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Eculizumab in refractory generalized myasthenia gravis previously treated with rituximab: subgroup analysis of REGAIN and its extension study

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[Correction added on 6th December, after first online publication: Online open statement has been added.]

Abstract

Introduction/Aims: Individuals with refractory generalized myasthenia gravis (gMG) who have a history of rituximab use and experience persistent symptoms represent a population with unmet treatment needs. The aim of this analysis was to evaluate the efficacy and safety of eculizumab in patients with refractory anti-acetylcholine receptor antibody-positive (AChR$^+$) gMG previously treated with rituximab.

Methods: This *post hoc* subgroup analysis of the phase 3 REGAIN study (NCT01997229) and its open-label extension (OLE; NCT02301624) compared baseline characteristics, safety, and response to eculizumab in participants who had previously received rituximab with those who had not. Rituximab use was not permitted within the 6 months before screening or during REGAIN/OLE.

Results: Of 125 REGAIN participants, 14 had received rituximab previously (7 received placebo and 7 received eculizumab). In the previous-rituximab group, 57% had used at least four other immunosuppressants compared with 16% in the no-previous-rituximab group. Myasthenia Gravis Activities of Daily Living total scores from eculizumab baseline to week 130 of eculizumab treatment improved in both the previous-rituximab and no-previous-rituximab groups (least-squares mean −4.4, standard error of the mean [SEM] 1.0 [n = 9] and least-squares mean −4.6, SEM 0.3 [n = 67], respectively; difference = 0.2, 95% confidence interval −1.88 to 2.22). In addition, in both groups, most patients who were treated with eculizumab for 130 weeks achieved a Myasthenia Gravis Foundation of America post-intervention status of minimal manifestations (66.7% and 65.0%, respectively). The

eculizumab safety profile was similar between groups and consistent with its established profile.

Discussion: Eculizumab is an effective therapy for patients with refractory AChR$^+$ gMG, irrespective of whether they had received rituximab treatment previously.

KEYWORDS
acetylcholine receptor, eculizumab, myasthenia gravis, refractory, rituximab

1 | INTRODUCTION

Most patients with generalized myasthenia gravis (gMG; 70%-93%) have autoantibodies against acetylcholine receptors (AChRs) that activate the complement cascade.[1-6] The 10% to 15% of patients with gMG whose condition responds inadequately to immunosuppressive therapies (ISTs) are characterized as having refractory disease.[7-9] Treatment options are limited for refractory anti–AChR antibody–positive (AChR$^+$) gMG, and the chimeric, anti-CD20 monoclonal antibody rituximab is frequently used off label.[8,10] Rituximab targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes, which results in B-cell lysis.[11,12] To date, no phase 3, randomized, controlled trials have examined rituximab efficacy in gMG.[11,13-22] Data from several small studies suggest that rituximab may provide clinical benefit as a treatment for refractory, muscle-specific kinase antibody–positive (MuSK$^+$) gMG with a poor response to initial IST.[14,16,18,22] In patients with AChR$^+$ gMG, however, the evidence for rituximab efficacy is less robust, and suggests a lower response rate and a smaller steroid-sparing effect than in patients with MuSK$^+$ gMG.[10,17,21,23] Treatment guidelines recommend rituximab as an option for treatment of patients with refractory AChR$^+$ gMG for whom other ISTs have an inadequate effect or are not tolerated.[10] Therefore, patients with a history of rituximab use and persistent symptoms represent a population with unmet treatment need.

Complement inhibition is an alternative treatment strategy for patients who do not respond or are intolerant to IST.[24] Eculizumab is a humanized monoclonal antibody that specifically inhibits cleavage of terminal complement protein C5.[25] The 6-month, phase 3, randomized, placebo-controlled REGAIN study and its open-label extension (OLE) evaluated efficacy and safety of eculizumab in refractory AChR$^+$ gMG.[26,27] Although the primary endpoint in REGAIN (change from baseline to week 26 in Myasthenia Gravis Activities of Daily Living [MG-ADL] total score based on a worst-rank analysis of covariance) was not met, eculizumab-treated participants nonetheless showed rapid and sustained (through 130 weeks) improvements in MG-ADL score and key secondary endpoints.[26,27]

Some patients in REGAIN had a history of treatment with rituximab. We report a *post hoc*, exploratory subgroup analysis of data from REGAIN and its OLE investigating the efficacy and safety of eculizumab in patients treated previously with rituximab.

2 | METHODS

2.1 | Study design and participants

REGAIN and the OLE study were approved by the relevant ethics committee/institutional review board at each study site, and informed consent was obtained from all participants. REGAIN (NCT01997229) was a 6-month (26-week), phase 3, randomized, double-blind, placebo-controlled study of eculizumab (Alexion Pharmaceuticals, Boston, Massachusetts) in patients with refractory AChR$^+$ gMG. Participants who completed REGAIN could enroll in the OLE study (NCT02301624) within 2 weeks of REGAIN completion and receive open-label eculizumab for a maximum of up to 4 years.

Patients were eligible to participate in REGAIN if they were at least 18 years old, had confirmed gMG, and tested seropositive for AChR autoantibodies. Full methodology and inclusion criteria have been described previously.[27] Patients were defined as having refractory disease if they had received at least two ISTs, or at least one IST with intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) given at least four times per year, for 12 months without symptom control.[27] All REGAIN participants were required to receive vaccination against *Neisseria meningitidis*, and were revaccinated according to local guidelines.[27] Patients who had used rituximab more than 6 months before screening were eligible for enrollment in REGAIN; patients who had used rituximab within the 6 months before screening were not eligible, and rituximab treatment was not permitted during REGAIN or the OLE.

2.2 | Dosing

Eculizumab and placebo administration during REGAIN and its OLE has been described previously.[26-28] During REGAIN, participants were randomized to receive eculizumab for 26 weeks at the maintenance dose of 1200 mg every 2 weeks after a 4-week induction period (900 mg on day 1 and at weeks 1, 2, and 3, and 1200 mg at week 4), or were given placebo on the same schedule.[27] During the OLE, all

participants received open-label eculizumab 1200 mg every 2 weeks (after a 4-week blinded induction period) for up to 4 years.[26]

2.3 | Assessments

MG-ADL, Quantitative MG (QMG), MG Composite (MGC), and 15-item MG Quality of Life questionnaire (MG-QOL15) total scores; Myasthenia Gravis Foundation of America (MGFA) post-intervention status; and achievement of "minimal symptom expression" (MG-ADL total score of 0-1 [range, 0-24] or an MG-QOL15 total score of 0-3 [range, 0-60]) were assessed throughout REGAIN and the OLE, and at the end-of-study visit in the OLE.[26-29] In addition, MG-related hospitalizations were evaluated as rates per 100 patient-years (PY) of observation. Safety assessments included adverse events (AEs) and serious AEs.

2.4 | Statistical analysis

For all participants randomized and treated in the REGAIN study, demographics and MG history at REGAIN baseline were summarized for groups based on previous treatment with rituximab. Safety and efficacy data were evaluated by group for all participants who received at least one dose of eculizumab during either REGAIN or the OLE. Baseline and safety data were summarized using descriptive statistics.

Changes in efficacy parameters were evaluated from eculizumab baseline to week 130 of eculizumab treatment. Eculizumab baseline was the last available assessment before the first eculizumab dose (ie, the REGAIN baseline for participants randomized to the eculizumab treatment arm in REGAIN and the OLE baseline for participants randomized to the placebo treatment arm in REGAIN).

Restricted maximum-likelihood–based repeated-measures analysis of change from baseline was used to quantify changes in MG-ADL, QMG, MGC, and MG-QOL15 total scores and the data are presented as least-squares (LS) means and 95% confidence intervals (CIs). The repeated-measures models included terms for baseline value (at start of eculizumab treatment) of the endpoint in question, rituximab history group, visit, and the rituximab history group-by-visit interaction. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). This study did not have a data monitoring committee.

3 | RESULTS

3.1 | Study population

Of the 125 participants treated in the REGAIN study, 14 had received rituximab previously: 7 were treated with eculizumab and 7 were given placebo. All but one of these patients (from the placebo group) continued into the OLE. Patient disposition by rituximab history is summarized in Figure 1.

At REGAIN baseline, participants in the previous-rituximab group (n = 14) were, on average, younger at MG diagnosis, had a longer mean disease duration from time of MG diagnosis, and were more likely to have received IVIg or to have undergone a thymectomy compared with participants in the no-previous-rituximab group (n = 111). In addition, the majority of patients in the previous-rituximab group had a history of using four or more ISTs, whereas the majority of patients in the no-previous-rituximab group had a history of using two ISTs (Table 1).

Participants in the previous-rituximab group had been treated with a variety of rituximab regimens. Their median time between last
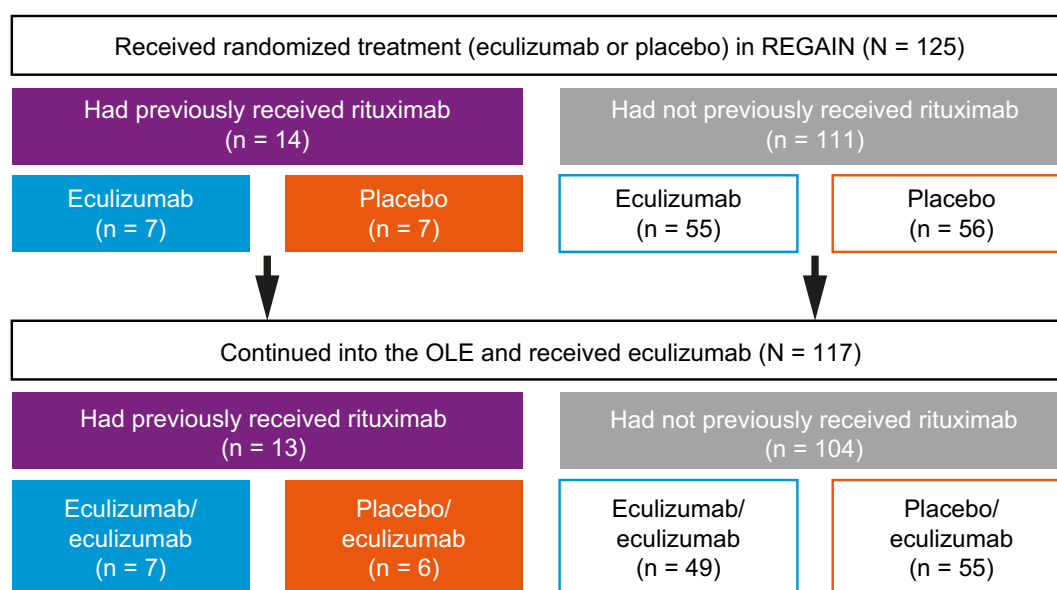

FIGURE 1 Patient disposition in REGAIN and its OLE study. Abbreviation: OLE, open-label extension

TABLE 1 Patient demographics and MG history at REGAIN baseline

	Previous rituximab, n = 14	No previous rituximab, n = 111	P value
Female, n (%)	12 (85.7%)	70 (63.1%)	.1357
Age (years) at MG diagnosis, mean (SD)	27.6 (14.8)	39.4 (18.7)	.0244
Duration (years) of MG,[a] mean (SD)	13.9 (10.5)	9.0 (7.8)	.0350
Any previous hospitalizations for MG, n (%)	11 (78.6%)	84 (75.7%)	1.0000
Duration (days) of stay, mean (SD)	12.8 (5.1)	9.0 (7.8)	.2309
Treatment history, n (%)			
2 ISTs	1 (7.1%)	57 (51.4%)	
3 ISTs	5 (35.7%)	34 (30.6%)	
≥4 ISTs	8 (57.1%)	18 (16.2%)	
			.0010
IVIg	14 (100.0%)	85 (76.6%)	.0406
PLEX	9 (64.3%)	51 (45.9%)	.2592
History of thymectomy, n (%)	12 (85.7%)	56 (50.5%)	.0201
Baseline disease activity scores, mean (SD)			
MG-ADL	10.6 (3.48)	10.1 (2.76)	.5891
QMG	16.9 (5.90)	17.1 (5.27)	.9152
MGC	21.4 (7.43)	19.4 (5.87)	.2450
MG-QOL15	31.9 (10.50)	32.2 (12.78)	.9478

Abbreviations: IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QOL15, 15-item Myasthenia Gravis Quality of Life questionnaire; MGC, Myasthenia Gravis Composite; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.
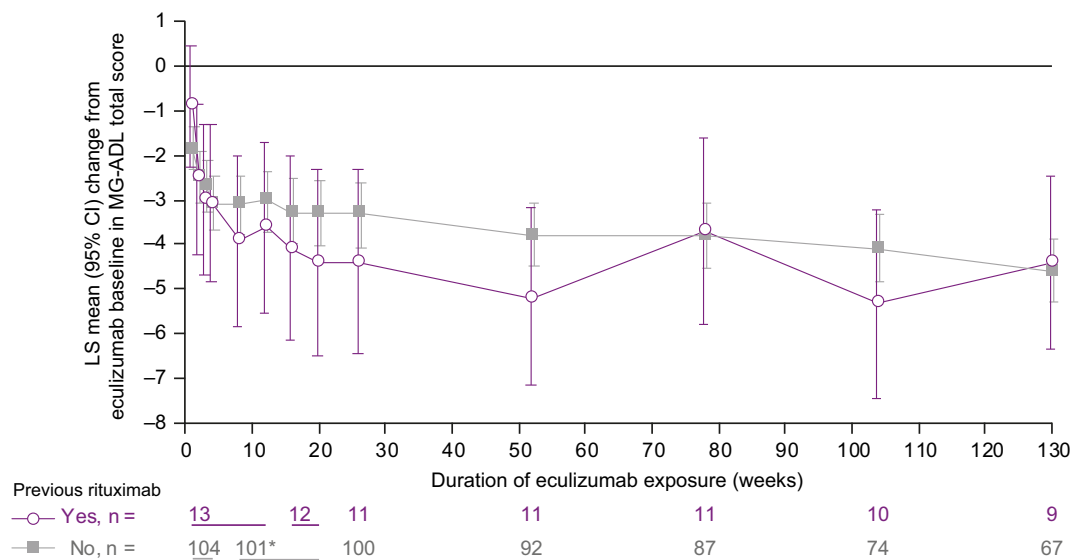
[a]Time from MG diagnosis.

FIGURE 2 MG-ADL total score from eculizumab baseline in eculizumab-treated patients with and without previous rituximab treatment. Changes in efficacy parameters were evaluated from eculizumab start at week 0 to week 130 of eculizumab treatment. Eculizumab baseline was the last available assessment before the first eculizumab dose (ie, REGAIN baseline for participants randomized to eculizumab in REGAIN and OLE baseline for participants who initiated eculizumab in the OLE). Changes from eculizumab baseline were measured using a repeated-measures model. *n = 103 at week 12. Abbreviations: CI, confidence interval; LS, least-squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; OLE, open-label extension

rituximab dose and first dose of study treatment (eculizumab or placebo) in REGAIN was 18.6 (range, 7.4-34.9) months in the eculizumab arm (n = 7) and 20.9 (range, 5.9-109.3) months in the placebo arm (n = 7). Four participants (two in each treatment group) had received rituximab in the year (between 6 and 12 months) before starting study treatment in REGAIN.

3.2 | Efficacy analyses

The LS mean (standard error of the mean [SEM]) change in MG-ADL score from eculizumab baseline to week 130 was −4.4 (1.0) in the previous-rituximab group and −4.6 (0.3) in the no-previous-rituximab group (difference in LS means between groups, 0.2; 95% CI, −1.88 to 2.22; Figure 2). The differences in LS means between groups for QMG, MGC, and MG-QOL15 total scores were 0.5 (95% CI, −2.42 to 3.37), 1.1 (95% CI, −2.99 to 5.14), and −2.9 (95% CI, −9.81 to 4.00), respectively (Figure 3). The interaction effect between the previous- and no-previous-rituximab groups, assessed at each visit during eculizumab treatment, was not statistically significant for any of the four efficacy endpoints, at every timepoint (P values for the rituximab history group-by-visit
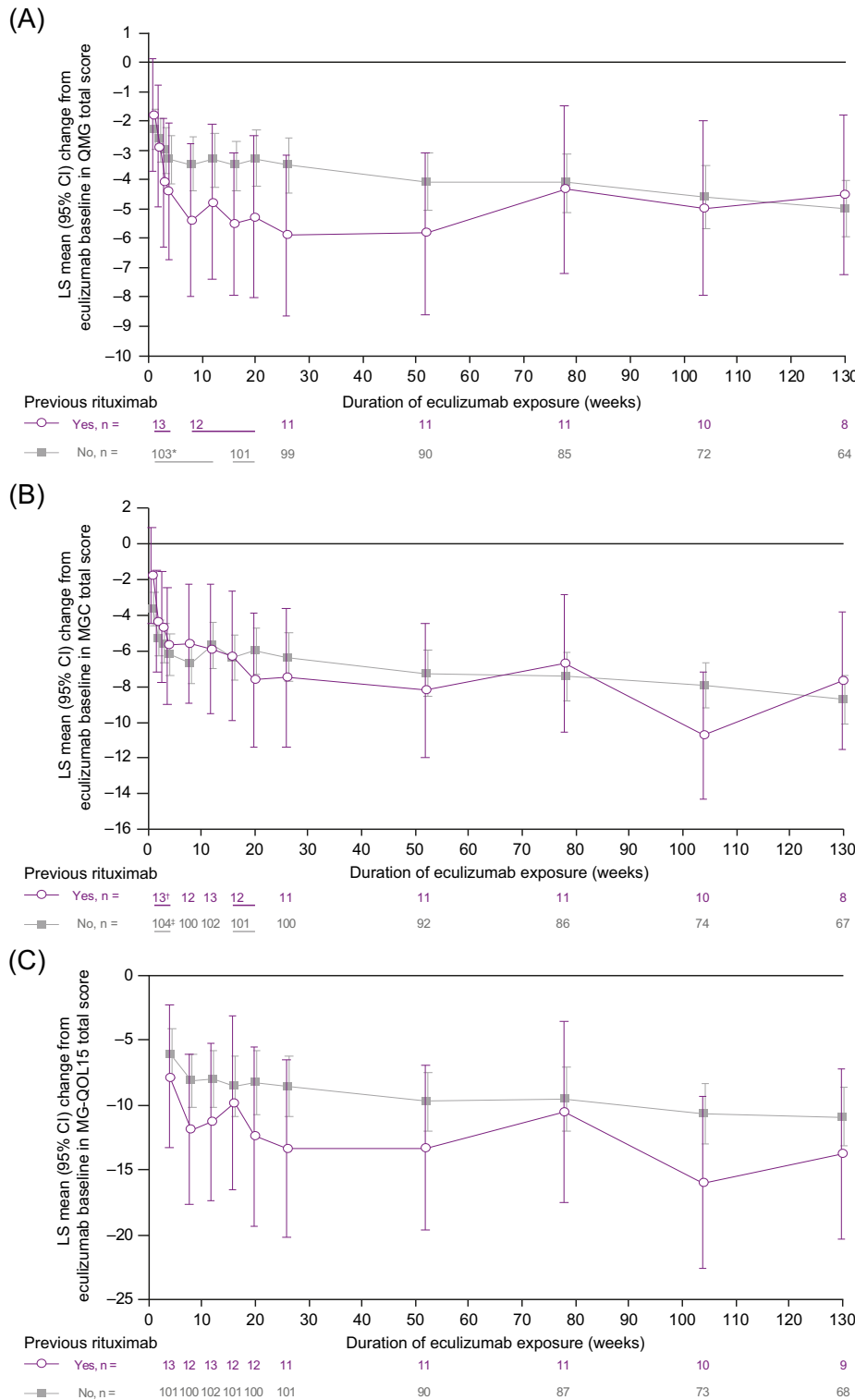

FIGURE 3 Disease score changes from eculizumab baseline in eculizumab-treated patients with and without previous rituximab treatment. Changes in efficacy parameters, (A) QMG, (B) MGC, and (C) MG-QOL15 total scores, were evaluated from eculizumab start at week 0 to week 130 of eculizumab treatment. Eculizumab baseline was the last available assessment before the first eculizumab dose (ie, REGAIN baseline for participants randomized to eculizumab in REGAIN and OLE baseline for participants who initiated eculizumab in the OLE). Changes from baseline were measured using a repeated-measures model. *n = 102 at week 3, n = 100 at week 8; †n = 12 at week 1; ‡n = 103 at weeks 2 and 4. Abbreviations: CI, confidence interval; LS, least-squares; MG-QOL15, 15-item Myasthenia Gravis Quality of Life questionnaire; MGC, Myasthenia Gravis Composite; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis

TABLE 2 Eculizumab safety profile during REGAIN and the OLE

	Previous rituximab, n = 13	No previous rituximab, n = 110	All patients, N = 123
Patients with AEs, n (%)	12 (92.3%)	109 (99.1%)	121 (98.4%)
Most common AEs,[a] n (%) (>15% of all patients)			
Headache	2 (15.4%)	51 (46.4%)	53 (43.1%)
Nasopharyngitis	4 (30.8%)	41 (37.3%)	45 (36.6%)
Diarrhea	5 (38.5%)	28 (25.5%)	33 (26.8%)
MG[b]	3 (23.1%)	29 (26.4%)	32 (26.0%)
URTI	4 (30.8%)	28 (25.5%)	32 (26.0%)
Nausea	5 (38.5%)	23 (20.9%)	28 (22.8%)
Arthralgia	4 (30.8%)	20 (18.2%)	24 (19.5%)
Influenza	2 (15.4%)	21 (19.1%)	23 (18.7%)
Cough	1 (7.7%)	21 (19.1%)	22 (17.9%)
UTI	3 (23.1%)	18 (16.4%)	21 (17.1%)
Pain in extremity	2 (15.4%)	18 (16.4%)	20 (16.3%)
Patients with SAEs, n (%)	6 (46.2%)	60 (54.5%)	66 (53.7%)
Most common SAEs,[a] n (%) (>15% of all patients)			
MG[b]	1 (7.7%)	19 (17.3%)	20 (16.3%)

Note: Data expressed as number (%) and exclude 2 patients who did not receive treatment with eculizumab.

Abbreviations: AE, adverse event; MG, myasthenia gravis; OLE, open-label extension; SAE, serious adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

[a]Medical Dictionary for Regulatory Activities preferred terms.

[b]Worsening (increased frequency and/or intensity) of a pre-existing condition, including myasthenia gravis, is considered to be an AE.

interaction were $P = .2484$ for MG-ADL, $P = .4331$ for QMG, $P = .2041$ for MGC, and $P = .2875$ for MG-QOL15).

The proportion of participants achieving an MGFA post-intervention status of "improved" at week 130 of eculizumab treatment was 75.0% in the previous-rituximab group and 89.6% in the no-previous-rituximab group (Table S1). The proportions of participants achieving MM status at week 130 were 66.7% and 65.0%, respectively. The proportions of participants achieving "minimal symptom expression" at week 130 were 22.2% and 31.3%, respectively (based on MG-ADL score) and 22.2% and 22.1%, respectively (based on MG-QOL15 score). Corresponding data over a range of timepoints are summarized in Table S1.

In the previous-rituximab group, the exacerbation rate in the pre-study year was 42.86/100 PY (6 events in 5 patients during 14.0 PY) and this was reduced by 80.0% to 8.57/100 PY (3 events in 2 patients during 35.0 PY) during treatment with eculizumab. In participants without previous rituximab treatment, the pre-study exacerbation rate was 117.33/100 PY (130 events in 56 patients during 110.8 PY) and this was reduced by 77.1% to 26.89/100 PY (73 events in 34 patients during 271.5 PY) during treatment with eculizumab. The relative risk of exacerbation was lower in the previous-rituximab group than in the no-previous-rituximab group before the study (0.37; 95% CI, 0.16 to 0.83; $P = .0159$) but not during eculizumab treatment (0.32; 95% CI, 0.10 to 1.01; $P = .0522$).

Among participants who had received rituximab previously, the MG-related hospitalization event rate was 8.57/100 PY (3 events in 2 patients during 35.0 PY) during REGAIN and the OLE, compared with 7.14/100 PY (1 event in 1 patient during 14.0 PY) before the study. Hospitalization rates during REGAIN and the pre-study year were also examined for the no-previous-rituximab group; however, the number of patients and PY in the previous-rituximab group were too small to draw comparisons between the two groups.

3.3 | Safety

The safety profile of eculizumab was similar in the previous-rituximab and no-previous-rituximab groups (Table 2). In participants who received rituximab during the year before starting REGAIN (2 placebo and 2 eculizumab), three AEs of infection (two incidences of upper respiratory tract infection and one of oral herpes) were reported in the eculizumab arm within the first year of treatment; no AEs of infection were reported in the placebo arm and no serious infections were reported in either treatment arm.

4 | DISCUSSION

This *post hoc* analysis has shown that outcomes improved during eculizumab treatment in both the previous-rituximab and the no-previous-rituximab groups across all assessment measures. These data suggest that response to eculizumab is not less favorable in patients with refractory gMG who have previously used and then discontinued rituximab than in patients with no history of rituximab use.

The long-term safety profile of eculizumab was generally similar in patients who had used rituximab previously, in those who had not used rituximab previously, and in the overall study population, and was consistent with the known safety profile from over 10 years of clinical use of eculizumab in other indications.[26-28,30-35]

The primary limitation of this analysis is the small number of patients in the previous-rituximab group. REGAIN was not powered for subgroup analyses; however, the consistency of the findings with the overall REGAIN population are encouraging and serve as a basis for more extensive study.

The rapid and sustained response to eculizumab observed in REGAIN and its OLE were notable given that the study population had treatment-refractory AChR+ gMG and a long disease duration. This analysis has shown that patients who were treated with rituximab previously, and who may therefore represent a patient group with an unmet treatment need, also experienced rapid and long-term clinical improvements with eculizumab, similar to those seen in the general study population. These data provide evidence that eculizumab can be an effective treatment for patients with AChR+ gMG, irrespective of their disease features and treatment history, including patients with refractory disease who have received rituximab treatment previously.

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CONFLICTS OF INTEREST

Z.A.S. and T.M. have served on an advisory board for Alexion Pharmaceuticals. R.J.N. has received research support from Alexion Pharmaceuticals, argenx, Genentech, Grifols, Immunovant, Momenta, the Myasthenia Gravis Foundation of America, the National Institutes of Health (National Institute of Neurological Disorders and Stroke and National Institute of Allergy and Infectious Diseases), and Ra Pharma; and consultancy fees from Alexion Pharmaceuticals, argenx, CSL Behring, Grifols, Immunovant, Momenta, Ra Pharma, Roivant, and Viela Bio. F.O'B. and M.Y. are employees of, and hold stock in, Alexion Pharmaceuticals. F.P. reports no disclosures relevant to this work.

Alexion Pharmaceuticals, Inc., became part of AstraZeneca on July 21, 2021, and is now Alexion, AstraZeneca Rare Disease.

AUTHOR CONTRIBUTIONS

All authors contributed to the acquisition, analysis or interpretation of data, and to drafting/critical revision of the manuscript for important intellectual content and final approval of the manuscript. F.O'B. contributed to the concept and design of the study. REGAIN study group members who provided and cared for study patients and collected data from them are listed as study co-investigators in the Supplementary Material.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed-consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development. Link to data-request form: https://alexion.com/contact-alexion/medical-information.

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