IV every 2 weeks for 6 additional doses versus placebo for 16 weeks followed by 5-week washout and crossover | 86% of actively treated patients versus 57% receiving placebo achieved the primary endpoint (QMG drop by more than 3 points) in period 1 of the study. 57% of patients on eculizumab achieved an 8-point reduction in QMG compared with only 14% on placebo during period 1 of the study |

AChEI, acetylcholinesterase inhibitor; NA, not applicable.

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effects, and white blood cell count. There was a statistically significant reduction in mean daily doses of corticosteroid in both active group and placebo-treated group after 6 months of treatment, but the reduction was more significant in the cyclophosphamide group. This difference was also evident at 12 months (14.4 mg/d vs. 32.45 mg/d). Five patients in the treated group were able to stop corticosteroids completely at 12 months, and 4 remained free of steroids through 36 months. No significant adverse events were reported from cyclophosphamide. Two smaller noncontrolled studies each reported safety and efficacy for cyclophosphamide in refractory MG, in which all patients demonstrated clinical improvement.[29,32]

## ECULIZUMAB

Eculizumab is a more recent addition to the treatment of refractory MG. Eculizumab is a humanized murine monoclonal antibody that blocks activation of complement by binding to C5, preventing its enzymatic cleavage to C5a and C5b, thus preventing proinflammatory effects of C5a and prothrombotic effects of C5b. As a result, there is impaired chemotaxis of inflammatory cells and membrane attack complex–mediated cell activation and lysis.[34] The role of complement in the pathophysiology of MG is well established. The binding of AChRAb to the acetylcholine receptor leads to complement-mediated damage at the neuromuscular junction.[35] MG patients with AChRAb have lower serum complement levels in direct correlation with the titer.[36–38] Older studies have shown that complement inhibition using cobra venom prevents the development of experimental autoimmune MG.[39]

Howard et al[40] conducted a phase 2 pilot trial designed to study the efficacy and safety of eculizumab in severe refractory AChRAb-positive MG. The entry criteria required moderate-to-severe weakness despite the use of at least 2 immunosuppressants including prednisone for at least 1 year and a Quantitative MG score (QMG) ≥12. Fourteen patients were randomized at a 1:1 ratio to receive either eculizumab (600 mg every week for 4 weeks, 900 mg on week 5 followed by 900 mg every 2 weeks for 6 additional doses) or placebo for 16 weeks. Initial treatment was followed by a 5-week washout period after which the subjects were crossed over to the other arm for an additional 16-week period. The primary endpoints were frequency of adverse events and percentage of patients with QMG scores that fell by at least 3 points. All patients experienced mild side effects, most commonly nausea, back pain, nasopharyngitis, and headache. Eighty-six percent of actively treated patients versus 57% receiving placebo achieved the primary endpoint (QMG drop by more than 3 points) in period 1, which was felt to be more meaningful than period 2 where a carryover effect from eculizumab seemed to be present. About 57% of patients on eculizumab achieved an 8-point reduction in QMG compared with only 14% of those on placebo during period 1 of the study. When data were considered from both treatment periods 1 and 2 of the study, a repeated-measures mixed statistical model just failed to reach significance between eculizumab and placebo-treated groups ($P = 0.0577$). A phase 3 study of eculizumab in MG is currently in development.

## THYMECTOMY

Thymectomy has been routinely performed in MG for some 75 years and could be considered the first immunotherapy for the disease.[7] The benefit of thymectomy, however, may be delayed for months or years after surgery. In selected refractory patients who have previously undergone thymectomy, repeat thymectomy stands as a treatment option. Miller et al[41] described the outcome of 6 patients with refractory disease who underwent repeat thymectomy using an extended thymectomy approach. Their previous thymectomy procedure had been less invasive. Five of the patients experienced significant improvement in symptoms, but none attained complete remission. All patients experienced a substantial reduction in the

prednisone and acetylcholinesterase inhibitor dosing, as well as in the number of plasma exchanges. Residual thymic tissue was found in 5 of the 6 patients, despite preoperative computed tomogram scanning failing to demonstrate residual tissue in any. A lack of imaging findings was also noted by Kornfield et al,[42] who described 5 refractory patients who underwent multiple chest imaging modalities to evaluate for residual thymic tissue. All studies were negative except for magnetic resonance imaging in 1 patient, although all patients were found to have residual thymic tissue on surgical reexploration.

Pompeo et al[43] reported on their experience with thoracoscopic thymectomy in 8 patients with refractory MG. The inclusion criteria were lack of significant clinical improvement 3 years after thymectomy, deterioration for at least 24 months after initial improvement not adequately controlled with maximal medical therapy, the requirement for repeated treatment with plasma exchange, or evidence of residual thymic tissue or thymomatous transformation on computed tomogram or magnetic resonance imaging. The mean time elapsed since the initial surgery was 129 ± 71 months. Gross (5 patients) or microscopic (3 patients) thymic tissue was found in all instances. Two patients experienced postoperative myasthenic crisis. After a mean follow-up duration of 28 months, no patient was in complete remission but significant clinical improvement was reported in 6 of the 8 patients, with the Osserman scores declining from 3.37 to 2.12. The mean prednisone dose fell from 43 ± 12 mg/d to 20 ± 15 mg/d. There was no analogous decline in pyridostigmine or azathioprine doses, nor were there significant differences in the number of plasma exchanges per year after the repeat thymectomy. The authors noted that all 6 patients who improved returned to normal activities of daily living.

Zielinski et al[44] performed extended video-assisted thymectomy in 21 patients who experienced no change or worsening after initial thymectomy. The mean time after initial thymectomy was 3.4 years (range, 1–7). Retained thymic tissue was discovered in 18 of 21 patients (81%). Results of the follow-up were available for 17 patients. Clinical improvement was noted in 11, with 2 entering complete remission. There were no instances of clinical deterioration in any of the 17 patients. Six of 12 patients on corticosteroids or other immunosuppressants were able to discontinue the drug. It seems from these studies that repeat thymectomy has potential benefit in carefully selected patients despite negative imaging studies for retained thymic tissue.

## BONE MARROW TRANSPLANTATION

There is a single case report of bone marrow transplantation in refractory MG.[45] The patient was a 17-year-old man who developed myasthenic symptoms at 11 months of age. Previous treatment with pyridostigmine, prednisone, azathioprine, mycophenolate, IVIg, plasmapheresis, rituximab, high-dose cyclophosphamide, and thymectomy was unsuccessful. He underwent peripheral hematopoietic stem cell transfer from an human leukocyte antigen-matched sibling after reduced-toxicity conditioning. By 40 months after transplantation, he had profound improvement with only residual ophthalmoplegia. Studies with a longer-term follow-up have not yet been published. Despite this promising observation, there have been several case reports of MG developing in subjects after transplantation for hematologic malignancies.[46] Similar to ablative high-dose cyclophosphamide therapy, bone marrow transplantation should be considered a therapy of last resort for refractory MG.

Although most patients with MG are able to be managed using acetylcholinesterase inhibitors, prednisone, or conventional immunosuppresants,[47] a notable minority have refractory disease. In these challenging cases, evidence is emerging that treatments such as rituximab, high-dose cyclophosphamide, and eculizumab may be useful. Of these agents, rituximab seems to be the best tolerated and has demonstrated good efficacy in patients

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with refractory disease. Although controlled studies are only now underway, observational series suggest a robust effect lasting up to several years. Although cyclophosphamide demonstrates good efficacy, the meticulous care that these patients require and the relatively high risk of side effects makes this option less attractive. Eculizumab is a promising new agent, and it is hoped that the results of the ongoing phase 3 trial will shed more light on its clinical utility in patients with MG. Repeat thymectomy is another option in carefully selected patients, although with the advance of radiological and surgical techniques, the chance of residual thymic tissue may be declining. These treatment options may be labeled as aggressive, but the literature suggests that they are generally safe and effective and can lead to prolonged symptomatic control in most patients who previously were poorly controlled and were restricted in their activities.

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