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RESEARCH ARTICLE

Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis

The BeatMG Study

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Abstract

Background and Objective

To determine whether rituximab is safe and potentially beneficial, warranting further investigation in an efficacy trial for acetylcholine receptor antibody-positive generalized myasthenia gravis (AChR-Ab+ gMG).

Methods

The B-Cell Targeted Treatment in MG (BeatMG) study was a randomized, double-blind, placebo-controlled, multicenter phase 2 trial that utilized a futility design. Individuals 21–90 years of age, with AChR-Ab+ gMG (MG Foundation of America Class II–IV) and receiving prednisone ≥15 mg/d were eligible. The primary outcome was a measure of steroid-sparing effect, defined as the proportion achieving ≥75% reduction in mean daily prednisone dose in the 4-weeks prior to week 52 and with clinical improvement or no significant worsening as compared to the 4-week period prior to randomization. The coprimary outcome was safety. Secondary outcomes included MG-specific clinical assessments. Fifty-two individuals were randomized (1:1) to a 2-cycle rituximab/placebo regimen, with follow-up through 52 weeks.

Results

Of the 52 participants included, mean ± SD age at enrollment was 55.1 ± 17.1 years; 23 (44.2%) were women and 31 (59.6%) were Myasthenia Gravis Foundation of America Class II. The mean ± SD baseline prednisone dose was 22.1 ± 9.7 mg/d. The primary steroid-sparing outcome was achieved in 60% of those on rituximab vs 56% on placebo. The study reached its futility endpoint ($p = 0.03$), suggesting that the predefined clinically meaningful improvement of 30% due to rituximab over placebo was unlikely to be achieved in a subsequent, larger trial. No safety issues were identified.

Discussion

Although rituximab was safe and well-tolerated, these results suggest that there is a low probability of observing the defined clinically meaningful steroid-sparing effect over a 12-month period in a phase 3 trial of mild to moderately symptomatic AChR-Ab+ gMG.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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NeuroNEXT NN103 BeatMG Study Team coinvestigators are listed at links.lww.com/WNL/B682.

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Glossary

AChR-Ab+ = acetylcholine receptor antibody-positive; **AE** = adverse event; **AUDTC** = area under the dose time curve; **CI** = confidence interval; **gMG** = generalized myasthenia gravis; **IST** = immunosuppressive therapy; **IVIg** = IV immunoglobulin; **LLN** = lower limit of normal; **MG** = myasthenia gravis; **MG-ADL** = Myasthenia Gravis–Activities of Daily Living; **MG-QoL** = 15-item Myasthenia Gravis Quality of Life questionnaire; **MGC** = Myasthenia Gravis Composite; **MGFA** = Myasthenia Gravis Foundation of America; **MSE** = minimal symptom expression; **MuSK-Ab+** = muscle-specific kinase antibody-positive; **OR** = odds ratio; **PLEX** = plasma exchange; **QMG** = Quantitative Myasthenia Gravis; **SAE** = serious adverse event.

Classification of Evidence

This study provides Class I evidence that for mild to moderate AChR-Ab+ gMG, compared with placebo, rituximab is safe but unlikely to reduce steroid use by an absolute difference of at least 30% at 1 year.

Trial Registration Information

ClinicalTrials.gov identifier: NCT02110706.

Despite available therapies, 10%–15% of patients with myasthenia gravis (MG) have inadequately controlled disease or experience intolerable medication side effects and are categorized as medically resistant.[1] As there are few proven effective therapies for these patients, there is a need for other agents in the management of MG. Ideal therapeutics should be safe, well-tolerated, efficacious, and steroid-sparing.

A B-cell–directed therapy would naturally be appropriate for further investigation as autoreactive Bcells play an important role in the immunopathogenesis of MG.[2] Over the past decade, several uncontrolled studies have suggested potential benefit of rituximab, an anti-CD20 biologic, in MG[3-8] as well as in several other autoimmune conditions.[9-13]

Promising anecdotal reports and retrospective studies suggesting a potential beneficial effect of rituximab in MG supported the need for further investigation.[14,15] The aim of our study was to assess the safety, tolerability, and potential benefit of rituximab in acetylcholine receptor antibody-positive generalized MG (AChR-Ab+ gMG) and to identify putative biomarkers predictive of treatment response. Our primary goal was to determine whether rituximab warranted a further efficacy trial in the same patient population. We limited our study to AChR-Ab+ patients as they represent the majority of gMG cases and due to drug availability sample size constraints and initial feasibility concerns of enrolling only treatment-refractory or muscle-specific kinase antibody-positive (MuSK-Ab+) patients.

Methods

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled phase 2 study with the primary goal of determining whether treatment with rituximab is a safe (Class of Evidence I) and potentially beneficial therapeutic option for gMG that would warrant further examination in a larger phase 3 efficacy trial. We utilized a futility (nonsuperiority) design for the primary outcome that tested the null hypothesis that rituximab-treated participants would achieve at least a 30% absolute increase in the frequency of favorable responses vs placebo-treated participants.[16] A finding of futility (i.e., rejecting the null hypothesis) would imply that there would be a low probability for a future successful efficacy trial in this population, whereas not finding futility (i.e., not able to reject the null hypothesis) would suggest that there could be a clinically meaningful effect, thus supporting exploration in a larger, phase 3 trial (Class of Evidence I).

Participants were randomized (1:1) to either rituximab or placebo, with randomization stratified on baseline prednisone dose (≤35 mg/d vs >35 mg/d) and concomitant immunosuppressive therapy (IST) use at baseline. Eligibility was initially restricted to patients on prednisone alone, but criteria were amended to allow concomitant IST use due to early recruitment challenges.

Participants were assigned a unique study ID to identify the center and subject. The data coordination center generated a randomization table for each of the strata using a permuted block design with random block sizes. All participants, investigators, and study staff were blinded to treatment assignment until after database lock. Clinical evaluators assessing outcomes were also blinded to adverse events.

Standard Protocol Approvals, Registrations, and Patient Consents

This study (clinicaltrials.gov Unique Identifier: NCT02110706) was performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines, ethical procedures outlined in the Declaration of Helsinki, and other applicable regulatory requirements. A centralized institutional review

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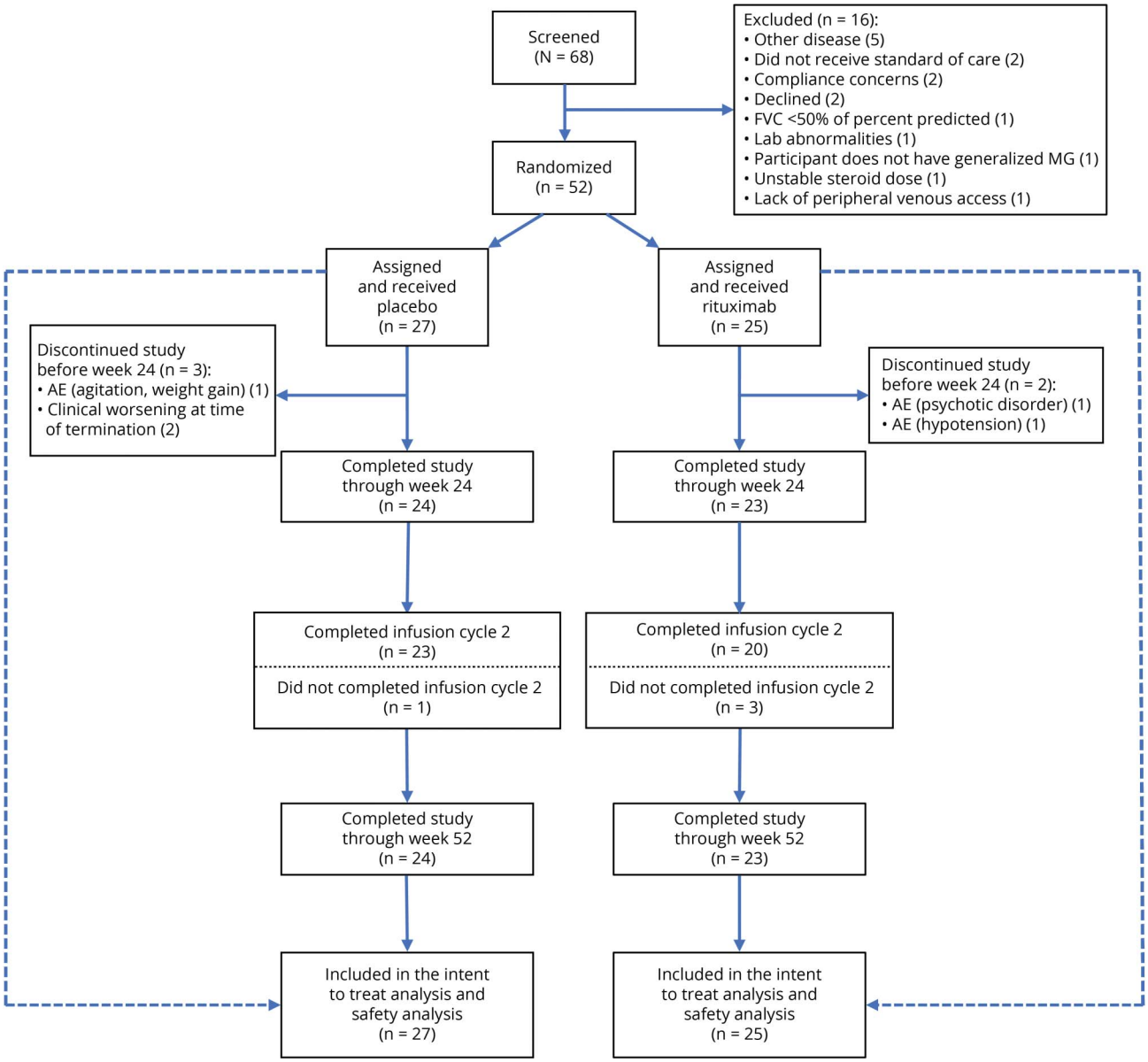
Figure 1 CONSORT Flow Diagram



AE = adverse event; FVC = forced vital capacity; MG = myasthenia gravis.

board and independent ethics committee provided approval for the study protocol and all amendments. All participants provided written informed consent prior to study entry.

Participants

Individuals age 21–90 with a diagnosis of AChR-Ab+ gMG and Myasthenia Gravis Foundation of America (MGFA) Class II–IV were enrolled across 16 of the 26 National Institute of Neurological Disorders and Stroke–sponsored NeuroNEXT (Network for Excellence in Neuroscience Clinical Trials) centers across the United States between August 2014 and July 2016. Eligible participants were on a stable dose of either prednisone alone (≥15 mg/d) for 4 weeks prior to baseline visit or prednisone and a stable dose of another IST for ≥6 months prior to baseline. Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, and methotrexate were permitted. Exclusion criteria included history of thymic neoplasm, thymectomy in the previous 6 months, previous treatment with rituximab, or IV immunoglobulin/plasma exchange (IVIg/PLEX) treatment within 4 weeks of baseline.

Intervention

The treatment group received a 2-cycle rituximab regimen separated by 6 months. Each cycle was defined as 1 weekly infusion (375 mg/m^2) for 4 consecutive weeks. Cycle 1 was administered

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in weeks 0–3 and cycle 2 was given in weeks 24–27. The placebo group received an infusion that contained only vehicle components. A predetermined steroid taper schedule was utilized (eFigure 1, links.lww.com/WNL/B681). Prednisone dose was gradually reduced based on the taper schedule beginning at week 8, but only after confirming clinical improvement or stable symptoms based on the Myasthenia Gravis Composite (MGC) score (≤2-point increase as compared to baseline or prior study visit). If the MGC score change was ≥3 points and due to MG as judged by the investigator, the prednisone dose was increased until symptoms resolved or at least stabilized to baseline status (based on MGC score). After symptom stabilization, prednisone taper was resumed at the next study visit.

Outcomes

The first primary outcome measure was based on prednisone dose and MGC score. Participants were considered to have achieved a successful primary endpoint if they achieved a ≥75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 (weeks 49–52) compared to the 4-week period prior to randomization and with clinical improvement or no significant worsening of symptoms (≤2-point increase in MGC score from randomization to week 52). The prednisone-sparing aspect of the endpoint was computed by comparing the mean daily prednisone dose during the 4-week period prior to randomization vs the 4-week period at the end of the study. For participants who had their prednisone dose changed after or who missed their week 48 visit, the primary endpoint was determined by using the last prednisone dose recorded prior to week 52. The MGC aspect of the endpoint was computed by comparing the MGC obtained at baseline to the MGC obtained at week 52. For the primary analysis, we imputed an outcome of failure for any participant who terminated the study early, for whom the prednisone dose in the last 4 weeks was unknown, or for whom the MGC score was missing at week 52. A series of sensitivity analyses was conducted to confirm that results were resistant to potential effects of missing data.

The co-primary outcome assessed safety. Safety analyses were performed for all participants randomized and focused on examining differences in treatment-related adverse events (AEs) and serious AEs (SAEs) between the rituximab and placebo groups.

Analysis of the key secondary outcomes, MGC and Quantitative Myasthenia Gravis (QMG) scores, from baseline to week 52 was completed to evaluate clinical changes. Exploratory clinical outcomes included the Myasthenia Gravis–Activities of Daily Living (MG-ADL) and Myasthenia Gravis–Quality of Life (MG-QoL) scores and MG exacerbation rate. As a measure of steroid-sparing effect along with steroid burden throughout the course of the study, the area under the dose time curve (AUDTC) was calculated starting at week 8 for the 47 participants who completed the study using prednisone diaries with the prescribed dose. If a study participant was missing dosage information at an observed visit, the dose was assumed not to have changed. AChR-Ab levels were measured at baseline, week 24, and week 52 (Mayo Medical Laboratories; reference range: positive >0.02 nmol/L). Total B-cell counts (CD19+/CD20– plus CD19+/CD20+ cells) were measured at baseline, week 24, and week 52 to monitor for successful depletion (University of Rochester Laboratory; reference range: 120–725 cells/μL).

Statistical Analysis

All primary analyses were performed using the intent-to-treat paradigm, which included all randomized participants. Because this was a midphase trial, the analyses of the primary and secondary endpoints were performed using a 0.10 level of significance. Continuous variables were summarized using means and SDs, or with medians, minimum, and maximum values. Categorical variables were summarized using counts/percentages.

The primary futility hypothesis tested was that rituximab-treated participants would achieve at least a 30% absolute increase in the frequency of successful primary endpoints compared to placebo. Logistic regression, adjusted for the 2 stratification variables, was used to estimate the odds ratio (OR) and the 90% 1-sided confidence interval (CI). Assuming a placebo response rate of 40%, an absolute 30% increase in the frequency of successful outcomes corresponds to an OR of 3.5. Thus, the null hypothesis would be rejected if the upper limit of the 90% 1-sided CI excludes 3.5. Rejecting the null hypothesis suggests futility in the sense that it appears unlikely that conducting a phase 3 clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If the null hypothesis was not rejected, that would provide justification for proceeding to a larger, confirmatory clinical trial.

The primary safety hypothesis was evaluated by examining the frequency of treatment-related AEs in the 2 groups. Logistic regression was used to estimate the OR for treatment-related AEs and SAEs. Similar analyses were also performed to assess overall AEs and SAEs. An additional post hoc safety analysis was performed using similar methods to compare the rate of MG-related exacerbations across the groups.

To address the secondary objectives, the change in MGC and QMG scores from baseline to week 52 were modeled, adjusting for baseline score and the stratification variables. The model-adjusted difference in mean change over time was compared for the 2 groups. Multivariable linear regression models were used for these analyses. The change in score from baseline was the outcome variable. The predictor variables were treatment group, 2 strata variables, and baseline score.

An exploratory responder analysis was also implemented for MGC and QMG scores. A series of increasing thresholds for clinical improvement were modeled using logistic regression to estimate the odds of clinical improvement for rituximab vs placebo-treated participants. Similar exploratory analyses were conducted for the MG-ADL and MG-QoL measurements. Post hoc exploratory analyses were also conducted on the AUDTC, B-cell counts, and AChR-Ab levels using similar methods. Due to skewness, a nonparametric rank-based

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Table 1 Study Population Baseline Characteristics

Demographics	Total (n = 52)	Rituximab (n = 25)	Placebo (n = 27)
Female	23 (44.2)	11 (44)	12 (44.4)
Age at enrollment, y	55.1 (17.1)	53.2 (17.5)	56.8 (17)
Age at diagnosis, y	49.6 (18.7)	46.6 (18.7)	52.4 (18.7)
Time from diagnosis to randomization, y	5.5 (5.9)	6.7 (6.5)	4.4 (5.3)
Race/ethnicity			
Asian	1 (1.9)	0 (0)	1 (3.7)
African American	11 (21.2)	2 (8)	9 (33.3)
Hispanic	5 (9.6)	3 (12)	2 (7.4)
Non-Hispanic White	35 (67.3)	20 (80)	15 (55.6)
Current and previous treatments			
Baseline therapy by actual strata[a]			
Prednisone only	34 (65.4)[b]	17 (68)[b]	17 (63)[b]
Moderate dose (15–35 mg/d), n	29	15	14
High dose (>35 mg/d), n	5	2	3
Prednisone + ISTs	18 (34.6)[b]	8 (32)[b]	10 (37)[b]
Moderate dose prednisone (15–35 mg/d), n	17	7	10
High-dose prednisone (>35 mg/d), n	1	1	0
Baseline prednisone dose, mg/d	22.1 (9.7)	23 (11.2)	21.3 (8.3)
Pyridostigmine	39 (75)	19 (76)	20 (74.1)
Baseline pyridostigmine dose, mg/d	230.0 (98.4)	230.5 (93.8)	229.5 (105)
Previous IVIg/PLEX	27 (51.9)	13 (52)	14 (51.9)
Prior thymectomy	12 (23.1)	8 (32)	4 (14.8)
Time from thymectomy to randomization, y	7.7 (9.1)	8.0 (8.6)	7.0 (11.5)
Baseline clinical disease activity			
MGC score	9.8 (5.2)	11.1 (6.1)	8.5 (4.0)
QMG score	10.1 (4.5)	11.0 (5.1)	9.2 (3.9)
MG-ADL score	4.9 (3.6)	5.8 (3.6)	4.0 (3.4)
MG-QoL score	20.1 (12.5)	22.7 (14.1)	17.7 (10.6)
MSE	8/50 (16)[c]	1/24 (4.2)[c]	7/26 (26.9)[c]
MGFA Clinical Class			
Class I	1 (1.9)[d]	0 (0)	1 (3.7)[d]
Class II	31 (59.6)	15 (60)	16 (59.3)
Class III	18 (34.6)	9 (36)	9 (33.3)
Class IV	2 (3.9)	1 (4)	1 (3.7)

Abbreviations: IST = immunosuppressive therapy (azathioprine, cyclosporine, mycophenolate, methotrexate); IVIg = IV immunoglobulin; MG-ADL = Myasthenia Gravis–Activities of Daily Living; MG-QoL = 15-item Myasthenia Gravis Quality of Life questionnaire; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MSE = minimal symptom expression (defined as an Myasthenia Gravis–Activities of Daily Living score 0–1); PLEX = plasma exchange; QMG = Quantitative Myasthenia Gravis.
Data are mean (SD) or n (%).
[a] Baseline therapy reported by actual strata (see mis-stratification details[b]).
[b] There were 4 mis-stratifications, 2 in each treatment group. In the rituximab group, 2 participants were originally classified in the prednisone + IST/moderate dose strata, when they were actually in the prednisone only/moderate dose strata. Originally, 40% of the rituximab group was classified in the prednisone + IST strata (collapsing over prednisone dose). Due to the mis-stratifications, 32% of rituximab patients are actually in the prednisone + IST strata (collapsing over prednisone dose). In the placebo group, 1 participant was originally classified in the prednisone + IST/moderate dose strata but was actually in the prednisone only/moderate dose strata, and 1 other participant was originally classified in the prednisone only/moderate dose but was actually in the prednisone + IST/moderate dose strata. There was no net change in the placebo group breakdown as the original and actual classifications were opposite of one another.
[c] As 2 of the 52 participants had missing MG-ADL scores at baseline (1 in each group), MSE % reported are for those with available data.
[d] Although the patient was categorized as MGFA Class I at study entry, this was an individual with a history of generalized MG. Because this participant was eligible based on an earlier version of the protocol and had already received study drug, the participant was allowed to continue and included per intent to treat statistical analysis plan.

analysis was used to compare AChR-Ab levels over time adjusting for both stratification variables and baseline AChR-Ab. Similarly, for comparing AUDTC, a nonparametric rank-based analysis was used to compare median values over time in a model adjusting for both stratification variables.

Prespecified sensitivity analyses using different methods to impute missing endpoint data were conducted that included observed data only, last observation carried forward, multiple imputation, and best and worst case scenarios. In these analyses, with the exception of those based on observed data only, all participants who terminated from the study due to AE or had clinical worsening (MGC score >2 above baseline) at the time of termination were considered primary endpoint failures. Only endpoints for participants with missing data due to other reasons (lost to follow-up, discontinuation for reasons other than AEs) were imputed. Additional post hoc sensitivity analyses were conducted to account for the potential effect of rescue therapy and differences in baseline disease burden.

Sample Size Justification

We assumed that 40% of participants assigned placebo would achieve a ≥75% prednisone dose reduction based on a study of mycophenolate mofetil in AChR-Ab+ gMG where 39% of placebo-treated participants had a reduction of prednisone dose by at least 78%.[17] In addition, we assumed that a 30% increase in favorable response over placebo would be clinically

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Table 2 Change in Clinical Outcome Measures From Baseline to Week 52

Steroid-sparing effect				
Reduction in mean daily prednisone dose ≥75% with stable MGC score	**Rituximab (n = 25), %**	**Placebo (n = 27), %**	**OR (1-sided 90% CI)**	***p* Value**
Primary[a] (n = 52)	60	56	1.1 (0, 2.4)	0.03[c]
Observed[b] (n = 47)	65	63	1.1 (0, 2.4)	

Observed change in clinical outcome measures from baseline to week 52				
Clinical outcome measure	**Rituximab (n = 25)**	**Placebo (n = 27)**	**Model adjusted difference (2-sided 90% CI)**	***p* Value**
Prespecified secondary outcomes				0.93
MGC score, mean ± SD	−5.7 ±7.3	−4.0 ± 4.1	−0.1 (−2.2, 2)	
Min, max	−24, 9	−11, 5		
QMG score, mean ± SD	−4.0 ± 5.4	−1.7 ± 3.9	−1.1 (−3.2, 1)	0.39
Min, max	−15, 6	−10, 5		
Exploratory outcomes				
MG-ADL score, mean ± SD	−2.7 ± 3.3	−2.0 ± 3.2	0.2 (−0.9, 1.4)	0.73
Min, max	−11, 3	−12, 4		
MG-QoL score, mean ± SD	−8.0 ± 9.3	−7.5 ± 9.1	0.9 (−3.1, 5)	0.70
Min, max	−34, 15	−28, 6		

Abbreviations: CI = confidence interval; MG-ADL = Myasthenia Gravis–Activities of Daily Living; MG-QoL= 15-item Myasthenia Gravis Quality of Life questionnaire; MGC = Myasthenia Gravis Composite; OR = odds ratio; QMG = Quantitative Myasthenia Gravis.
[a] Primary refers to all study participants including early terminations, who were included in the intent to treat and safety analysis.
[b] Observed refers to the actual number of study participants who completed the study at week 52.
[c] The *p* value of 0.03 indicates that the null hypothesis of a ≥30% increase in the frequency of favorable response in the rituximab vs placebo group should be rejected, supporting the conclusion of futility with respect to conducting a larger, confirmatory phase 3 trial.

meaningful and that 70% of participants assigned rituximab would achieve the primary binary endpoint. Trial design was somewhat restricted due to the fact that active drug was only available for 25 participants. As a consequence, this study entailed more of a sample size justification (for the sample size fixed by external factors) as opposed to a standard sample size calculation that determines the required sample size for a fixed target power. When the true success rate for rituximab is near or below the assumed success rate of 40% for placebo, the study would declare futility with a power of 74% or greater. Likewise, when the true success rate for rituximab was ≥30% than that for placebo, the study has <10% chance of incorrectly declaring futility (eFigure 2, links.lww.com/WNL/B681). Thus, the chosen sample size provided a reasonable chance for a successful study that was able to answer the main question of interest regarding whether there is clear evidence to rule out an effect of rituximab in this population (i.e., declare futility) or to provide evidence to justify a future phase 3 trial.

Data Availability

The full trial protocol is available as an online appendix and is also freely available from the US National Library of Medicine (clinicaltrials.gov; NCT02110706). A deidentified dataset will be archived and upon request will be available from the National Institute of Neurologic Disorders and Stroke (crliaison@ninds.nih.gov).

The study protocol and statistical analysis plan are available for further reference in eSAP 1 and eSAP 2 (links.lww.com/WNL/B681), respectively.

Results

Baseline Characteristics

We screened 68 individuals for eligibility, with 52 participants randomized to rituximab (n = 25) or placebo (n = 27) (Figure 1). Participants were predominantly male (55.8%) with a mean (±SD) age of 55.1 (±17.1) years and disease duration of 5.5 (±5.9) years at study entry (Table 1). Baseline demographics were balanced between groups with the exception of more African Americans in the placebo group. Baseline immunotherapy regimens were generally well-matched between groups. The mean daily prednisone dose was 22.1 mg (range 15–60 mg/d) with 65.4% on prednisone only and 34.6% on prednisone plus an IST. Disease severity was predominately mild and balanced between groups with most participants assigned MGFA Class II (rituximab 60%, placebo 59.3%). However, disease burden may have been greater in the rituximab group in comparison to the placebo

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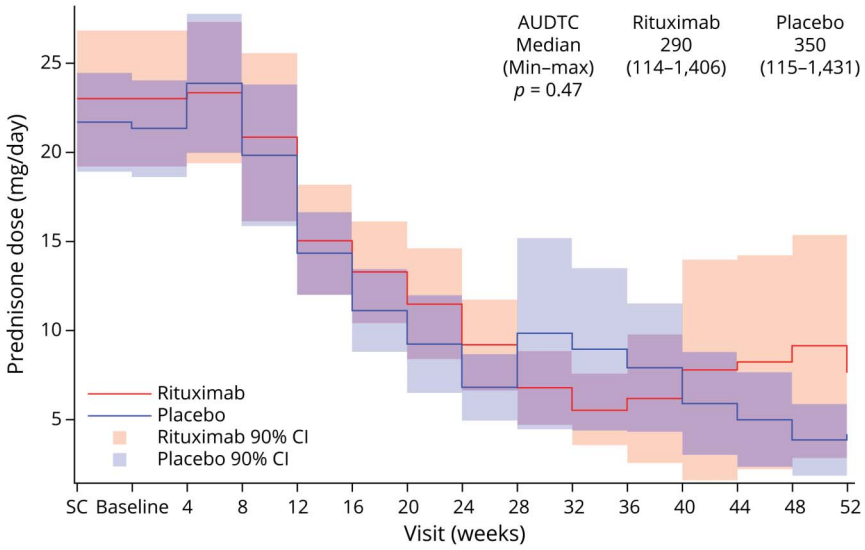
Figure 2 Steroid-Sparing Effect



Mean prednisone dose over time for participants undergoing a forced steroid taper in the rituximab and placebo arms over 52 weeks. The area under the dose time curve (AUDTC) was compared for 47 participants completing the study through week 52 utilizing a nonparametric rank-based analysis. CI = confidence interval.

group overall as the MG-specific scales had higher mean scores (significance level met for MGC [p = 0.07] and MG-ADL [p = 0.09]). In addition, a greater proportion of participants in the placebo group had minimal symptom expression (MSE), defined as an MG-ADL score of 0–1, at baseline (p = 0.05). There were 2 patients with missing MG-ADL scores at baseline, 1 in each treatment group, who were excluded from analyses (Table 1). Median AChR-Ab level in the rituximab group was 4.2 nmol/L (range 0.02–193) vs 1.5 nmol/L (range 0–12.4) in the placebo group (p = 0.02). There were 2 participants with negative antibody levels at baseline (1 rituximab, 1 placebo).

Primary Futility Outcome

The primary steroid-sparing outcome as defined in our study was achieved in 60% (15/25) vs 56% (15/27) of participants in rituximab and placebo groups (OR 1.14%; 90% 1-sided CI 0–2.4), respectively (Table 2, Figure 2). As the upper limit of the 1-sided CI excluded the value of 3.5 corresponding to the predefined clinical meaningful response rate improvement of 30% due to rituximab vs placebo, the null hypothesis was rejected (p = 0.03), indicating futility. Based on our model, the estimated difference in percent of success between groups is a 6% increase in success rates associated with treatment and an upper 90% 1-sided CI of 24%.

In the rituximab group, 10 (40%) participants did not meet the primary endpoint (5 did not achieve ≥75% prednisone dose reduction but had no clinical worsening; 2 did not achieve the prednisone dose reduction and had clinical worsening; 1 achieved the ≥75% prednisone dose reduction but had clinical worsening; 2 withdrew from the study). In the placebo group, 12 (44%) participants did not meet the primary endpoint (8 did not achieve ≥75% prednisone dose reduction but had no clinical worsening; 1 did not achieve ≥75% prednisone dose reduction and had clinical worsening; 3 withdrew from the study).

Safety

The safety profile was assessed by examining the frequency of treatment-emergent and treatment-related SAEs and AEs between groups (Table 3, eTables 1, 2, links.lww.com/WNL/B681). A similar proportion of participants reported treatment-emergent AEs between the rituximab and placebo groups (100% vs 96%) with the most common AEs experienced by ≥15% participants being arthralgia, headache, upper respiratory tract infection, fatigue, back pain, nausea, muscular weakness, and paresthesia. Treatment-related AEs were also similar between groups (rituximab 76%, placebo 82%; p = 0.63). A similar proportion of participants reported treatment-emergent SAEs between the rituximab and placebo groups (36% vs 52%, p = 0.25) with the most common SAEs experienced by ≥2 participants being worsening of MG (rituximab 4%, placebo 11%) and pulmonary embolism (rituximab 4%, placebo 3.7%). Treatment-related SAEs were also similar between groups (rituximab 24%, placebo 30%; p = 0.65). Five participants withdrew early from the study (2 rituximab, 3 placebo) prior to week 24 for reasons not related to study treatment (Figure 1). Four additional participants (3 rituximab, 1 placebo) who remained in the study did not complete the second treatment cycle (intended 2-cycle regimen completion: rituximab 80%, placebo 85%).

Key Secondary Clinical Outcomes

Findings were similar for both key secondary outcomes, with neither showing a statistically significant difference over time. The change in mean MGC score was −5.7 vs −4.0, while the change in mean QMG score was −4.0 vs −1.7, for the rituximab and placebo groups, respectively (Figure 3, A and B).

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Table 3 Treatment-Emergent Adverse Events and Serious Adverse Events in Rituximab and Placebo Groups During the 52-Week Duration of Study

Safety analyses: treatment-emergent AEs and SAEs[a]	Rituximab, %	Placebo, %	*p* Value
Any treatment-emergent AEs	100	96	1.00
Any treatment-emergent SAEs	36	52	0.25

	Rituximab			Placebo			
Treatment-emergent AEs and SAEs	Participants, n (%)	Events, n	Rate	Participants, n (%)	Events, n	Rate	*p* Value
Treatment-emergent SAEs (in ≥2 participants)							
Worsening of MG[b]	1 (4)	1	0.003	3 (11.1)	4	0.013	0.36
Pulmonary embolism	1 (4)	1	0.003	1 (3.7)	1	0.003	0.96
Most common AEs (in ≥15% of participants in either group)							
Arthralgia	6 (24)	6	0.021	10 (37)	15	0.049	0.31
Headache	8 (32)	11	0.038	7 (25.9)	13	0.043	0.63
Upper respiratory tract infection	9 (36)	12	0.041	5 (18.5)	5	0.016	0.16
Fatigue	3 (12)	3	0.010	8 (29.6)	9	0.029	0.13
Back pain	2 (8)	2	0.007	9 (33.3)	11	0.036	0.04
Nausea	2 (8)	3	0.010	6 (22.2)	10	0.033	0.17
Muscular weakness	4 (16)	4	0.014	3 (11.1)	4	0.013	0.61
Paresthesia	0 (0)	0	0.000	5 (18.5)	7	0.023	0.05

MG exacerbations: post hoc analysis	Rituximab	Placebo	*p* Value
Total number of relapses requiring rescue therapy	3	11	
Participants treated with PLEX or IVIg, %	12	29.6	0.130
Relapse rate/30 days requiring IVIg or PLEX	0.010	0.036	0.055

Abbreviations: AE = adverse event; IVIg = IV immunoglobulin; MG = myasthenia gravis; PLEX = plasma exchange; SAE = serious adverse event;
Overall frequencies of treatment emergent-AEs and SAEs are shown along with any SAE occurring in more than 1 study participant and the most common AEs in either group with their respective rates/30 days. Comparisons of percent of participants with MG relapse, the total number of relapse events, and the rates of relapses requiring rescue therapy across the 2 treatment groups.
[a] Preferred terms in the Medical Dictionary for Regulatory Activities.
[b] For the purpose of this study, an MG relapse was not captured as an SAE unless the relapse required hospitalization for a rescue therapy. There were 14 disease exacerbations requiring rescue therapy (rituximab 3, placebo 11) in a total of 11 participants. Exacerbations requiring rescue therapy were observed in 12% (3/25) of those in the rituximab group vs 29.6% (8/27) of those in the placebo group.

Other Exploratory Outcomes

Steroid-Sparing Effect

The median AUDTC was 290 mg for rituximab and 350 mg for placebo ($p = 0.47$) (Figure 2).

Clinical Outcomes

Changes in mean MG-ADL and MG-QoL scores from baseline to week 52 showed no statistically significant model-adjusted differences between the groups (Table 2).

Responder Analyses

Responder analysis at week 52, including the logistic regression model, evaluating the proportion of participants improving by ≥3 points was 70% vs 67% and 65% vs 39% (rituximab vs placebo) for the MGC and QMG scores, respectively. While increasing the stringency of the responder definition with higher thresholds resulted in a greater proportion of participants in the rituximab group achieving a clinically meaningful response, there were no statistically significant differences observed at any threshold (Figure 3, C and D). Similar responder analyses of both the MG-ADL and MG-QoL scores showed no significant differences (data not shown).

Disease Exacerbations

There were 14 disease exacerbations requiring rescue therapy with either IVIg or PLEX (rituximab 3; placebo 11) in 11 participants during the 52-week study period (Table 3). Exacerbations requiring rescue therapy were observed in 12% (3/25) of those in the rituximab group vs 29.6% (8/27) of those in the placebo group ($p = 0.130$). The rate of MG relapses per 30 days requiring rescue therapy for the placebo group was 0.036 vs 0.010 in rituximab group ($p = 0.055$). A

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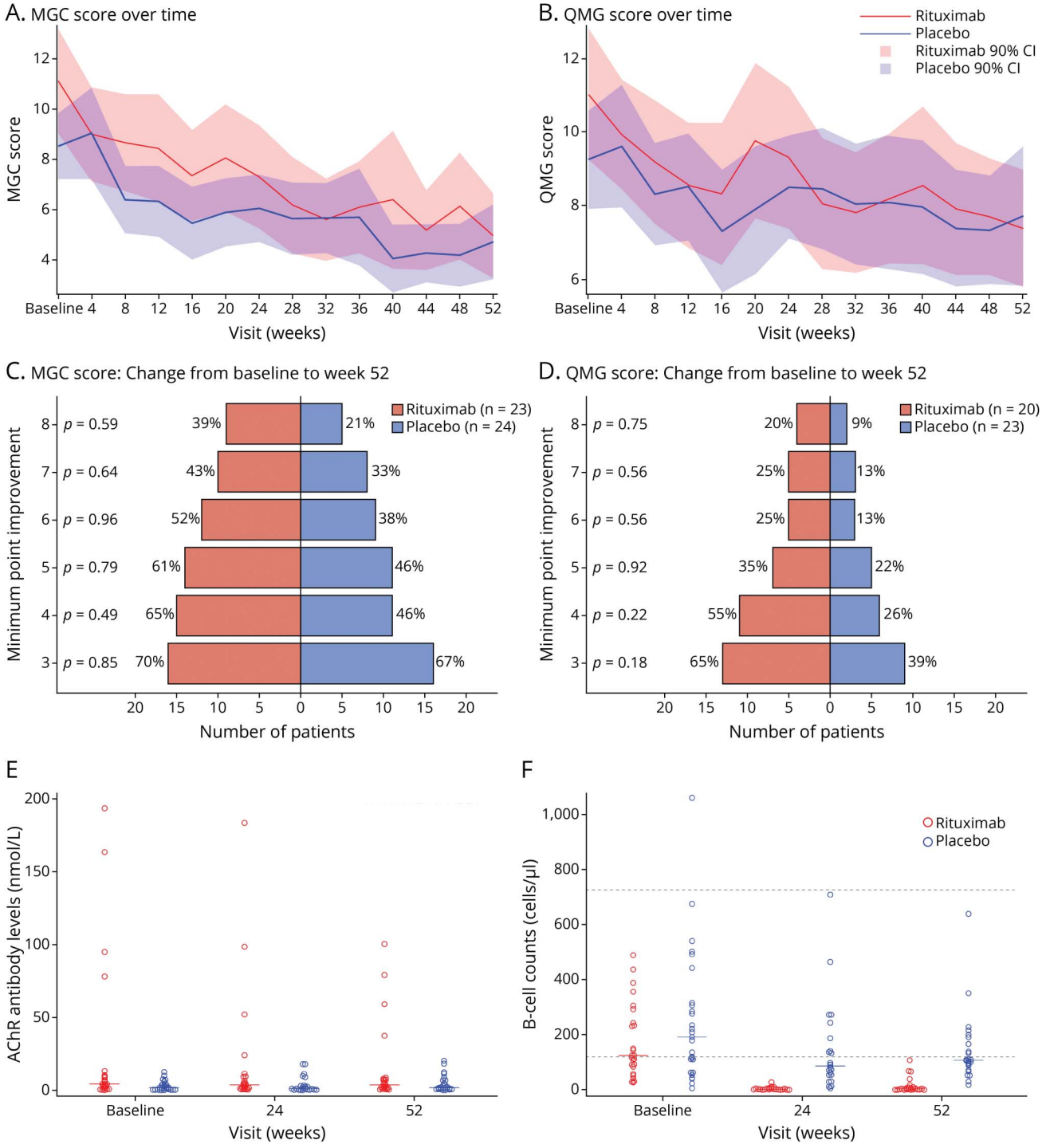
Figure 3 Clinical Outcome Measures



(A) Mean Myasthenia Gravis Composite (MGC) score over time by treatment group. (B) Mean Quantitative Myasthenia Gravis (QMG) score over time by treatment group. (C, D) Responder analysis: graphs show minimum point improvement at week 52 in the MGC and QMG scores for 47 participants completing the study. The initial threshold compares the percentage of participants achieving at least a 3-point improvement in MGC and QMG scores from baseline. (Due to convergence issues, the moderate/high dose prednisone strata variable was dropped from these models.) The upper threshold corresponded to an improvement of 8 points or greater for the MGC and 8 points or greater for the QMG scores. MGC score data were available for all 47 participants who completed the 52-week study period. QMG score data were available for 43 participants (3 participants in the rituximab group were either missing a baseline or 52-week score; 1 participant in the placebo group was missing a baseline score). (E) Median acetylcholine receptor (AChR) antibody levels (horizontal lines) at baseline (BL), week 24, and week 52 in the rituximab group were 4.2 (range 0.02–193), 3.47 (range 0.36–183), and 3.42 (range 0.41–100) nmol/L vs 1.5 (range 0–12.4), 0.9 (range 0.03–17.7), and 1.6 (range 0.07–20.1) nmol/L in the placebo group. Laboratory reference range: positive >0.02 nmol/L. (F) Median B-cell counts (horizontal lines) at BL, week 24, and week 52 for each participant. Normal reference range denoted by horizontal dashed lines: 120–725 cells/µL (CD19+/CD20– plus CD19+/CD20+ cells). CI = confidence interval.

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Table 4 Post Hoc Sensitivity Analysis for Primary Endpoint

Model	Reduction in mean daily prednisone dose ≥75% with stable MGC score, n (%)		Odds ratio (1-sided 90% CI)	*p* Value
	Rituximab	Placebo		
Modified primary endpoint (imputing endpoint failure if rescue therapy required), n (%)	14/25 (56)	14/27 (52)	1.14 (0, 2.39)	0.03
Primary endpoint (adjusting for baseline MSE variable), n (%)	15/24 (63)[a]	15/26 (58)[a]	1.53 (0, 3.43)	0.095
Primary endpoint (adjusting for baseline MGC score), n (%)	15/25 (60)	15/27 (56)	1.48 (0, 3.31)	0.086
Primary endpoint (adjusting for baseline MG-ADL score), n (%)	15/24 (63)[a]	15/26 (58)[a]	1.40 (0, 3.11)	0.072

Abbreviations: CI = confidence interval; MG-ADL = Myasthenia Gravis–Activities of Daily Living; MGC = Myasthenia Gravis Composite; MSE = minimal symptom expression (defined as an MG-ADL score of 0–1).
[a] There were 2 patients excluded from analysis (1 rituximab, 1 placebo) due to missing MG-ADL score at baseline.

reduced rate of MG relapses requiring rescue therapy was observed in the rituximab group, with the placebo group having over a threefold higher rate of MG relapses (Table 3).

AChR Autoantibody Levels

In the rituximab group, the median AChR-Ab level decreased from 4.16 nmol/L at baseline to 3.47 and 3.42 nmol/L at weeks 24 and 52, respectively (Figure 3E). In the placebo group, the median AChR-Ab level changed from 1.5 nmol/L at baseline to 0.91 and 1.63 nmol/L at weeks 24 and 52, respectively. Change from baseline did not differ significantly between the groups at either week 24 or 52. After adjusting for baseline AChR-Ab level differences on the rank-based scale and the 2 strata, the change from baseline over time was not significant.

B-Cell Counts

For the placebo group, the median B-cell counts at baseline, week 24, and week 52 were 192 (range 6–1,060), 86 (range 6–708), and 107 (range 17–638); for the rituximab group, they were 124 (range 26–488), 2 (0–27), and 4 (0–107), respectively (Figure 3F). Successful B-cell depletion was achieved in the treatment group. Notably, 42% (22/52) of participants had B-cell counts below the lower limit of normal (LLN) (<120 cells/μL) at baseline. The proportion of participants with baseline B-cell counts below the LLN did not differ across treatment groups (12 [48%] rituximab vs 10 [37%] placebo; $p = 0.42$). Interestingly, 15 participants (63%) in the placebo group continued to have B-cell count levels below the LLN at both week 24 and 52, compared to the rituximab group, where all were below the LLN.

Sensitivity Analysis

Post hoc sensitivity analyses (Table 4) used different imputation techniques. First, a modified primary endpoint was estimated, in which participants who received rescue therapy were imputed as primary endpoint failures. There were 11 patients who had at least 1 relapse requiring rescue therapy: 3 in the rituximab group and 8 in the placebo group. In the rituximab group, 1 out of 3 participants requiring rescue therapy had a successful primary endpoint, while in the placebo group, 1 out of 8 participants requiring rescue therapy had a successful primary endpoint. Imputing primary endpoint failures for these 2 patients resulted in 14 patients with successful primary endpoints in each group (56% [14/25] rituximab vs 52% [14/27] placebo; OR 1.14%; 90% 1-sided CI 0–2.39). The null hypothesis was rejected ($p = 0.03$), indicating futility. Due to observed differences in disease burden across groups, with 4.2% of the rituximab group vs 26.9% of the placebo group having an MG-ADL score 0–1 (MSE) at baseline, models were fit that adjusted for this variable using both the primary endpoint and the modified primary endpoint, which assumed endpoint failure for participants who required rescue therapy (Table 4). The odds of a successful primary endpoint were 1.53 times higher in the rituximab group relative to the placebo group (1-sided 90% CI 0–3.43). Using the modified primary endpoint, the odds of a successful endpoint were 1.37 times higher in the rituximab group relative to the placebo group (1-sided 90% CI 0–3.04). However, as the upper bound of the 1-sided CI did not exceed 3.5, the null hypothesis was rejected in both cases ($p = 0.095$ and $p = 0.066$, respectively, with a prespecified significance level of 0.10). Similarly, sensitivity analyses accounting for differences in MGC and MG-ADL baseline scores for the primary endpoint also rejected the null hypothesis (Table 4).

Discussion

In a previous single-center pilot study conducted at Yale University, 82% of patients with gMG who completed a 2-cycle rituximab regimen achieved ≥75% reduction in their prednisone dose at 52 weeks (95% CI 48%–98%). The BeatMG Study was designed to follow up on this observation and to determine whether rituximab was a safe and beneficial therapeutic that warranted further investigation in an efficacy trial. We found no significant difference in the prespecified measure of steroid-sparing effect between the rituximab and placebo groups. The futility analysis indicated that there was a low probability of observing a clinically meaningful steroid-sparing

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effect difference, as defined, in a phase 3 trial of a similar AChR-Ab+ gMG population at 1 year.

After accounting for baseline differences between the groups, statistically significant clinical improvement was not observed in key secondary outcomes, exploratory clinical outcomes, or responder analyses. However, additional exploratory analysis of MG exacerbations suggested a reduction in relapses requiring rescue therapy in the rituximab group, with participants on placebo having over a threefold higher rate of relapses relative to the rituximab group. This suggested that while participants in both groups were able to achieve the prespecified primary endpoint at a similar rate, the placebo group may have been less stable in their disease course. However, post hoc sensitivity analysis imputing primary endpoint failure for participants who received rescue therapy (modified primary endpoint) still supported the futility hypothesis.

Other possibilities explaining why clear clinical improvements may not have been apparent include (1) failure of anti-CD20 therapy in the majority of AChR-Ab+ gMG patients; (2) adequate B-cell reduction at baseline due to concomitant steroid or ISTs used; (3) use of a steroid-sparing outcome measure; or (4) trial inclusion of a disproportionate fraction of individuals with too mild disease who were adequately responsive to concomitant therapies. While additional subgroup analyses were considered to address some of these, they would be underpowered and difficult to interpret.

This study has several limitations. Prior positive studies primarily focused on difficult-to-control/refractory disease and included MuSK-Ab+ patients.[5,6,8,15] Given that we would have required an additional 38 participants for a trial that included MuSK-Ab+ gMG, these patients were excluded due to recruitment feasibility concerns and limited drug availability. It is important to highlight that a 2017 systematic review and recent multicenter blinded, prospective review support good clinical outcomes in MuSK-Ab+ patients with MG with rituximab.[15,18] In addition, we did not limit participation to patients with moderate to severe or refractory disease, primarily due to recruitment feasibility concerns. Higher than expected placebo response rate suggests that participants may have been on more prednisone than required, or that participants with mild disease respond well to prednisone and can be readily tapered, possibly affecting our primary outcome. Due to recruitment challenges and poor study accrual early on, the protocol was amended to allow the enrollment of individuals on prednisone plus ISTs, which accounted for ~1/3 of participants. The mild level of disease severity may have contributed to the ease of lowering prednisone dose based on the forced steroid taper protocol as well as to clinical scale insensitivity due to floor effects. More recently, studies are setting a minimum required baseline disease burden as entry criteria, such as MG-ADL ≥6 or QMG ≥12,[19,20] in an effort to mitigate this issue. The steroid taper protocol was linked to maintaining MGC score stability and was not driven by clinical improvement, which would allow participants to taper steroids if they already achieved a symptom plateau (e.g., minimal manifestation status) prior to study entry. While considered, there was no requirement to demonstrate a failed steroid taper prior to enrollment, which further complicated interpretation of results and could in part explain the higher than anticipated response rate in the placebo group. Finally, despite adequate power for the primary endpoint, this was a small study with an imbalance in disease burden (measured by MGC, QMG, MG-ADL, and MG-QoL scales) and autoantibody levels between groups, and only 80% of the rituximab group completed the intended 2-cycle regimen. As small participant numbers may have affected our findings, these key points need to be stressed in the overall interpretation of study results. Although additional post hoc sensitivity analyses accounting for rescue therapy use and baseline MSE (rituximab 4.2% vs placebo 26.9%) differences showed greater odds of success in the rituximab group, the null hypothesis was still rejected.

Although this study did not show a difference in steroid-sparing benefit between the treatment and placebo groups, we did learn important lessons that will instruct planning of future trials, including (1) the need to better define an adequately symptomatic population or disease of sufficient severity; (2) stratification strategies for disease burden differences; (3) a better understanding of how to control for the use of rescue therapy; and (4) the need to further evaluate and optimize the steroid-sparing outcome definition. Given the importance of steroids as a risk factor for cumulative organ damage and the potential masking of study drug benefit, further optimization is needed of a steroid-sparing outcome measure. As steroids have been used for decades as a first-line therapy for MG, the measure of steroid-sparing benefit is an important outcome for trials of any therapeutic. Because MG is characterized by a fluctuating course, the natural history of disease can influence placebo response separate from placebo effect, especially for studies with longer durations. An optimal outcome measure should be valid and reliable, measure clinically meaningful/relevant change, and be sensitive to measure treatment response.

This study failed to demonstrate a prespecified meaningful difference in steroid-sparing effect in a predominantly mildly symptomatic AChR-Ab+ gMG population on chronic immunotherapy at 1 year. These findings suggest that a larger, confirmatory phase 3 trial in this population with similar problematic features would have a low likelihood of observing this predetermined steroid-sparing effect. Rituximab was safe and well-tolerated in this cohort over a 52-week follow-up period. The higher than anticipated response rate in the placebo group suggests that participants may have been adequately responsive to concomitant therapies. Whether or not rituximab might be beneficial in patients with more treatment-resistant disease, or in MuSK-Ab+ MG, is not addressed by the current study. Many enrolled participants had low B-cell

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counts at baseline, possibly limiting the opportunity to demonstrate a beneficial therapeutic effect of further B-cell depletion. Additional analyses are planned to delve deeper into these results, and to further explore the role of B-cell depletion in this population, including the full effects of disease severity, B-cell counts, and use of concomitant ISTs at time of enrollment. Further insights are anticipated from the observational postintervention study, which includes follow-up through 96 weeks.

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Appendix 1 *(continued)*

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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B682

References

1. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. *Yale J Biol Med.* 2013;86(2):255-260.
2. Dalakas MC. Invited article: inhibition of B cell functions: implications for neurology. *Neurology.* 2008;70(23):2252-2260.
3. Lebrun C, Bourg V, Tieulie N, Thomas P. Successful treatment of refractory generalized myasthenia gravis with rituximab. *Eur J Neurol.* 2009;16(2):246-250.
4. Diaz-Manera J, Martinez-Hernandez E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology.* 2012;78(3):189-193.
5. Illa I, Diaz-Manera J, Rojas-Garcia R, et al. Sustained response to Rituximab in anti-AChR and anti-MuSK positive Myasthenia Gravis patients. *J Neuroimmunol.* 2008;201-202:90-94.
6. Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. *Ther Adv Neurol Disord.* 2011;4(5):259-266.
7. Zebardast N, Patwa HS, Novella SP, Goldstein JM. Rituximab in the management of refractory myasthenia gravis. *Muscle Nerve.* 2010;41(3):375-378.
8. Robeson KR, Kumar A, Keung B, et al. Durability of the rituximab response in acetylcholine receptor autoantibody-positive myasthenia gravis. *JAMA Neurol.* 2017;74(1):60-66.
9. Dorner T, Isenberg D, Jayne D, et al. Current status on B-cell depletion therapy in autoimmune diseases other than rheumatoid arthritis. *Autoimmun Rev.* 2009;9(2):82-89.
10. Dorner T, Lipsky PE. B-cell targeting: a novel approach to immune intervention today and tomorrow. *Expert Opin Biol Ther.* 2007;7(9):1287-1299.
11. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med.* 2004;350(25):2572-2581.
12. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. *Arthritis Rheum.* 2003;48(6):1484-1492.
13. Perosa F, Prete M, Racanelli V, Dammacco F. CD20-depleting therapy in autoimmune diseases: from basic research to the clinic. *J Intern Med.* 2010;267(3):260-277.
14. Ibrahim H, Dimachkie MM, Shaibani A. A review: the use of rituximab in neuromuscular diseases. *J Clin Neuromuscul Dis.* 2010;12(2):91-102.
15. Tandan R, Hehir MK II, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. *Muscle Nerve.* 2017;56(2):185-196.
16. Levin B. Selection and futility designs. In B. Ravina, J. Cummings, M. McDermott, & R. Poole, eds. *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge University Press; 2012:78-90.
17. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology.* 2008;71(6):400-406.
18. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as a treatment for anti-MuSK myasthenia gravis: multicenter blinded prospective review. *Neurology.* 2017;89(10):1069-1077.
19. Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol.* 2017;16(12):976-986.
20. *Safety and Efficacy Study of RA101495 in Subjects with Generalized Myasthenia Gravis.* Available at: clinicaltrials.gov; Unique Identifier: NCT03315130.

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