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BRIEF COMMUNICATION

Eculizumab improves fatigue in refractory generalized myasthenia gravis

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Abstract

Purpose To evaluate the effect of eculizumab on perceived fatigue in patients with anti-acetylcholine receptor antibody-positive, refractory, generalized myasthenia gravis (MG) using the Quality of Life in Neurological Disorders (Neuro-QOL) Fatigue subscale, and to evaluate correlations between improvements in Neuro-QOL Fatigue and other clinical endpoints.

Methods Neuro-QOL Fatigue, MG Activities of Daily Living (MG-ADL), Quantitative MG (QMG), and the 15-item MG Quality of Life (MG-QOL15) scales were administered during the phase 3, randomized, placebo-controlled REGAIN study (eculizumab, $n = 62$; placebo, $n = 63$) and subsequent open-label extension (OLE). Data were analyzed using repeated-measures models. Correlations between changes in Neuro-QOL Fatigue and in MG-ADL, QMG, and MG-QOL15 scores were determined at REGAIN week 26.

Results At REGAIN week 26, eculizumab-treated patients showed significantly greater improvements in Neuro-QOL Fatigue scores than placebo-treated patients (consistent with improvements in MG-ADL, QMG, and MG-QOL15 scores previously reported in REGAIN). Improvements with eculizumab were sustained through OLE week 52. Correlations between Neuro-QOL Fatigue and MG-QOL15, MG-ADL, and QMG scores were strong for eculizumab-treated patients at REGAIN week 26, and strong, moderate, and weak, respectively, for placebo-treated patients.

Conclusions Compared with placebo, eculizumab was associated with improvements in perceived fatigue that strongly correlated with improvements in MG-specific outcome measures.

Trial ID Registration: NCT01997229, NCT02301624.

Keywords Eculizumab · Myasthenia gravis · Fatigue · Neuro-QOL Fatigue · Quality of life · Terminal complement inhibition · Complement

Introduction

Patients with anti-acetylcholine receptor antibody-positive (AChR+), refractory, generalized myasthenia gravis (gMG) experience muscle weakness, which is associated with complement-mediated damage at the neuromuscular junction [1, 2]. Patients with MG experience muscle fatigability (difficulty initiating or sustaining muscle activities) [1, 3].

A complete list of study group investigators is included in electronic supplementary material.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11136-019-02148-2) contains supplementary material, which is available to authorized users.

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Perceived fatigue (a feeling of tiredness, lack of energy, and difficulty concentrating; referred to as fatigue hereafter) is also an important clinical issue for these patients and may be distinct from muscle weakness and fatigability [3–7].

Validated MG-specific assessments used to measure disease severity and response to intervention include the patient-reported MG Activities of Daily Living (MG-ADL) and 15-item MG Quality of Life (MG-QOL15) scales, and the physician-completed Quantitative MG (QMG) assessment of muscle strength [8–10]. None of these evaluate the impact of fatigue in gMG. The Quality of Life in Neurological Disorders (Neuro-QOL) assessment is designed to measure health-related quality of life across 13 subscales in patients with neurological conditions [11]. Neuro-QOL has been validated in a range of disorders, including multiple sclerosis, Parkinson's disease, and epilepsy, but not in MG [12–14]. The Neuro-QOL Fatigue subscale comprises a 19-item, patient self-assessment of fatigue that encompasses 'sensations ranging from tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decrease one's capacity for physical, functional, social, and mental activities' [15]. A short form Neuro-QOL Fatigue subscale is also available; this was recently validated in patients with MG [7].

Eculizumab is a humanized monoclonal antibody that binds to complement protein C5, inhibiting the activation of the terminal complement component proteins that are believed to mediate damage at the neuromuscular junction in AChR+ gMG [2, 16]. In the phase 3 REGAIN study, eculizumab demonstrated clinically meaningful improvements in patients with AChR+ refractory gMG, evaluated using MG-ADL, QMG, and MG-QOL15 assessments (NCT01997229) [17].

The current analysis investigated the effect of eculizumab versus placebo on fatigue in patients with AChR+ refractory gMG, and assessed the relationship between fatigue and MG-specific measures. We used the Neuro-QOL Fatigue subscale to evaluate changes in patients' self-reported assessment of fatigue during REGAIN and its open-label extension study (NCT02301624; interim analysis, 31 December 2017) [18]. We also measured the correlation between outcomes measured using the Neuro-QOL Fatigue subscale and the MG-ADL, QMG, and MG-QOL15 scales in REGAIN.

Methods

Study design

REGAIN was a 26-week, phase 3, randomized, double-blind, placebo-controlled study evaluating eculizumab efficacy and safety [17]. Briefly, patients were randomized 1:1 to receive eculizumab ($n = 62$; induction: 900 mg for 4 weeks; maintenance: 1200 mg at week 4 and then every 2 weeks until week 26) or placebo ($n = 63$) [17]. The primary endpoint was the change in MG-ADL total score with eculizumab versus placebo.

The Neuro-QOL Fatigue subscale was used to assess fatigue, and the MG-ADL, QMG, and MG-QOL15 scales were used to measure MG-specific activities of daily living, muscle strength, and quality of life, respectively. In REGAIN, all assessments were performed at baseline (day 1), every 4 weeks to week 20, and at week 26. MG-ADL and QMG assessments were also conducted at weeks 1, 2, and 3. Details of scoring for MG-ADL, QMG, and MG-QOL15 during REGAIN have been reported previously; briefly, for each measure, a reduction from baseline total score indicates improvement [17]. The response scale for Neuro-QOL Fatigue items was: 1 = never; 2 = rarely; 3 = sometimes; 4 = often; and 5 = always. The range of potential total scores was 19–95. Higher Neuro-QOL Fatigue subscale total scores indicate greater fatigue; a reduction from baseline total score indicates improvement [15].

Patients who completed REGAIN could enroll into the extension study [18]. Following a 4-week blinded induction phase, all patients received open-label eculizumab (1200 mg) at week 4 and every 2 weeks thereafter. Assessments occurred as in REGAIN to week 26, then at week 40, week 52, and every 6 months [18].

Statistical analysis

A repeated-measures model was used to test whether changes in Neuro-QOL Fatigue total scores from baseline to REGAIN week 26 for eculizumab and placebo were equal (Fig. 1). Model-estimated changes from REGAIN baseline data were reported up to open-label study week 52 (interim analysis, 31 December 2017) (Fig. 1). To evaluate the treatment effect on Neuro-QOL Fatigue subscale individual items at REGAIN week 26, a repeated-measures proportional odds model was implemented using the GEEORD SAS Macro (Table 2) [19]. Missing scores were not imputed in either model.

Pearson correlation coefficients (r) were calculated for the treatment arms using observed changes from baseline to REGAIN week 26 for Neuro-QOL Fatigue total scores versus observed changes for MG-ADL, QMG, and MG-QOL15 total scores (Fig. 2). The strength of association for absolute values of r was classified as follows: very weak, 0–0.19; weak, 0.2–0.39; moderate, 0.40–0.59; strong, 0.6–0.79; and very strong, 0.8–1 [20]. Within each treatment arm, the null hypothesis was $r = 0.4$ (the lower limit for moderate correlations). For all evaluations, statistical significance was

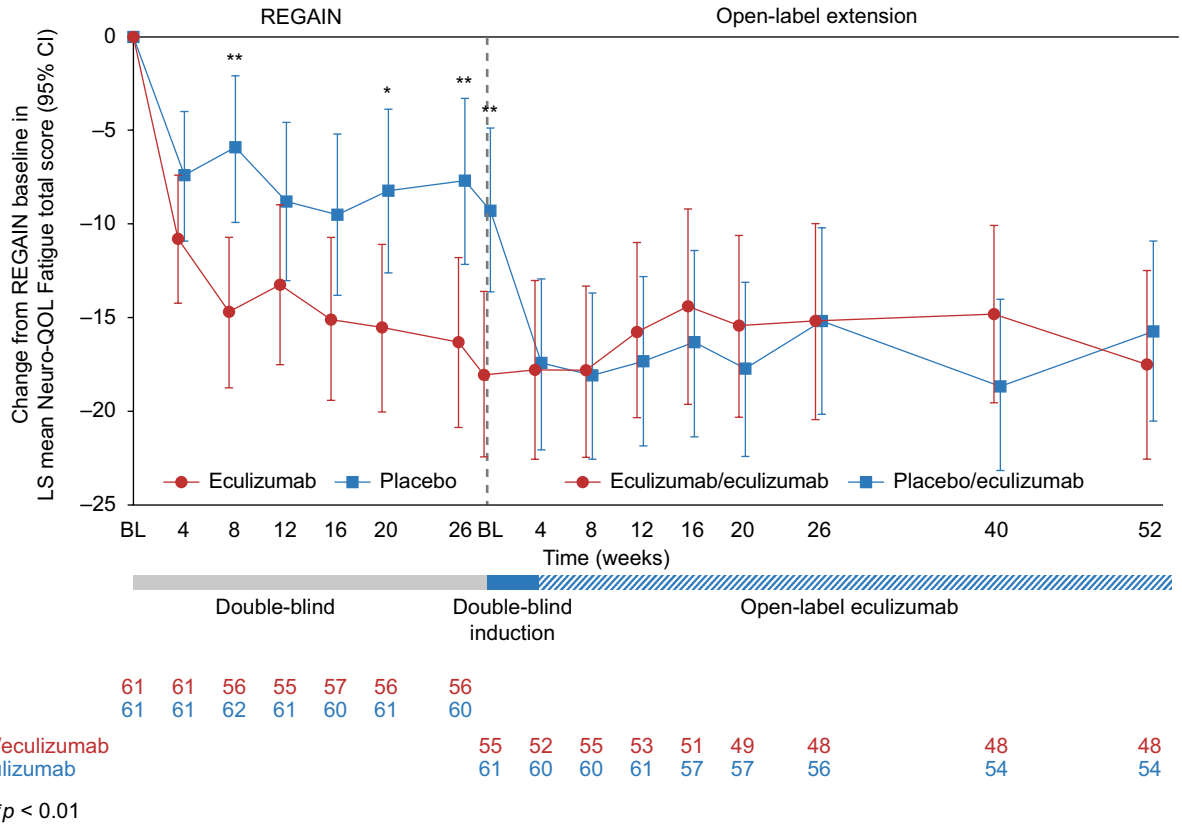

Fig. 1 Change in Neuro-QOL Fatigue subscale total score from REGAIN baseline to week 52 of the open-label study using a repeated-measures model.[a] [a]A repeated-measures model using the restricted maximum likelihood for the changes from baseline was used to compare the two treatment groups at each assessment visit and over time. The model included the following terms: treatment, visit, treatment by visit interaction, pooled Myasthenia Gravis Foundation of America (MGFA) randomization stratification variable (based on their MGFA classification at screening, patients were assigned to one of two categories: IIa/IIIa/IVa [a, symptoms predominantly affecting limb or axial muscles, or both] or IIb/IIIb/IVb [b, symptoms predominantly affecting oropharyngeal or respiratory muscles, or both]), and Neuro-QOL Fatigue total score at baseline. [b]Number of patients who completed the assessment at each time point. Some patients did not complete all items of the questionnaire at every timepoint. When this occurred, total scores could not be computed at that time point. Missing scores were not imputed. *BL* baseline, *CI* confidence interval, *Neuro-QOL Fatigue* Quality of Life in Neurological Disorders Fatigue subscale, *REGAIN* Eculizumab for REfractory GenerAlIzed MyastheNia Gravis

established using a two-sided *p* value of less than 0.05, without any multiplicity adjustment.

Results

Baseline demographics and characteristics were similar between treatment groups, with the exception of a higher proportion of Asian patients in the placebo group (Table 1). All patients were assessed using the Neuro-QOL Fatigue subscale (Table 1); mean (standard deviation) baseline total score was 64.1 (14.1) for the eculizumab group and 61.8 (15.9) for the placebo group.

Eculizumab was associated with greater improvements in fatigue than placebo. At REGAIN week 26, patients receiving eculizumab had a model-estimated mean change from baseline Neuro-QOL Fatigue total score of − 16.3 (95% confidence interval [CI]: − 20.8, − 11.8) versus − 7.7 (95% CI − 12.1, − 3.3) for placebo (model-estimated mean difference − 8.6 [95% CI − 14.8, − 2.3; $p = 0.0081$]) (Fig. 1). By week 4 of the open-label study, patients who had received eculizumab in both studies (eculizumab/eculizumab arm) had reductions from REGAIN baseline of − 17.8 (95% CI − 22.5, − 13.0) compared with − 17.4 (95% CI − 22.0, − 12.9) for patients who received placebo during REGAIN and eculizumab during the open-label study (placebo/eculizumab arm) (Fig. 1). Improvements in Neuro-QOL Fatigue score, from REGAIN baseline, were maintained through open-label study week 52 (–17.5 [95% CI − 22.5, − 12.5] and − 15.7 [95% CI − 20.5, − 10.9] for the eculizumab/eculizumab and placebo/eculizumab arms, respectively).

At REGAIN week 26, the proportional odds ratios for all 19 Neuro-QOL Fatigue items were greater than 1, indicating that a greater proportion of eculizumab-treated patients than

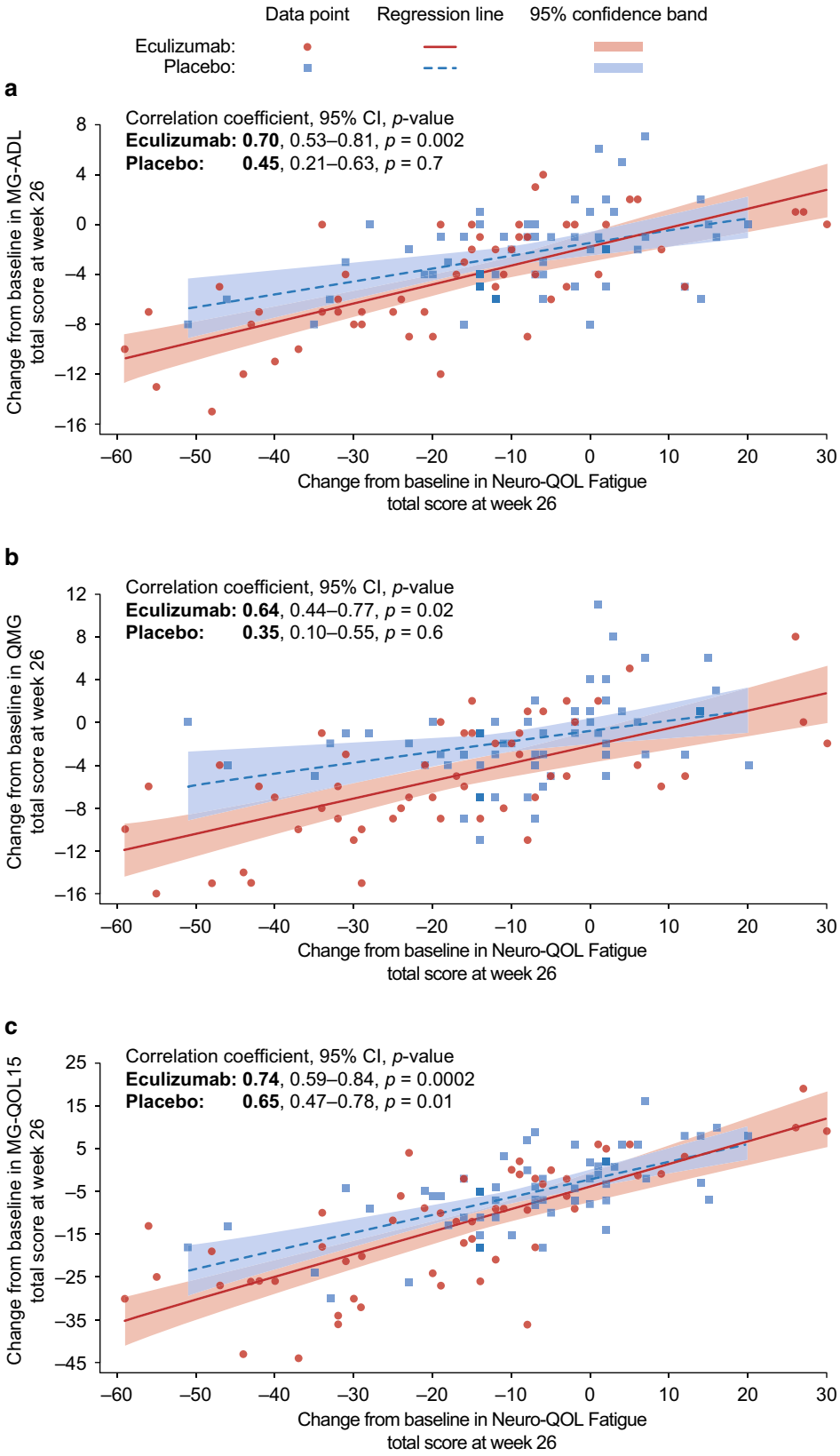

Fig. 2 Correlation between change from REGAIN baseline to week 26, in Neuro-QOL Fatigue subscale total score and **a** MG-ADL, **b** QMG, and **c** MG-QOL15 total scores by treatment group (eculizumab, $n=54$; placebo, $n=58$). Improvements in Neuro-QOL Fatigue total score correlated with improvements in **a** MG-ADL, **b** QMG, and **c** MG-QOL15 total scores more strongly in patients treated with eculizumab than in those who received placebo. Within treatment arms, the null hypothesis was $r=0.4$ (the lower limit for moderate correlations). *CI* confidence interval, *MG-ADL* Myasthenia Gravis-Activities of Daily Living, *MG-QOL15* 15-item Myasthenia Gravis Quality of Life, *Neuro-QOL Fatigue* Quality of Life in Neurological Disorders Fatigue subscale, *QMG* quantitative myasthenia gravis

Table 1 Baseline demographics and characteristics of patients in REGAIN

	Eculizumab ($n=62$)	Placebo ($n=63$)
Age at diagnosis, years, mean (SD)	38.0 (17.8)	38.1 (19.6)
Age at first study dose, years, mean (SD)	47.5 (15.7)	46.9 (18.0)
Sex, *n* (%)		
Male	21 (34%)	22 (35%)
Female	41 (66%)	41 (65%)
Race, *n* (%)		
Asian	3 (5%)	16 (25%)
Black or African American	0	3 (5%)
White	53 (85%)	42 (67%)
Other	6 (10%)	2 (3%)
BMI, kg/m^2, mean (SD)	31.4 (9.0)	30.5 (8.4)
Myasthenia gravis duration, years, mean (SD)	9.9 (8.1)	9.2 (8.4)
Neuro-QOL Fatigue total score, mean (SD); median[a]	64.1 (14.1); 64.0	61.8 (15.9); 64.0
Neuro-QOL Fatigue item score, mean (SD); median[a]		
I felt exhausted	3.6 (0.82); 4.0	3.5 (1.09); 4.0
I felt that I had no energy	3.7 (1.04); 4.0	3.7 (0.98); 4.0
I felt fatigued	3.8 (0.88); 4.0	3.7 (0.91); 4.0
I was too tired to do my household chores	3.5 (1.01); 4.0	3.3 (1.03); 3.0
I was too tired to leave the house	3.2 (1.01); 3.0	3.2 (0.99); 3.0
I was frustrated by being too tired to do the things I wanted to do	3.7 (1.08); 4.0	3.4 (1.21); 3.0
I felt tired	3.8 (0.80); 4.0	3.8 (0.97); 4.0
I had to limit my social activity because I was tired	3.6 (1.00); 4.0	3.4 (1.13); 4.0
I needed help doing my usual activities because of my fatigue	3.0 (1.24); 3.0	2.9 (1.22); 3.0
I needed to sleep during the day	3.3 (1.29); 3.0	3.4 (1.23); 4.0
I had trouble starting things because I was too tired	3.3 (0.89); 3.0	3.1 (1.13); 3.0
I had trouble finishing things because I was too tired	3.5 (0.99); 4.0	3.2 (1.06); 3.0
I was too tired to take a short walk	3.4 (1.19); 4.0	3.1 (1.29); 3.0
I was too tired to eat	2.6 (1.07); 3.0	2.3 (1.09); 2.0
I was so tired that I had to rest during the day	3.7 (1.06); 4.0	3.6 (1.07); 4.0
I felt weak all over	3.3 (1.07); 3.0	3.3 (1.13); 3.0
I needed help doing my usual activities because of weakness	2.9 (1.24); 3.0	2.9 (1.18); 3.0
I had to limit my social activity because I was physically weak	3.3 (1.23); 3.0	3.3 (1.04); 3.0
I had to force myself to get up and do things because I was physically too weak	3.0 (1.18); 3.0	2.9 (1.17); 3.0

SD standard deviation

[a]Some patients did not complete all items of the questionnaire. When this occurred, total scores could not be computed and the specific item score is missing for those patients

placebo-treated patients selected lower scoring responses (i.e., more selected 'never' or 'rarely,' and fewer selected 'often' or 'always') (Table 2). This was statistically significant for 15 of 19 items (range of common odds ratios with $p<0.05$: 1.8–2.9; Table 2), indicating that eculizumab treatment was associated with milder fatigue than placebo.

For the eculizumab group, there were significant correlations (i.e., different from $r=0.4$) for changes in total score from baseline to REGAIN week 26 between Neuro-QOL Fatigue and MG-QOL15 ($r=0.74$), MG-ADL ($r=0.70$), and QMG ($r=0.64$) (Fig. 2). For the placebo-treated group, a strong correlation for change from baseline to REGAIN week 26 was observed between Neuro-QOL Fatigue and MG-QOL15 ($r=0.65$); conversely, correlations between Neuro-QOL Fatigue and QMG and MG-ADL were not significantly different from $r=0.4$ ($r=0.45$ [moderate] and $r=0.35$ [weak]) (Fig. 2).

Discussion

This was the first use of the extended Neuro-QOL Fatigue subscale in patients with AChR+ refractory gMG. In REGAIN, levels of fatigue at baseline were generally

Table 2 Neuro-QOL Fatigue individual item responses and results from a repeated-measures proportional odds model at REGAIN week 26

Parameter	Treatment	Observed responses for Neuro-QOL Fatigue items at REGAIN week 26					Repeated-measures model estimate for REGAIN week 26		
		1 = Never, *n* (%)	2 = Rarely, *n* (%)	3 = Sometimes, *n* (%)	4 = Often, *n* (%)	5 = Always, *n* (%)	Proportional odds ratio (95% CI)[b]	*p* value for odds ratio[b,c]	*p* value for proportional odds assumption[d]
I felt exhausted	ECU ($n^a = 57$)	9 (15.8)	14 (24.6)	19 (33.3)	13 (22.8)	2 (3.5)	2.4 (1.3, 4.4)	0.0038	0.1099
	PLC ($n^a = 60$)	5 (8.3)	9 (15.0)	25 (41.7)	16 (26.7)	5 (8.3)			
I felt that I had no energy	ECU ($n^a = 57$)	9 (15.8)	15 (26.3)	21 (36.8)	9 (15.8)	3 (5.3)	1.9 (1.1, 3.5)	0.0322	0.5692
	PLC ($n^a = 60$)	5 (8.3)	10 (16.7)	23 (38.3)	15 (25.0)	7 (11.7)			
I felt fatigued	ECU ($n^a = 57$)	7 (12.3)	16 (28.1)	22 (38.6)	8 (14.0)	4 (7.0)	1.8 (1.0, 3.4)	0.0467	0.3357
	PLC ($n^a = 60$)	2 (3.3)	14 (23.3)	24 (40.0)	15 (25.0)	5 (8.3)			
I was too tired to do my household chores	ECU ($n^a = 56$)	16 (28.6)	15 (26.8)	13 (23.2)	7 (12.5)	5 (8.9)	1.9 (1.0, 3.4)	0.0437	0.6454
	PLC ($n^a = 60$)	11 (18.3)	11 (18.3)	19 (31.7)	17 (28.3)	2 (3.3)			
I was too tired to leave the house	ECU ($n^a = 57$)	22 (38.6)	12 (21.1)	12 (21.1)	8 (14.0)	3 (5.3)	2.5 (1.4, 4.7)	0.0033	0.2162
	PLC ($n^a = 60$)	12 (20.0)	11 (18.3)	20 (33.3)	15 (25.0)	2 (3.3)			
I was frustrated by being too tired to do the things I wanted to do	ECU ($n^a = 57$)	20 (35.1)	14 (24.6)	11 (19.3)	8 (14.0)	4 (7.0)	2.5 (1.4, 4.5)	0.0032	0.4059
	PLC ($n^a = 60$)	14 (23.3)	7 (11.7)	16 (26.7)	18 (30.0)	5 (8.3)			
I felt tired	ECU ($n^a = 57$)	9 (15.8)	9 (15.8)	22 (38.6)	12 (21.1)	5 (8.8)	2.3 (1.2, 4.4)	0.0092	0.3737
	PLC ($n^a = 60$)	0 (0.0)	9 (15.0)	26 (43.3)	17 (28.3)	8 (13.3)			
I had to limit my social activity because I was tired	ECU ($n^a = 57$)	15 (26.3)	16 (28.1)	13 (22.8)	9 (15.8)	4 (7.0)	2.6 (1.4, 4.7)	0.0026	0.6225
	PLC ($n^a = 60$)	8 (13.3)	11 (18.3)	18 (30.0)	17 (28.3)	6 (10.0)			
I needed help doing my usual activities because of my fatigue	ECU ($n^a = 57$)	26 (45.6)	10 (17.5)	10 (17.5)	7 (12.3)	4 (7.0)	2.3 (1.2, 4.2)	0.0104	0.5279
	PLC ($n^a = 60$)	14 (23.3)	11 (18.3)	20 (33.3)	12 (20.0)	3 (5.0)			
I needed to sleep during the day	ECU ($n^a = 57$)	14 (24.6)	14 (24.6)	13 (22.8)	10 (17.5)	6 (10.5)	1.5 (0.8, 2.7)	0.2164	0.4892
	PLC ($n^a = 60$)	12 (20.0)	7 (11.7)	16 (26.7)	15 (25.0)	10 (16.7)			
I had trouble starting things because I was too tired	ECU ($n^a = 57$)	16 (28.1)	18 (31.6)	13 (22.8)	6 (10.5)	4 (7.0)	2.2 (1.2, 4.1)	0.0096	0.1930
	PLC ($n^a = 60$)	15 (25.0)	7 (11.7)	18 (30.0)	13 (21.7)	7 (11.7)			
I had trouble finishing things because I was too tired	ECU ($n^a = 57$)	20 (35.1)	13 (22.8)	13 (22.8)	8 (14.0)	3 (5.3)	2.5 (1.4, 4.5)	0.0027	0.8333
	PLC ($n^a = 60$)	12 (20.0)	11 (18.3)	18 (30.0)	13 (21.7)	6 (10.0)			
I was too tired to take a short walk	ECU ($n^a = 57$)	19 (33.3)	14 (24.6)	11 (19.3)	9 (15.8)	4 (7.0)	1.5 (0.8, 2.7)	0.1896	0.9608
	PLC ($n^a = 60$)	17 (28.3)	10 (16.7)	15 (25.0)	14 (23.3)	4 (6.7)			
I was too tired to eat	ECU ($n^a = 57$)	30 (52.6)	12 (21.1)	10 (17.5)	1 (1.8)	4 (7.0)	1.2 (0.6, 2.3)	0.5365	0.9093
	PLC ($n^a = 60$)	25 (41.7)	17 (28.3)	11 (18.3)	7 (11.7)	0 (0.0)			
I was so tired that I had to rest during the day	ECU ($n^a = 57$)	10 (17.5)	11 (19.3)	13 (22.8)	17 (29.8)	6 (10.5)	1.2 (0.7, 2.3)	0.4697	0.4873
	PLC ($n^a = 60$)	9 (15.0)	8 (13.3)	19 (31.7)	14 (23.3)	10 (16.7)			
I felt weak all over	ECU ($n^a = 57$)	23 (40.4)	9 (15.8)	13 (22.8)	7 (12.3)	5 (8.8)	2.5 (1.4, 4.7)	0.0032	0.4309
	PLC ($n^a = 60$)	12 (20.0)	12 (20.0)	14 (23.3)	17 (28.3)	5 (8.3)			
I needed help doing my usual activities because of weakness	ECU ($n^a = 57$)	26 (45.6)	12 (21.1)	10 (17.5)	6 (10.5)	3 (5.3)	2.3 (1.2, 4.2)	0.0095	0.3340
	PLC ($n^a = 60$)	14 (23.3)	13 (21.7)	17 (28.3)	14 (23.3)	2 (3.3)			
I had to limit my social activity because I was physically weak	ECU ($n^a = 57$)	19 (33.3)	18 (31.6)	6 (10.5)	10 (17.5)	4 (7.0)	2.9 (1.6, 5.3)	0.0006	0.1119
	PLC ($n^a = 60$)	10 (16.7)	8 (13.3)	20 (33.3)	15 (25.0)	7 (11.7)			

Table 2 (continued)

Parameter	Treatment	Observed responses for Neuro-QOL Fatigue items at REGAIN week 26					Repeated-measures model estimate for REGAIN week 26		
		1 = Never, *n* (%)	2 = Rarely, *n* (%)	3 = Sometimes, *n* (%)	4 = Often, *n* (%)	5 = Always, *n* (%)	Proportional odds ratio (95% CI)[b]	*p* value for odds ratio[b,c]	*p* value for proportional odds assumption[d]
I had to force myself to get up and do things because I was physically too weak	ECU ($n^a = 57$)	25 (43.9)	15 (26.3)	9 (15.8)	5 (8.8)	3 (5.3)	2.1 (1.1, 4.0)	0.0172	0.0927
	PLC ($n^a = 60$)	19 (31.7)	7 (11.7)	18 (30.0)	15 (25.0)	1 (1.7)			

The *p* values associated with the proportional odds assumption indicated that this assumption was upheld for each item

CI confidence interval, *ECU* eculizumab, *Neuro-QOL* Quality of Life in Neurological Disorders, *PLC* placebo

[a]Number of patients who completed the assessment at week 26; missing scores were not imputed for patients who did not complete the assessment (ECU, $n = 5$ [$n = 6$ for 'I was too tired to do my household chores']; PLC, $n = 3$)

[b]Proportional odds ratios and *p* values are based on a repeated-measures ordinal regression (implemented using the GEEORD SAS Macro). The model has the ordinal response (for each parameter) at each visit as the dependent variable with terms for treatment, visit, and treatment by visit interaction, assuming exchangeable correlation structure. A higher odds ratio indicates that eculizumab-treated patients are more likely to answer in the lower response categories than those receiving placebo at week 26 for that item

[c] *p* values are not adjusted for multiple comparisons

[d]A *p* value for proportional odds assumption < 0.05 may indicate non-proportionality

consistent with previously published reports for MG; however, in these previous studies, fatigue was assessed using a variety of measures, and patients were not explicitly refractory to treatment [6, 7, 21].

At REGAIN week 26, eculizumab-treated patients were approximately twice as likely to report improved scores for the 15 of 19 subscale items where significant differences were observed, compared with placebo (range for odds ratios: 1.8–2.9; Table 2).

Patients who received eculizumab for the first time during the open-label study had similar improvements in fatigue to those seen with eculizumab during REGAIN. These were sustained through to week 52 of the open-label study and were consistent with previously reported improvements in MG-validated measures of disease burden (QMG, MG-ADL, and MG-QOL15) [17, 22]. The consistently strong, positive correlations between changes in Neuro-QOL Fatigue and MG-QOL15, MG-ADL, and QMG observed in eculizumab-treated patients suggest that the effect of eculizumab on fatigue is a valid clinical outcome in this patient population. The greater variability in observed correlations in placebo-treated patients may reflect the degree of similarity between the items assessed by the Neuro-QOL Fatigue subscale and those assessed by the MG-QOL15 (most similar, strong correlation), the MG-ADL (some similarities, moderate correlation), and the QMG (least similar, weak correlation).

Our findings suggest that the Neuro-QOL Fatigue subscale may be used to assess the clinical impact of perceived fatigue and the effect of therapeutic interventions in patients with AChR+ refractory gMG. Use of this scale demonstrated that eculizumab provided sustained, clinically meaningful improvements in fatigue. Our results contribute to the consistency and totality of the data demonstrating that eculizumab lowers the clinical burden in patients with AChR+ refractory gMG.

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Compliance with Ethical Standards

Conflict of interest Henning Andersen, MD, DMSci, PhD, has received research and travel support, and speaker honoraria from CSL Behring, Eisai, Octapharma, Pfizer, Sanofi Genzyme and UCB Pharma and has served as a consultant on advisory boards for NMD Pharma, UCB Pharma and Sanofi Genzyme. Renato Mantegazza, MD, received funding for research and congress participation from Bayer, BioMarin, Sanofi Genzyme and Teva, and participated in Scientific Advisory Boards for Alexion Pharmaceuticals, Argenx BVBA and BioMarin. Jing Jing Wang, MD, was formerly employed by, and owns stock in, Alexion Pharmaceuticals. Fanny O'Brien, PhD, and Kaushik Patra, PhD, are employees of, and own stock in, Alexion Pharmaceuticals. James F. Howard, Jr, MD, obtained: research support from Alexion Pharmaceuticals during the conduct of the study; grants from Alexion Pharmaceuticals; research support from Research Triangle Institute/Centers for Disease Control and Prevention; grants from National In-

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Research involving human participants This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice (ICH E6[R1]) and applicable regulatory requirements.

Informed consent Written informed consent was obtained from all participants.

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