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# Rituximab as treatment for anti-MuSK myasthenia gravis

## Multicenter blinded prospective review

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## ABSTRACT

**Objective:** To evaluate the efficacy of rituximab in treatment of anti-muscle-specific kinase (MuSK) myasthenia gravis (MG).

**Methods:** This was a multicenter, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab. The primary clinical endpoint was the Myasthenia Gravis Status and Treatment Intensity (MGSTI), a novel outcome that combines the Myasthenia Gravis Foundation of America (MGFA) postintervention status (PIS) and the number and dosages of other immunosuppressant therapies used. A priori, an MGSTI of level ≤2 was used to define a favorable outcome. Secondary outcomes included modified MGFA PIS of minimal manifestations or better, mean/median prednisone dose, and mean/median doses of other immunosuppressant drugs.

**Results:** Seventy-seven of 119 patients with anti-MuSK MG evaluated between January 1, 2005, and January 1, 2015, at 10 neuromuscular centers were selected for analysis after review of limited clinical data by a blinded expert panel. An additional 22 patients were excluded due to insufficient follow-up. Baseline characteristics were similar between the rituximab-treated patients (n = 24) and the controls (n = 31). Median follow-up duration was >3.5 years. At last visit, 58% (14/24) of rituximab-treated patients reached the primary outcome compared to 16% (5/31) of controls ($p = 0.002$). Number needed to treat for the primary outcome is 2.4. At last visit, 29% of rituximab-treated patients were taking prednisone (mean dose 4.5 mg/day) compared to 74% of controls (mean dose 13 mg/day) ($p = 0.001$ and $p = 0.005$).

**Clinicaltrials.gov identifier:** NCT02110706.

**Classification of evidence:** This study provides Class IV evidence that for patients with anti-MuSK MG, rituximab increased the probability of a favorable outcome. *Neurology*® 2017;89:1–9

## GLOSSARY

**IRB** = institutional review board; **IVIg** = IV immunoglobulin; **MG** = myasthenia gravis; **MGFA** = Myasthenia Gravis Foundation of America; **MGSTI** = Myasthenia Gravis Status and Treatment Intensity; **MM** = minimal manifestations; **MuSK** = muscle-specific kinase; **PIS** = postintervention status; **PLEX** = plasma exchange; **RCT** = randomized control trial.

Anti-muscle-specific kinase (MuSK) antibodies are associated with a severe presentation of myasthenia gravis (MG) with early bulbar, neck, and respiratory muscle weakness.[1–3] Treatment requires exposure to multiple high-dose immunosuppressants.[1–5] Exposure of patients with anti-MuSK MG to treatment regimens that are costly and carry high adverse event risk highlights the need for other treatment strategies.

Case series describe clinical improvement and immunosuppressant dose reduction following rituximab treatment of anti-MuSK MG.[2,6–18] We have observed similar success with rituximab in our patients with anti-MuSK MG. Many insurance companies continue to deny coverage for rituximab due to lack of Class I, randomized control trial (RCT) data and high cost of rituximab.

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Patients with anti-MuSK MG were excluded from a current NIH trial evaluating rituximab in MG (NCT02110706). Because of our clinical experience and previous case series data, it is important to define the role of rituximab in anti-MuSK MG.

Rarity of anti-MuSK MG limits the ability to conduct RCTs. Alternative trial designs have great value to advance knowledge and clinical care in anti-MuSK MG.[19] The blinded prospective review is a retrospective trial design that mimics enrollment in an RCT with the goal of reducing confounding by indication.[20,21] Based on useful results with this method in cerebrovascular studies, an expert panel recommended this method for trial design in MG.[19]

We present data from a multicenter blinded prospective review of rituximab in anti-MuSK MG utilizing a large cohort of anti-MuSK patients treated at 10 neuromuscular centers.

## METHODS

**Primary research question/level of evidence.** Does treatment of patients with anti-MuSK MG with rituximab result in favorable clinical outcomes when compared to anti-MuSK MG controls? The study was designed to provide Class IV evidence.

**Trial design.** This is a multicenter blinded prospective review comparing patients with anti-MuSK-positive MG treated with rituximab to those not treated with rituximab.[19–21] In this method, clinical information about potential participants is reviewed by an expert panel blinded to actual treatment received. The panel determines whether it is equally appropriate to assign participants to prespecified treatment arms prior to collecting full clinical data for analysis.

The study is listed on clinicaltrials.gov (NCT02110706).

**Standard protocol approvals, registrations, and patient consents.** The institutional review boards (IRBs) at collaborating institutions approved this protocol. IRB-approved data sharing agreements were established between the University of Vermont and collaborating sites.

***Patients.*** All patients with laboratory-confirmed anti-MuSK MG treated at collaborating institutions between January 1, 2005, and January 1, 2015, were evaluated for inclusion in this study. Utilizing the blinded prospective review method, a team of 5 of the following 6 blinded neuromuscular experts from multiple clinical centers (M.K.H., T.M.B., N.J.S., C.B., L.D.H.-W., J. F.H.) reviewed clinical data about each patient from the first year of treatment or until the first dose of rituximab.[19,20] To preserve blinding, reviewers did not evaluate potential participants from their own institution and were unaware if patients were treated with rituximab. The panel was provided with patient age, maximal MG severity (Myasthenia Gravis Foundation of America [MGFA] status), a modified MGFA postintervention status (PIS), all previous and current immune-based treatments (excluding rituximab), number of MG hospitalizations, number of MG respiratory crises, and medical comorbidities from all visits during the first year of treatment for anti-MuSK MG. Based on these data, reviewers used clinical expertise as MG specialists to answer the question, "Would it be reasonable to enroll this patient with anti-MuSK MG in a clinical trial of rituximab vs placebo?" A priori we required ≥4/5 of the experts to respond yes in order to enroll a patient into the study. We chose this stringent enrollment criterion to reflect strong consensus among the diverse panel and reduce the bias of 1 or 2 of these experts in any one case. We also required that patients have at least one follow-up visit 6 months or more following the baseline visit.

Enrolled patients were assigned to the rituximab-treated group or the control group. A priori, we established a common time 0 to allow longitudinal comparison between the 2 groups. Time 0 in the rituximab group was defined as the time of first rituximab infusion. Time 0 in the controls was set as the median percent duration of MG prior to starting rituximab in the treatment arm (median 40% total MG disease course). Therefore, time 0 in controls was set at 40% of each subject's total MG disease course (e.g., time 0 was set at 14 months for a patient with a 36-month total disease course). Median percent duration was chosen over absolute duration of MG prior to infusion because of variability in the absolute duration of MG prior to infusion and variability in the frequency and duration of follow-up in both arms. Data were collected by chart review from all clinic visits: up to 24 months prior to time 0 until the final follow-up visit through January 1, 2015.

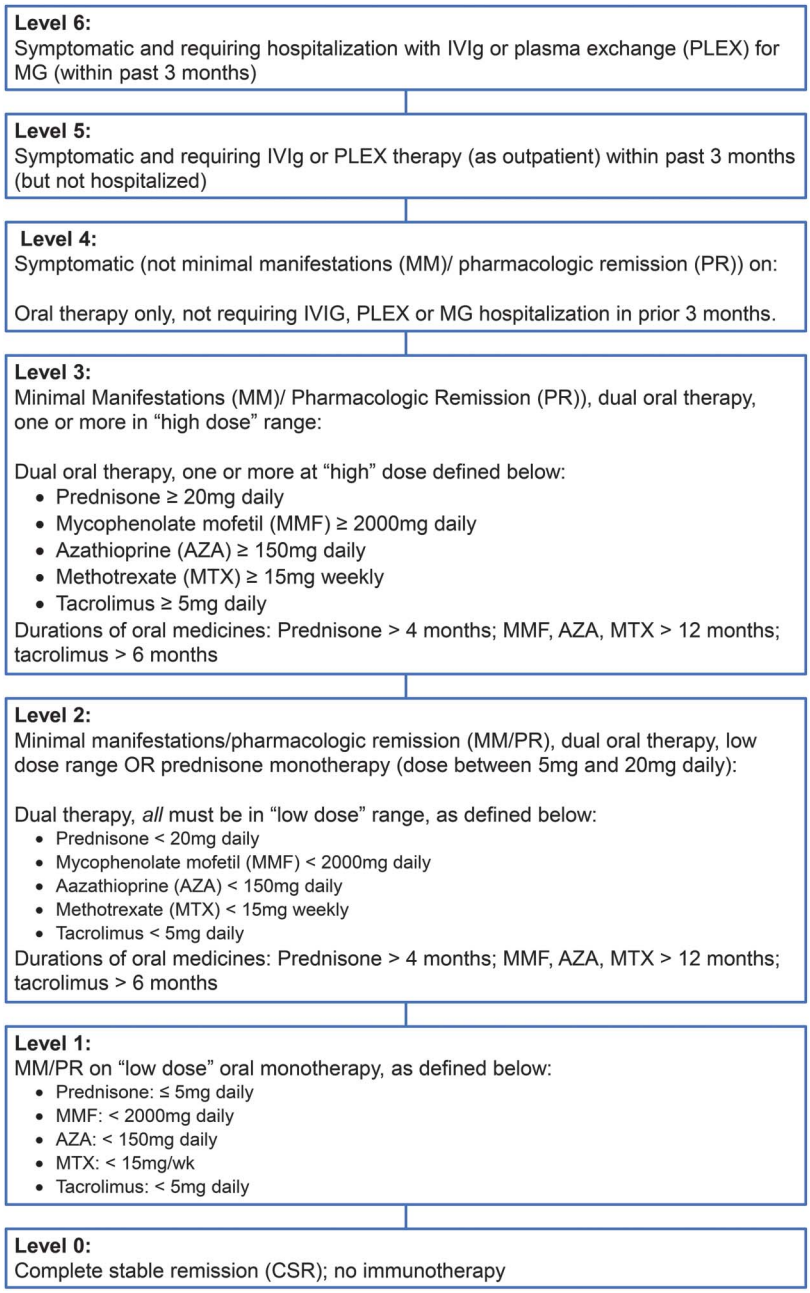
Baseline data included sex, age at MG onset, age at last visit, medical comorbidities, thymectomy status, worst MGFA Clinical Classification,[22] and duration of disease at first rituximab infusion. At all visits preceding time 0 by up to 24 months and following time 0 we collected modified MGFA PIS score, immunosuppressant dose at beginning of visit (included prednisone, mycophenolate mofetil, azathioprine, cyclosporine, methotrexate), IV immunoglobulin (IVIg) or plasma exchange (PLEX) since last visit as surrogate measure of MG exacerbation, hospitalization for MG since last visit, mechanical ventilation since last visit, and any side effects. Based on MGFA PIS definitions, patients were classified into the categories of minimal manifestations (MM), pharmacologic remission, complete stable remission, and symptomatic.[22] MGFA PIS application was modified to allow scoring based on chart review.

***Trial outcomes.*** The goal of care in MG is to achieve maximal clinical benefit on low-dose immunosuppressants.[23] We designed a primary clinical endpoint for this study, the Myasthenia Gravis Status and Treatment Intensity (MGSTI) score. MGSTI combines the modified MGFA PIS and immunosuppressant doses (figure 1). A priori, we defined a desirable clinical outcome as a MGSTI of level 2 or better. This score is defined as PIS status of MM or better while taking a low dose of immunosuppressants. Secondary outcome measures included MGSTI of level 1 or better, modified MGFA PIS of MM or better, mean/median prednisone dose, and mean/median doses of other immunosuppressants.

***Statistical methods.*** Characteristics of the rituximab and control participants were compared at baseline and at the final visit. Statistical analysis of percentages was performed using the Fisher exact test. Means were analyzed with 2-tailed *t* test and medians analyzed with the Wilcoxon rank sum test.

Survival analysis with associated Kaplan-Meier plot of the proportion of patients not achieving the primary outcome measure (MGSTI level 2 or better) in the 2 groups was performed. In the time period between −24 months and time 0, the last observation was carried forward for patients missing data at particular time points. Following time 0, the last observation was carried forward in the survival analysis only until the time of the subject's last visit due to the tendency for patients with MG to have relapses requiring medication adjustments.

**Figure 1** Myasthenia Gravis Status and Treatment Intensity (MGSTI) score




Clinical status of symptomatic, minimal manifestations, pharmacologic remission, and complete stable remission defined by Myasthenia Gravis Foundation of America postintervention status.[22] IVIg = IV immunoglobulin; MG = myasthenia gravis; PLEX = plasma exchange.

**RESULTS** **Baseline data.** As part of the blinded prospective review, the expert panel evaluated a blinded, limited dataset, from the first year of treatment for 119 patients with anti-MuSK MG from 10 neuromuscular centers. Based on this review, 77/119 patients were deemed appropriate for enrollment by ≥4 members of the expert panel. An additional 22 patients were excluded after panel review due to insufficient follow-up data. Twenty-four patients were included in the rituximab treatment arm and 31 patients were included in the control arm (figure 2).

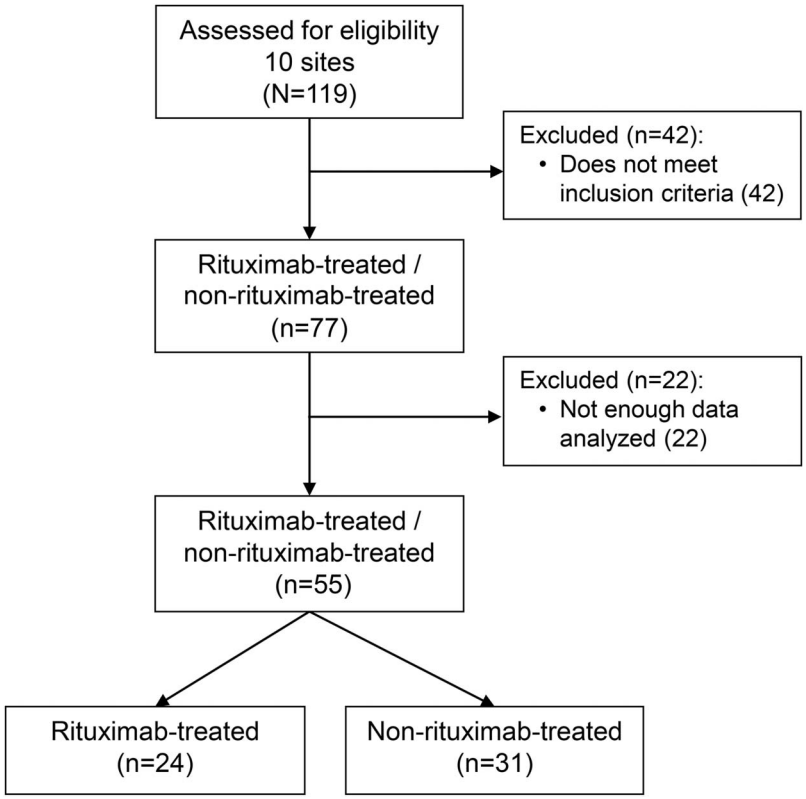
Baseline characteristics of the rituximab arm and controls were similar (table 1). The majority of patients were young women (mean age at onset <40 years). Median follow-up duration in both groups was greater than 3.5 years. Use of immunosuppressant medications, and number of patients who received thymectomy, were also similar. Disease severity as measured by MGFA class (median worst MGFA score IV) was similar between the groups, reflecting the often severe anti-MuSK MG phenotype. However, more patients were treated with IVIg or PLEX and were hospitalized due to MG prior to time 0 in the rituximab group, possibly reflecting a more severe baseline phenotype. Eighty percent of both groups were treated with prednisone with a mean dose of 20 mg daily; 50% of both groups were treated with multiple immune system medications.

The patients excluded by the expert panel had a slightly less severe MG phenotype (median worst MGFA score III, $p = 0.001$, Wilcoxon rank sum). Excluded patients were similar in age (mean 34 years, $p = 0.95$, 2-tailed $t$ test) and sex (85% female, $p = 0.89$, Fisher exact) compared to the group included for analysis. Seventy percent of excluded patients were treated with prednisone at time of adjudication with mean dose of 13 mg per day. Twenty-six percent of excluded patients were treated with rituximab.

**Analysis of primary outcome.** Fifty-eight percent of patients in the rituximab arm reached the primary outcome (MGSTI level 2 or better) at the last visit compared to 16% of controls ($p = 0.002$) (table 2). A median MGSTI of 1 was observed in the rituximab arm compared to a median MGSTI of 4 in controls ($p = 0.02$). Kaplan-Meier survival analysis determined a median time to achieve an MGSTI level 2 or better of 54 months in the rituximab arm ($p = 0.005$); median time to achieve the primary outcome in controls could not be calculated because fewer than 50% of patients reached this endpoint (figure 3). The number needed to treat to achieve the primary outcome at the final visit is 2.4.

**Secondary outcomes.** Sixty-seven percent of patients in the rituximab arm achieved an MGFA PIS score of MM or better at the final visit compared to 26% in controls ($p = 0.003$) (table 2). Fifty-four percent of patients in the rituximab group reached an even more stringent MGSTI score of level 1 or better at last visit compared to 6.5% of controls ($p = 0.001$) reflecting good clinical outcome on very low dose immunosuppressants. At last visit, only 29% of patients in the rituximab arm were taking prednisone (mean dose of 4.5 mg daily); only 8% of these patients were on multiple immune system medications. For controls, the number treated with prednisone (74%) and taking multiple immunosuppressant medications

**Figure 2** Inclusion/exclusion results of blinded expert panel




(58%) was similar at last visit compared to baseline. While the final mean dose of prednisone (13 mg daily) did decrease from baseline (20 mg daily) in controls, this final dose was significantly higher than that of the rituximab arm (4.5 mg daily) ($p = 0.005$).

**Rituximab dosing.** The initial dose of rituximab in all treated patients was 375 mg/m$^2$ weekly for a total of 4 doses. Fifteen patients received more than one course during the period of observation. Thirteen were re-treated with the standard 375 mg/m$^2$ weekly × 4 doses. The other 2 patients were treated with 1,000 mg weekly × 2 when retreated; one of these patients met the primary outcome at the final visit.

Seventy-three percent (11/15) of patients who received multiple courses of rituximab achieved the primary outcome vs 33% (3/9) who received a single course. This corresponds to a number needed to treat of 2.5. These results were not statistically significant ($p = 0.092$, Fisher exact test). Four patients were treated with repeated courses of rituximab every 6 months (2–4 courses) and entered prolonged periods of clinical remission (30, 72, 76, and 78 months). Two of these patients received 3 courses of rituximab before achieving the primary endpoint, 1 achieved after 2 courses, and the final after the first course. Another 4 patients achieved favorable clinical responses after a single course but then relapsed (12, 18, 24, 96 months); all returned to favorable response following a second course of rituximab. One responder received an additional course at 3 months before achieving MGSTI level 2. A final patient required repeat doses at 24 and 30 months prior to achieving the primary outcome. Among the 4 nonresponders to multiple courses of rituximab, one received a course at baseline and 7 months. The other 3 patients did not respond to rituximab despite repeated intermittent courses (3, 4, and 9 courses) between 6 and 48 months apart.

Among the 3 patients who responded to a single course of rituximab, favorable response, as defined by the MGSTI, was observed until final visits at 17, 24, and 48 months. Another patient did not achieve the primary outcome at last visit (6 months) due to immunosuppressant doses but did reach an MGFA PIS of MM. An additional patient achieved the primary outcome by 12 months following rituximab but relapsed at 72 months without retreatment; this patient was coded as a failure. Three patients showed no improvement by final visits (18, 24, and 42 months); reason for not pursuing a second course is unknown. One nonresponder had a side effect after the first dose of rituximab; the course was not completed.

**DISCUSSION** This multicenter, blinded prospective review of rituximab in a large cohort of patients with anti-MuSK MG provides Class IV evidence that treatment with rituximab increases the probability of a favorable outcome in anti-MuSK MG. Previous reports of benefit from rituximab have been restricted to case reports, case series, and clinical experience.[2,6–18] More patients treated with rituximab in our cohort (58%) achieved good clinical outcomes on low doses of immunosuppressants compared to controls (16%). Excellent clinical outcome was durable in many of the rituximab-treated patients. Only 29% of rituximab patients were treated with prednisone and 8% with multiple immunosuppressants at the final visit compared to 74% and 58%, respectively, in controls. This difference could reflect a more aggressive tapering of immunosuppressants in the rituximab group by actual treating physician. However, better clinical status in the rituximab arm compared to controls (67% vs 26% PIS of MM or better) at final visit suggests medication tapering was performed in response to clinical improvement. Lower immunosuppressant dose and fewer immunosuppressant drugs are associated with less risk of adverse events.

All patients treated with rituximab received an initial course of 375 mg/m$^2$ weekly × 4 doses. Most rituximab responders required multiple courses of treatment. While this difference was not statistically significant, comparing subsets of a small treatment

**Table 1** Baseline characteristics

| | Rituximab-treated (n = 24) | Control (n = 31) | *p* Value |
|---|---|---|---|
| % (n) Female | 88 (21/24) | 81 (25/31) | 0.72[a] |
| Age at onset, y, mean ± SD | 31.3 ± 14.9 | 37.2 ± 13.6 | 0.13[b] |
| Age at last visit, y, mean ± SD | 40.5 ± 14.7 | 48.1 ± 15.5 | 0.07[b] |
| Median months followed (min-max) | 45 (6-116) | 54 (6-184) | 0.90[c] |
| Thymectomy, % (n) | 46 (11/24) | 48 (15/31) | 1.0[a] |
| Hospitalized for MG prior, % (n) to time 0 | 58 (14/24) | 13 (4/31) | 0.001[a] |
| MGFA worst grade | | | |
| Median MGFA, n (%) | IVB | IVB | 0.81[c] |
| IIA | 1 (4.2) | 1 (3.2) | |
| IIB | 3 (12.5) | 1 (3.2) | |
| IIIA | 1 (4.2) | 1 (3.2) | |
| IIIB | 5 (20.8) | 10 (32.3) | |
| IVA | 1 (4.2) | 2 (6.5) | |
| IVB | 6 (25.0) | 7 (22.6) | |
| V | 7 (29.2) | 9 (29.0) | |
| Baseline MGSTI, n (%) | | | |
| Median level | Level 4 | Level 4 | 0.29[c] |
| 6 | 3 (12.5) | 1 (3.23) | |
| 5 | 6 (25) | 8 (25.81) | |
| 4 | 13 (54.17) | 17 (54.84) | |
| 3 | 1 (4.17) | 3 (9.68) | |
| 2 | 1 (4.17) | 1 (3.23) | |
| 1 | 0 (0) | 1 (3.23) | |
| 0 | 0 (0) | 0 (0) | |
| Baseline immunosuppressants, % (n) | | | |
| On prednisone | 83 (20/24) | 77 (24/31) | 0.74[a] |
| On MMF | 25 (6/24) | 39 (12/31) | 0.39[a] |
| On AZA | 17 (4/24) | 23 (7/31) | 0.74[a] |
| On CYA | 13 (3/24) | 6 (2/31) | 0.64[a] |
| On IVIg/PLEX prior to time 0 | 88 (21/24) | 42 (13/31) | <0.001[a] |
| On prednisone plus other drugs | 50 (12/24) | 55 (17/31) | 0.79[a] |
| Mean baseline prednisone, mg/d | 20.8 ± 16.8 (median 20) | 18.6 ± 16.1 (median 20) | 0.64[b] |

Abbreviations: AZA = azathioprine; CYA = cyclosporine A; IVIg = IV immunoglobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MGSTI = Myasthenia Gravis Status and Treatment Intensity; MMF = mycophenolate mofetil; PLEX = plasma exchange; RCT = randomized control trial.
[a] Fisher exact test.
[b] Two-tailed *t* test.
[c] Wilcoxon rank sum.

arm (n = 24) may have resulted in type 2 error. Four patients who achieved prolonged periods of remission received regular courses of rituximab every 6 months (2–4 courses). Circulating B-lymphocytes typically reach nadir within 4 weeks from completion of a rituximab cycle. B-lymphocyte counts usually begin to increase between 24 and 31 weeks postrituximab infusion.[18] Based on our observations in this study and knowledge about the effects of rituximab on the immune system, it is reasonable to consider retreatment with rituximab as lymphocyte counts recover if there is no response to the first course.

Forty-two percent of rituximab-treated patients did not achieve the primary outcome. Nonresponse may partly be explained by inconsistent rituximab treatment regimens and our stringent primary outcome measure. However, at least 3 rituximab-treated patients (12.5%) showed no clinical

**Table 2** Outcomes at time of last visit

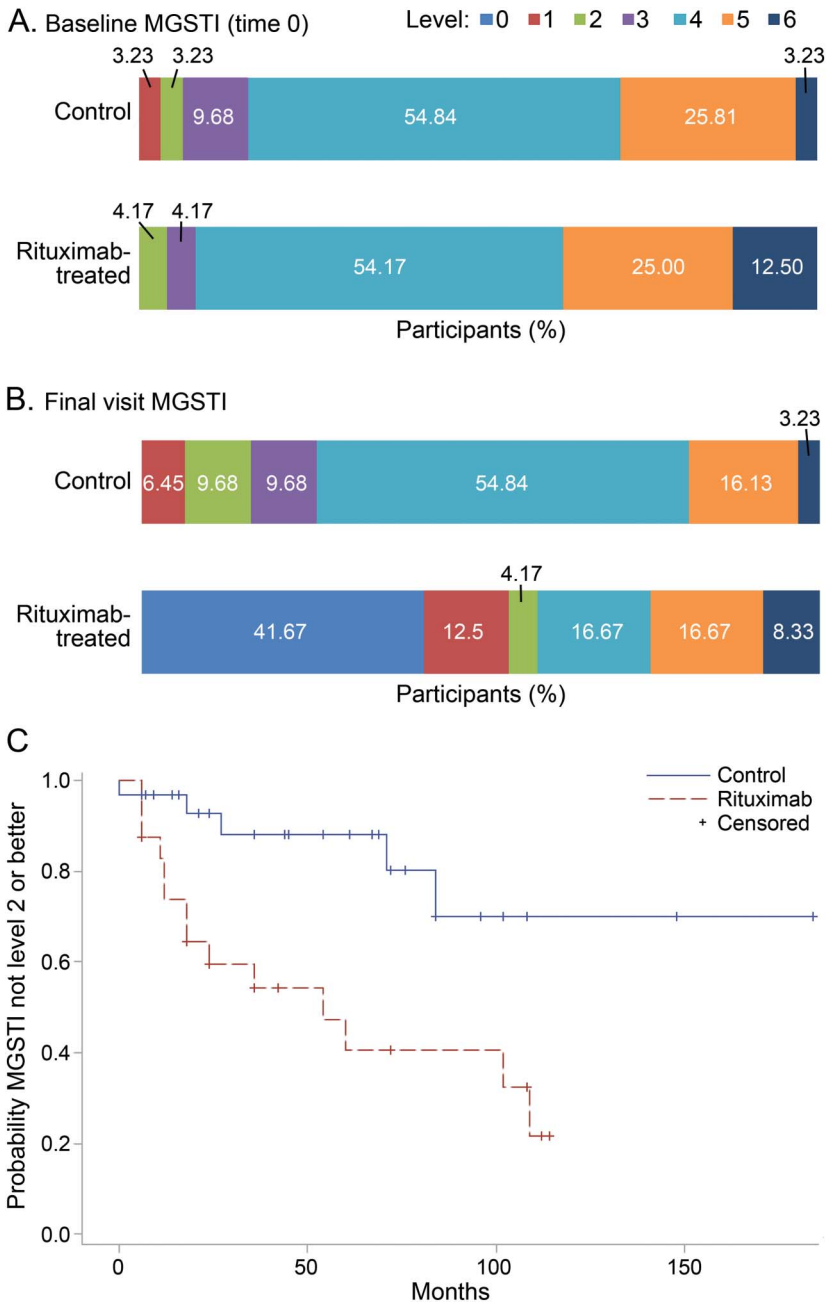
| | Rituximab-treated (n = 24) | Control (n = 31) | *p* Value |
|---|---|---|---|
| MGSTI, % (n) | | | |
| Level 2 or better at end of period | 58 (14/24) | 16 (5/31) | 0.002[a] |
| Level 1 or better at end of period | 54 (13/24) | 6.45 (2/31) | <0.001[a] |
| MGFA modified PIS MM or better final visit, % (n) | 67 (16/24) | 26 (8/31) | 0.003[a] |
| Final MGSTI | | | |
| Median level, n (%) | Level 1 | Level 4 | 0.02[b] |
| 6 | 2 (8.33) | 1 (3.23) | |
| 5 | 4 (16.67) | 5 (16.13) | |
| 4 | 4 (16.67) | 17 (54.84) | |
| 3 | 0 (0) | 3 (9.68) | |
| 2 | 1 (4.17) | 3 (9.68) | |
| 1 | 3 (12.5) | 2 (6.45) | |
| 0 | 10 (41.67) | 0 (0) | |
| Final MGFA modified PIS score | | | |
| Median PIS, n (%) | Minimal manifestations | Symptomatic | 0.01[b] |
| Symptomatic | 8 (33.3) | 22 (71.0) | |
| Minimal manifestations | 6 (25.0) | 8 (25.8) | |
| Pharmacologic remission | 3 (12.5) | 1 (3.2) | |
| Complete stable remission | 7 (29.2) | 0 (0) | |
| Hospitalized for MG at any time after time 0, % (n) | 25 (6/24) | 6 (2/31) | 0.07[a] |
| Hospitalized for MG at final visit, % (n) | 8 (2/24) | 3 (1/31) | 0.6[a] |
| Immune medications at final visit, % (n) | | | |
| On prednisone | 29 (7/24) | 74 (23/31) | 0.001[a] |
| On MMF | 4 (1/24) | 52 (15/31) | <0.001[a] |
| On AZA | 8 (2/24) | 23 (7/31) | 0.27[a] |
| On CYA | 0 | 10 (3/31) | 0.25[a] |
| On prednisone plus other at last visit | 8 (2/24) | 58 (18/31) | <0.001[a] |
| Final prednisone dose, mg/d | 4.5 ± 8.1 (median 0) | 12.7 ± 11.8 (median 10) | 0.005[c] |
| On IVIg/PLEX | 25 (6/24) | 16 (5/31) | 0.50[a] |

Abbreviations: AZA = azathioprine; CYA = cyclosporine A; IVIg = IV immunoglobulin; MGFA = Myasthenia Gravis Foundation of America; MGSTI = Myasthenia Gravis Status and Treatment Intensity; MM = minimal manifestations; MMF = mycophenolate mofetil; PIS = postintervention status; PLEX = plasma exchange; RCT = randomized control trial.
[a] Fisher exact test.
[b] Wilcoxon rank sum.
[c] Two-tailed *t* test.

improvement despite 3, 4, and 9 courses of rituximab and likely represent medically refractory patients. In one previous study, 80% of immunosuppressant-treated patients with anti-MuSK MG, excluding rituximab, met criteria for refractory MG.[24,25] In patients who do not respond to an adequate course of rituximab (including redosing at 6 months, for example), our data indicate that it may be prudent to consider alternative treatment strategies.

It is logistically challenging to conduct RCTs in rare diseases like anti-MuSK MG. We utilized the blinded prospective review trial design and recruited patients from 10 neuromuscular centers to obtain the best data possible short of a prospective RCT. The blinded prospective review method mimics enrollment into an RCT to reduce bias associated with retrospective research.[20] In addition, we utilized a stringent, clinical endpoint, the MGSTI, which combined immunosuppressant dose and MGFA PIS. Although not previously validated, the MGSTI reflects the ultimate MG treatment goal of achieving maximal clinical benefit with minimal dose of immunosuppressants. MGSTI tracked with but did not completely correlate with the MGFA PIS due to incorporation of medication dosing. The MGSTI and target score for a favorable outcome should be

**Figure 3** Product-limit survival estimates




Percent subjects in each MGSTI category at baseline (A) and final visit (B). Survival analysis of not achieving the primary outcome measure of MGSTI level 2 or better (C). Median time to level 2 in rituximab group 54 months ($p = 0.005$ by log-rank test). Median time to level 2 in control group could not be calculated as only 16% of cases reached primary outcome. MGSTI = Myasthenia Gravis Status and Treatment Intensity.

validated in other MG cohorts and future prospective MG trials. Similar methods can be employed in studies of other rare neurologic disorders.

Our cohorts were matched for the majority of baseline characteristics. A higher percentage of rituximab-treated patients were hospitalized due to MG and treated with IVIg or PLEX prior to time 0. These baseline differences likely reflect a more severe baseline phenotype in the rituximab group even though baseline MGFA status was similar between the groups. Insurance status was not recorded in this study. While this baseline difference in IVIg/PLEX administration could reflect reduced insurance coverage in controls, the higher rate of baseline hospitalization in rituximab arm and similarity in IVIg/PLEX administration at final visit in both groups argues against this possibility.

We acknowledge that the study is limited because data were obtained retrospectively. We attempted to reduce bias by utilizing the blinded prospective

review. We also normalized time 0 for both groups to allow comparison over time. Finally, we employed a stringent clinical endpoint to measure clinical relevance while limiting type 1 error. Although our sample size was small, we observed a robust, strongly statistically significant, clinical benefit from rituximab in this cohort.

This study provides Class IV evidence that for patients with anti-MuSK MG, rituximab increased the probability of a favorable outcome. The use of innovative trial design and collaboration among multiple institutions allowed us to evaluate a treatment strategy in this rare disease. This method is applicable to other rare neurologic diseases. In our cohort, multiple courses of rituximab were necessary to achieve good clinical outcomes. In patients who do not respond to an initial course of rituximab, we recommend considering repeated courses of rituximab 375 mg/m$^2$ × 4 weeks before classifying a patient as medically refractory to rituximab. Although a prospective RCT may not be logistically feasible given the rarity of anti-MuSK MG, this study provides baseline data to design such a study. The observed robust clinical response suggests that a smaller sample size would provide enough power to detect a difference between rituximab and other treatments in an RCT.

## AUTHOR CONTRIBUTIONS

Dr. Hehir: study design, expert panel, data collection, data analysis, statistical analysis, and manuscript composition. Dr. Hobson-Webb: study design, expert panel, data collection, data analysis, and critical revision of manuscript. Dr. Benatar: study design, data collection, data analysis, and critical revision of manuscript. Dr. Barnett: study design, expert panel, data collection, data analysis, and critical revision of manuscript. Dr. Silvestri: expert panel, data analysis, and critical revision of manuscript. Dr. Howard Jr.: expert panel, data analysis, and critical revision of manuscript. D. Howard: statistical analysis and critical revision of manuscript. Dr. Visser: data collection, data analysis, and critical revision of manuscript. Dr. Crum: data collection, data analysis, and critical revision of manuscript. Dr. Nowak: data collection, data analysis, and critical revision of manuscript. Dr. Beekman: data collection, data analysis, and critical revision of manuscript. Dr. Kumar: data collection, data analysis, and critical revision of manuscript. Dr. Ruzhansky: data collection, data analysis, and critical revision of manuscript. Dr. Chen: data collection, data analysis, and critical revision of manuscript. Dr. Pulley: data collection, data analysis, and critical revision of manuscript. Dr. Laboy: data collection, data analysis, and critical revision of manuscript. Dr. Fellman: data collection, data analysis, and critical revision of manuscript. Dr. Greene: data collection, data analysis, and critical revision of manuscript. Dr. Pasnoor: data collection, data analysis, and critical revision of manuscript. Dr. Burns: study design, expert panel, data collection, data analysis, and manuscript composition.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