Received: 2 March 2023 | Accepted: 15 May 2023

DOI: 10.1111/ene.15872

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Efficacy of innovative therapies in myasthenia gravis: A systematic review, meta-analysis and network meta-analysis

Francesco Saccà[1] | Chiara Pane[1] | Pablo Ezequiel Espinosa[2] | Maria Pia Sormani[2] | Alessio Signori[2]

[1]Department of Neurosciences and Reproductive and Odontostomatological Sciences, University "Federico II", Naples, Italy

[2]Department of Health Sciences, University of Genoa, Genoa, Italy

Correspondence
Francesco Saccà, Department of Neurosciences and Reproductive and Odontostomatological Sciences, University "Federico II", Via Pansini, 5, Napoli 80131, Italy.
Email: francesco.sacca@unina.it

Abstract

Background and purpose: Therapy for myasthenia gravis (MG) is undergoing a profound change, with new treatments being tested. These include complement inhibitors and neonatal Fc receptor (FcRn) blockers. The aim of this study was to perform a meta-analysis and network meta-analysis of randomized and placebo-controlled trials of innovative therapies in MG with available efficacy data.

Methods: We assessed statistical heterogeneity across trials based on the Cochrane Q test and I^2 values, and mean differences were pooled using the random-effects model. Treatment efficacy was assessed after 26 weeks of eculizumab and ravulizumab, 28 days of efgartigimod, 43 days of rozanolixizumab, 12 weeks of zilucoplan, and 16, 24 or 52 weeks of rituximab treatment.

Results: We observed an overall mean Myasthenia Gravis-Activities of Daily Living scale (MG-ADL) score change of −2.17 points (95% confidence interval [CI] −2.67, −1.67; $p < 0.001$) as compared to placebo. No significant difference emerged between complement inhibitors and anti-FcRn treatment ($p = 0.16$). The change in Quantitative Myasthenia Gravis scale (QMG) score was −3.46 (95% CI −4.53, −2.39; $p < 0.001$), with a higher reduction with FcRns (−4.78 vs. −2.60; $p < 0.001$). Rituximab did not significantly improve the MG-ADL (−0.92 [95% CI −2.24, 0.39]; $p = 0.17$) or QMG scores (−1.9 [95% CI −3.97, 0.18]; $p = 0.07$). In the network meta-analysis, efgartigimod had the highest probability of being the best treatment, followed by rozanolixizumab.

Conclusion: Anti-complement and FcRn treatments both proved to be effective in MG patients, whereas rituximab did not show a significant benefit for patients. Within the limitations of this meta-analysis, including efficacy time points, FcRn treatments showed a greater effect on QMG score in the short term. Real-life studies with long-term measurements are needed to confirm our results.

KEYWORDS
comparative, complement inhibitor, FcRn inhibitor, innovative treatment, trial

See commentary by A. A. Habib and C. Schneider-Gold on page 3644.

INTRODUCTION

Generalized myasthenia gravis (gMG) is a rare autoimmune disease that causes debilitating muscle weakness [1]. Autoantibodies against the acetylcholine receptor (Ab-AChR) are found in up to 80% of gMG patients [2, 3]. Ab-AChR belong to immunoglobulin G (IgG) class 1 and can activate complement [4]. The remaining patients may have antibodies against muscle-specific kinase (MuSK) [5], usually IgG class 4, that do not activate complement, or against lipoprotein-receptor-related protein 4 (LRP4), usually IgG class 1 and 3 [6]. Patients negative to the previous antibodies are considered seronegative. This is a consequence of methodological issues, but the pathological mechanism is thought to be the same, namely, antibody-mediated.

There are three main mechanisms by which Ab-AChR lead to clinical signs of the disease: blockade of the neuromuscular junction; internalization and destruction of the AChR; and complement activation [7]. All three result in reduced neuromuscular transmission and are targets of therapeutic strategies.

Standard treatment consists of symptomatic treatment with pyridostigmine, which reduces acetylcholine destruction at the neuromuscular junction, immunomodulating therapies and thymectomy, the latter being able to have a positive impact on disease exacerbation, reduce the need for non-steroidal immunosuppressants (NSISTs), and reduce cumulative corticosteroid (CS) dose [8, 9]. Immunomodulation is obtained with the use of CSs and NSISTs. Both treatments are non-specific to the pathological mechanism of gMG and are unsatisfactory for several reasons. The use of CSs is associated with a burden of adverse events, both in the short and long term, which limits their use. NSISTs are associated with a long delay between treatment start and onset of effect, which may be up to 1 year. They also cause frequent intolerable adverse events (i.e., gastrointestinal intolerability, infections, cancer risk increase) [10].

Despite, symptomatic treatment, and use of CSs and NSISTs, many patients continue to experience symptoms [11, 12]. Several strategies have been proposed for these patients, and they include plasma exchange, or off-label treatments such as intravenous immunoglobulins, or rituximab [13].

Rituximab is an anti-CD20 monoclonal antibody approved for B-cell lymphoma, rheumatoid arthritis, and vasculitis. It eliminates B cells expressing the CD-20 antigen, and spares pre-B and plasma cells. Unfortunately, it failed to demonstrate efficacy across several outcomes in Ab-AChR-positive gMG patients in the BEATMG study, a Phase 2 randomized controlled trial [14]. In the RINOMAX trial, the primary endpoint was reached, with a higher percentage of treated patients having the minimal disease manifestation after 16 weeks of treatment, however, it did not affect Myasthenia Gravis-Activities of Daily Living Scale (MG-ADL) or Myasthenia Gravis Scale (QMG) scores after 16 or 24 weeks of treatment [15]. Despite these results, rituximab is recommended for off-label use in some national guidelines for gMG [16], based on the results of several observational studies and meta-analyses supporting its efficacy, mainly in MuSK-positive gMG [17–19].

Recently, two new treatment strategies have been proposed for the therapy of gMG and include complement blockade and neonatal Fc receptor (FcRn) antagonism.

The rationale of complement blockade consists in counteracting the effects of complement activation that result in neuromuscular junction membrane damage and morphology disruption. Complement inhibition also reduces local inflammation and the chemotactic activity of complement factor 5a (C5a) at the neuromuscular junction. To date, three compounds have been tested in Phase 3, randomized, placebo-controlled trials in gMG patients, and all target C5. These include eculizumab (humanized monoclonal antibody with intravenous administration every 2 weeks), ravulizumab (humanized monoclonal antibody with intravenous administration every 2 months), and zilucoplan (self-injected subcutaneous peptide).

Eculizumab was tested in a Phase 3 trial, the REGAIN study, which enrolled refractory gMG patients. It failed its primary endpoint of a reduction in MG-ADL score from baseline to Week 26, tested with a prespecified worst-rank analysis of covariance ($p = 0.0698$) [20]. However, the prespecified sensitivity analysis and the post hoc sensitivity worst-rank analysis of covariance showed significant improvements in MG-ADL score, which were confirmed in the open-label phase and maintained up to 3 years [21]. Ravulizumab is an improved version of eculizumab, engineered at its FcRn-binding site to have a longer half-life. It is administered intravenously every 2 months. In the Champion-MG trial it showed a significant reduction in MG-ADL score compared to placebo ($p < 0.0001$) [22]. Zilocuplan is a subcutaneously once-daily self-administered peptide which inhibits C5 that was tested in the Phase 3 RAISE trial and showed a significant reduction in MG-ADL score ($p < 0.001$) [23].

FcRn antagonists compete with naturally circulating IgG on the FcRn receptor and cause a rapid decline in circulating IgG levels, with a net reduction of 70% of their baseline levels [24]. This reduction is thought to counteract all three proposed pathological mechanisms present in Ab-AChR-positive gMG, namely, blockade of the neuromuscular junction, internalization and destruction of the AChR, and complement activation. To date, two anti-FcRn treatments have completed their Phase 3 placebo-controlled, randomized trials.

Efgartigimod is an engineered human Fc-fragment administered as cycles of four consecutive weekly intravenous infusions [25]. In the Phase 3 ADAPT trial, a significantly higher proportion of Ab-AChR-positive patients were MG-ADL responders after efgartigimod treatment as compared to placebo (68% vs. 30%; $p < 0.0001$). Rozanolixizumab is a subcutaneously infused monoclonal antibody with six consecutive weekly treatment cycles. In the MycarinG Phase 3 trial, two different doses (7 and 10 mg/kg body weight) were tested and showed a significant reduction in MG-ADL score compared to placebo ($p < 0.001$ for both doses) [26].

Other treatments with active Phase 3 trials whose results should be available in the next years include nipocalimab and batoclimab (FcRn antagonists) [27, 28], satralizumab (interleukin-6 receptor antagonist) [29], inebilizumab (anti-CD-19 antibody) [30], gefurulimab (an anti-C5 minibody) [31], and vemircopan (oral complement inhibitor) [32].

The aim of this study was to compare innovative treatments for gMG through a meta-analysis of already published or available data, as long as the trial design was randomized and placebo-controlled.

METHODS

This systematic review and network meta-analysis (NMA) was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

A systematic literature search was carried out mainly in PubMed, the Cochrane Library, and the American Academy of Neurology, European Academy of Neurology, and Myasthenia Gravis Foundation of America (MGFA) International Conference on Myasthenia and Related Disorders abstracts (all 1995–2022) to identify double-blind, randomized, placebo-controlled trials that studied the efficacy of therapy in myasthenia gravis.

Studies had to report information on therapy efficacy on the pre-planned outcomes of interest, namely, MG-ADL, QMG, Myasthenia Gravis–Composite (MGC) and 15-item Myasthenia Gravis Quality of Life (MG-QoL15) scores.

We used "myasthenia gravis" OR "MG" search terms for the clinical condition and "randomized controlled" for the type of study, and combined these in the search string. All studies published after 1 January 1995 up to 31 December 2022 were screened.

Article selection and data extraction

The article search started on 1 March 2021 and was completed on 31 December 2022. We included studies that fulfilled the following inclusion criteria: (i) randomized controlled trials; (ii) inclusion of at least the MG-ADL and QMG scores as outcome variables; and (iii) entire study cohort comprising patients with gMG.

The search was conducted by one author (C.P) and study selection was performed independently by two authors (C.P and A.S.). Any disagreements were resolved by a third author (F.S).

Data extraction was performed independently by two authors (C.P. and A.S.) and the accuracy of extraction was validated by consensus.

We collected the following details: (i) study ID, year of publication, phase of the study, therapy used, study period; (ii) number of patients per arm, gender, age (mean and range), prior thymectomy, MG type (ocular, generalized), serotypes (Ab-AChR -positive, anti-MuSK antibody-positive and seronegative MG), MGFA class, disease duration; and (iii) outcome data: MG-ADL, QMG, MGC and MG-QoL15 scores (mean, standard deviation [SD], range).

Outcome measures

The key efficacy outcomes of interest were:

(i) The MG-ADL, an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities during the prior week [33]. Total scores range from 0 to 24 points, with a higher score showing more severe gMG;
(ii) The QMG, an objective 13-item scale based on quantitative testing of sentinel muscle groups [34]. The QMG consists of 13 items and total score ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits);
(iii) The MGC, which combines participant-reported and investigator-reported test items to assess the clinical status of MG by measuring both symptoms and objective signs of the disease [35]. The MGC assesses 10 functional areas and total score ranges from 0 to 50;
(iv) The 15-item MG-QoL15, a short and self-administered questionnaire that assesses different aspects of quality of life in MG patients. It consists of 15 items and four dimensions [34]. The total score ranges from 0 to 60. A score of 0 represents the best quality of life, and a score of 60 predicts maximal impairment. The MG-QoL15 was used in the REGAIN study, whereas all other trials used the revised version (MG-QoL15r) [36].

Risk of bias assessment

Two authors (C.P and F.S.) independently assessed risk of bias using the Cochrane Risk of Bias 2 tool (RoB 2) [37], with respect to the primary outcome in the trial. Disagreements were resolved by a third author (A.S.). The RoB 2 tool was used to rate each study as having a low risk of bias, some concerns (hereafter described as medium risk with some concerns for bias), or a high risk of bias, for each domain and overall [37, 38].

Statistical methods

For each trial, the number of patients included for each treatment arm, the mean change from baseline and the SD or the standard error of the mean (SEM) for each outcome were extracted and the mean difference (MD) with the associated 95% confidence interval (CI) was calculated. When SEM was reported, SD was calculated by multiplying SEM by the square root of sample size. Hedge's standardized mean differences (SMDs) with the associated 95% CIs were calculated for the MG-QoL15 because one study reported the results for the original version while all the other studies used the more recent MG-QoL15r.

Automatic extraction of the individual trial data from the respective error bar plots was conducted on Web Plot Digitizer (WebPlotDigitizer Version 4.4 [computer program], Pacifica, California, USA [2020]) when results were not reported in the text or in the tables.

Since use of multiple arms from the same study creates "clustered" data, each contrast derived from a study with more than two arms was given a lower weight in the meta-analysis, according to a procedure previously described [39, 40].

Statistical heterogeneity across trials was assessed by means of the Cochrane Q test and I^2 values were reported. MDs were pooled with the random-effects model and heterogeneity was calculated using the restricted maximum likelihood (REML) approach. Results are presented as forest plots. Since fewer than 10 studies were included, publication bias was not assessed.

An explorative NMA was also conducted, limited to the MG-ADL and QMG outcomes. In particular, the surface under the cumulative ranking curve (SUCRA), which expresses the percentage of effectiveness each treatment has compared to an "ideal" treatment always ranked first without uncertainty, and the probability of being ranked as the best treatment or another rank for a specific outcome were reported. The only direct comparisons made were each treatment versus placebo and, as a consequence, we did not assess inconsistency between direct and indirect comparisons (no degrees of freedom for inconsistency and no loops in the network). Data analysis was performed using Stata 16.0 (StataCorp).

RESULTS

Study selection

We retrieved a total of 1290 studies after duplicate removal, and seven were finally included in the analysis (Figure 1). Characteristics of the included studies are reported in Tables 1 and 2. Figure 2 shows the risk of bias for each study considered for analysis.

Meta-analysis

Myasthenia Gravis-Activities of Daily Living scale

Figure 3a reports the forest plot for the MDs in MG-ADL score change during follow-up between treatment arms in each study. We observed an overall and significant ($p<0.001$) mean change of −2.17 (95% CI −2.67, −1.67) points on the MG-ADL among treated patients as compared to placebo. The effect was not significantly different when comparing complement inhibitors and anti-FcRn (p for subgroup differences = 0.16).

Quantitative Myasthenia Gravis scale

We found a significant overall effect ($p<0.001$) on the QMG scale when comparing new treatments with placebo (Figure 3b). The QMG score reduction was significantly ($p<0.001$) higher among anti-FcRn (MD −4.78; 95% CI −5.96, −3.61) compared to complement inhibitor treatments (MD −2.60; 95% CI −3.42, −1.78).

Myasthenia Gravis−Composite

We observed similar results for the MGC (Figure 3c), with a significant reduction in favor of treated patients (MD −4.10; 95% CI −5.29, −2.92; $p<0.001$). The MGC score improvement was higher with anti-FcRn treatment, although not significant (MD −5.12 vs. −3.24; $p=0.12$).

Myasthenia Gravis Quality of Life 15-item scale

New treatments are effective in improving quality of life (overall SMD −0.5; $p<0.001$; Figure 3d). Anti-FcRn treatment showed a greater effect of −0.84, compared with −0.37 for complement inhibitors ($p=0.01$).

Meta-analysis considering rituximab

Since rituximab trials were both Phase 2 and had a lower number of enrolled patients, we performed a separate analysis. Rituximab was not significantly effective in reducing MG-ADL score compared with placebo, with a mean change of −0.92 (95% CI −2.24, 0.39; $p=0.17$ [Figure 4a]). The same was evident for QMG (−1.90 [95% CI −3.97, 0.18]; $p=0.07$ [Figure 4b]), for MGC (−1.70 [95% CI −4.89, 1.49]; Figure 4c) and MGQoL-15 scores (−0.13 [95% CI −0.54, 0.29]; $p=0.55$ [Figure 4d]).

Myasthenia Gravis-Activities of Daily Living scale network meta-analysis

Indirect comparisons derived from the NMA did not show significant differences among treatments (Figure 5a) except for the comparison of rituximab versus efgartigimod, with an estimated worst MG-ADL change for rituximab (MD 1.70; 95% CI 0.03–3.38). A trend for worst MG-ADL change was also observed for the comparisons of rituximab versus both doses of rozanolixizumab. For the 7-mg dose, we estimated an advantage of rozanolixizumab of 1.68 (95% CI −0.03, 3.39), and for the 10-mg dose an advantage of 1.71 (95% CI −0.07, 3.50).

A higher SUCRA was observed for efgartigimod (77.4), followed by rozanolixizumab at both doses (76.5 and 75.2). The lowest SUCRA, after placebo, was for rituximab. Similarly, the estimated probability of being the best treatment for this outcome was 31.5% for efgartigimod, and 28.1% and 20.6% for both doses of rozanolixizumab (Table 3). Tables S1–S2 show the probabilities for each treatment of being the best to the worst in the ranking based on treatment effect on MG-ADL.

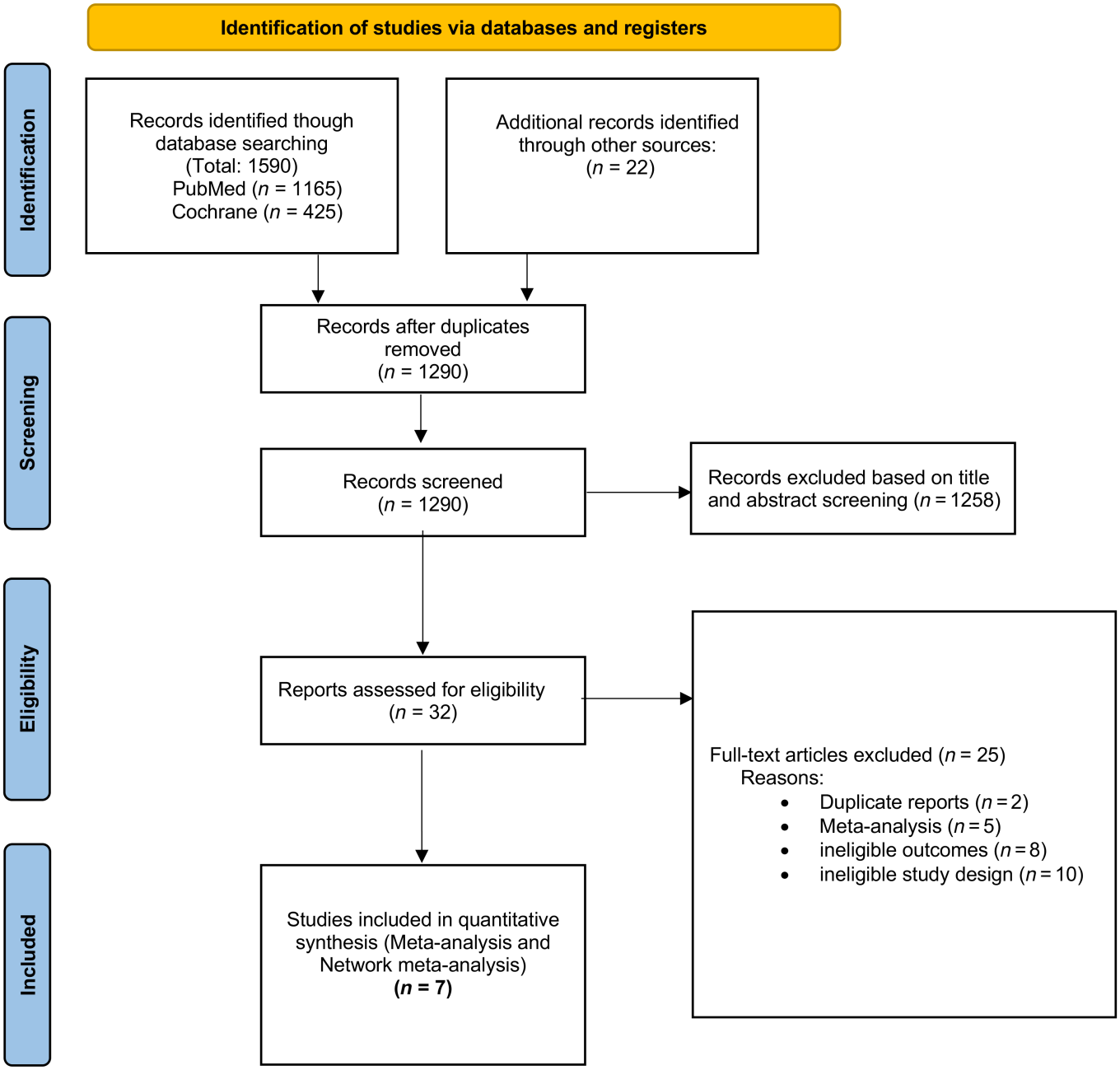

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram describing the systematic literature search and study selection.

Quantitative Myasthenia Gravis scale network meta-analysis

From the indirect comparisons (Figure 5b) with regard to QMG score, efgartigimod was better than ravulizumab (MD 3.20 [95% CI 1.24, 5.16]) and rituximab (MD 3.34 [95% CI 0.80, 5.88]) and showed a trend towards better response than eculizumab (MD 2.20) and zilucoplan (MD 2.13). Further, rozanolixizumab 10 mg was found to be consistently superior to ravulizumab (MD 2.76 [95% CI 0.64, 4.88]) and rituximab (2.90 [95% CI 0.23, 5.56]).

Efgartigimod had the highest SUCRA of 93.2 and a probability of being the best treatment of 62.6% (Table 3). Table S2 shows the probabilities of each treatment of being the best- to worst-ranked, based on treatment effect on QMG.

DISCUSSION

Historical standard therapy has been able to achieve disease control in a majority of gMG patients, but the quality of published data

TABLE 1 Demographics of selected studies.

Study name	MycarinG	CHAMPION	RAISE	RINOMAX	BeatMG	REGAIN	ADAPT
Intervention	Rozanolixizumab	Ravulizumab	Zilucoplan	Rituximab	Rituximab	Eculizumab	Efgartigimod
Year of publication	–	2022	–	2022	2022	2017	2021
Study duration, weeks	14	26	12	48	52	26	26
Phase of the study	3	3	3	2	2	3	3
Number of patients per arm							
Placebo	67	89	88	22	27	63	83
Drug	133	86	87	25	25	62	84
Sex, female, *n* (%)							
Placebo	47 (70)	45 (51)	41 (47)	7 (32)	12 (44)	41 (66)	55 (66)
Drug	RLZ 7 mg/kg 39 (59)	44 (51)	34 (40)	7 (28)	11 (44)	41 (66)	63 (75)
	RLZ 10 mg/kg 35 (52.2)						
Age, years, mean (SD)							
Placebo	50.4 (18)	53.3 (16)	53.3 (16)	58.0 (19)	56.8 (17)	46.9 (18)	48.2 (15)
Drug	RLZ 7 mg/kg 53.2 (15)	58.0 (14)	52.6 (15)	67.4 (14)	53.2 (18)	47.5 (16)	45.9 (14)
	RLZ 10 mg/kg 51.9 (17)						
MGFA class at baseline, *n* (%)							
Class II a/b							
Placebo	23 (34)	39 (44)	27 (31)	6 (35)	16 (59)	29 (46)	31 (37)
Drug	RLZ 7 mg/kg 29 (44)	39 (46)	22 (26)	9 (53)	15 (60)	18 (29)	34 (40)
	RLZ 10 mg/kg 26 (39)						
Class III a/b							
Placebo	41 (61)	45 (50)	57 (65)	11 (65)	9 (33)	29 (46)	49 (59)
Drug	RLZ 7 mg/kg 34 (52)	41(48)	60 70)	8 (47)	9 (36)	37 (61)	47 (56)
	RLZ 10 mg/kg 39 (58)						
Class IV a/b							
Placebo	3 (5)	5 (5)	4 (5)	–	1 (4)	5 (8)	3 (4)
Drug	RLZ 7 mg/kg 3 (5)	6 (7)	4 (5)	–	1 (4)	7 (11)	3 (4)
	RLZ 10 mg/kg 2 (3)						
Serotypes							
Placebo	AChR or MuSK Ab+	AChR Ab+	AChR Ab+	AChR Ab+ and seronegative MG	AChR Ab+	AChR Ab+	AChR or MuSK Ab+ and seronegative MG
Drug							

(Continues)

TABLE 1 (Continued)

Study name	MycarinG	CHAMPION	RAISE	RINOMAX	BeatMG	REGAIN	ADAPT
Duration of disease, years, mean (SD)							
Placebo	9.4 (9)	10.0 (9)	9.0 (10)	0.4 (0)	4.4 (5)	9.2 (8)	8.8 (8)
Drug	RLZ 7 mg/kg 6.9 (7)	9.8 (10)	9.3 (10)	0.4 (0)	6.7 (7)	9.9 (8)	10.1 (9)
	RLZ 10 mg/kg 9.6 (10)						
MG-ADL score at baseline, mean (SD)							
Placebo	8.4 (3)	8.9 (2)	10.9 (3)	4,5 (3)	4.0 (3)	9.9 (3)	8.8 (3)
Drug	RLZ 7 mg/kg: 8.4 (4)	9.1 (3)	10.3 (3)	5,1 (3)	5.8 (4)	10.5 (3)	9.2 (3)
	RLZ 10 mg/kg: 8.1 (3)						
QMG score at baseline, mean (SD)							
Placebo	15.8 (4)	14.5 (5)	19.4 (5)	9,3 (4)	9.2 (4)	16.9 (6)	15.5 (5)
Drug	RLZ 7 mg/kg: 15.4 (4)	14.8 (5)	18.7 (4)	9.4 (5)	11.0 (5)	17.3 (5)	16.2 (5)
	RLZ 10 mg/kg: 15.6 (4)						
Previous thymectomy, *n* (%)							
Placebo	–	–	37 (42)	–	4 (15)	31 (49)	36 (43)
Drug	–	–	45 (52)	–	5 (32)	37 (60)	59 (70)
	–						
Any NSIST, *n* (%)							
Placebo	33 (49)	–	42 (45)	–	–	56 (88)	51 (61)
Drug	RLZ 7 mg/kg: 32 (49)	–	50 (57)	–	–	58 (93)	51 (61)
	RLZ 10 mg/kg: 38 (57)						
MGC score, mean (SD)							
Placebo	–	–	21.6 (7)	–	8.5 (4)	18.9 (6)	18.3 (6)
Drug	–	–	20.1 (6)	–	11.1 (6)	20.4 (6)	18.8 (6)
MG-QoL15r score, mean (SD)							
Placebo	–	–	18.9 (7)	22,2 (13)	17.7 (11)	30.7 (13)	16.8 (6)
Drug	–	–	18.6 (7)	20.1 (11)	22.7 (14)	33.6 (12)	16.1 (6)
Prior thymectomy, *n* (%)							
Placebo	–	–	37 (42)	1 (5)	4 (15)	31 (49)	36 (43)
Drug	–	–	45 (52)	–	8 (32)	37 (60)	59 (70)

Abbreviations: Ab+, antibody positive; AChR, acetylcholine receptor; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis–Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, Myasthenia Gravis Quality of Life 15-item scale; MG-QoL15r, revised Myasthenia Gravis Quality of Life 15-item scale; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis scale; RLZ, rozanolixizumab; SD, standard deviation.

TABLE 2 Treatment, population, and main results of selected trials.

Treatment class	Treatment - mechanism of action	Pharmacology and dosing	Included Population	Efficacy results
Anti-complement	Eculizumab: Inhibits terminal complement/MAC activation	Humanized antibody anti-C5 Infused i.v. every 14 days Fixed dosing *Loading dose* 900 mg i.v. weekly for 4 weeks *Maintenance* 1200 mg i.v. every 2 weeks	Adults with Ab-AChR+ gMG MG-ADL score ≥6 MGFA class II–IV ≥2 NSIST or ≥1 NSIST+IVIG/PLEX	MG-ADL score −4.2 vs. −2.3 points ($p=0.0058$) QMG score −4.6 vs. −1.6 points ($p=0.0006$) MGC score −8.1 vs. −4.8 points ($p=0.0134$) MG-QoL15 score −12.6 vs. −5.4 ($p=0.0010$)
	Ravulizumab - Inhibits terminal complement/MAC activation	Humanized antibody anti-C5 Infused i.v. every 8 weeks Variable dosing *Loading dose* 40 to <60 kg: 2400 mg i.v. 60 to <100 kg: 2700 mg i.v. ≥100 kg: 3000 mg i.v. *Maintenance* 40 to <60 kg: 3000 mg i.v. q8W 60 to <100 kg: 3300 mg i.v. q8W ≥100 kg: 3600 mg i.v. q8W	Adults with Ab-AChR+ gMG MG-ADL score ≥6 MGFA class II–IV	MG-ADL score −3.1 vs. −1.4 points ($p<0.001$) QMG score −2.8 vs. −0.8 points ($p<0.001$) MG-QoL15 score −3.3 vs. −1.6 ($p=$NA)
	Zilucoplan - Inhibits terminal complement/MAC activation	Short 35 kDa macrocyclic peptide targeting C5/C5b Daily s.c. injections 0.3 mg/Kg BW	Adults with Ab-AChR+ gMG MG-ADL score ≥6 QMG score ≥12 MGFA class II–IV	MG-ADL score −4.43 vs. −2.31 points ($p<0.001$) QMG score −6.32 vs. −3.25 points ($p<0.001$) MGC score −8.5 vs. −5.3 points ($p=0.0023$) MG-QoL15 score −5.6 vs. −3.1 ($p=0.0122$)
FcRn antagonists	Efgartigimod - Reduces autoantibody levels and recycling	Human anti-FcRn IgG1 Fc fragment 10 mg/Kg BW i.v. one infusion per week for 4 consecutive weeks	Adults with Ab-AChR+ and Ab-AChR- gMG stable dose of ≥1 SOC MG-ADL score ≥5 MGFA class II–IV	MG-ADL score −4.45 vs. −1.84 points ($p<0.001$) QMG score −6.21 vs. −1.01 points ($p<0.001$) MGC score −9.1 vs. −3.6 points ($p<0.05$) MG-QoL15 score −7.7 vs. −2.61 ($p<0.05$)
	Rozanolixizumab - Reduces autoantibody levels	Human anti-FcRn IgG4 whole antibody 7 or 10 mg/Kg BW s.c. weekly for 7 weekly infusions	Phase 3 Adults with Ab-AChR+ or MuSK+ gMG MG-ADL score ≥3 QMG score ≥11 MGFA class II–IVa	*7 mg/kg BW* MG-ADL score −3.50 vs. −0.91 points ($p<0.001$) QMG score −4.32 vs. −0.84 points ($p<0.001$) MGC score −5.1 vs. −1.2 points ($p<0.001$) *10 mg/kg BW* MG-ADL score −3.53 vs. −0.91 points ($p<0.001$) QMG score −5.60 vs. −0.84 points ($p<0.001$) MGC score −6.7 vs. −1.2 points ($p<0.001$)
Anti CD-20	Rituximab (RINOMAX) - Depletes CD20 cell levels	Chimeric anti-CD20 IgG1 1000 mg i.v. single infusion at baseline	Adults with onset of generalized symptoms within 12 months or less QMG score ≥6 no history of thymoma or thymectomy, no history of NSISTs or high dose CS	MG-ADL score −1.7 vs. −0.5 points ($p=0.34$) QMG score −6.9 vs. −5.8 points ($p=0.79$) MG-QoL15 score −9.2 vs. −7.0 ($p=0.47$)
	Rituximab (Phase 2) - Depletes CD20 cell levels	One cycle every 6 months Each cycle with weekly i.v. infusions of 375 mg/m^2 for 4 consecutive weeks	Adults 21–90 years of age, with AChR-Ab+ gMG, MGFA class II–IV Prednisone ≥ 15 mg/day	MG-ADL score −2.7 vs. −2.0 points ($p=0.73$) QMG score −4.0 vs. −1.7 points ($p=0.39$) MGC score −5.7 vs. −4.0 points ($p=0.93$) MG-QoL15 score −8.0 vs. −7.5 ($p=0.70$)

Abbreviations: Ab-AChR, antibody against acetylcholine receptor; BW, body weight; C5, complement factor 5; CS, corticosteroids; FcRn, neonatal Fc receptor; i.v., intravenous; IgG1, type G1 immunoglobulin; IgG4, type G4 immunoglobulin; IVIG, intravenous immunoglobulins; MAC, membrane attack complex; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis–Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, Myasthenia Gravis Quality of Life 15-item Scale; MuSK, muscle-specific kinase; NA, Not available; NSIST, Non-steroidal Immunosuppressant; PLEX, Plasmapheresis; q8W, every 8 weeks; QMG, Quantitative Myasthenia Gravis scale; s.c., subcutaneous.

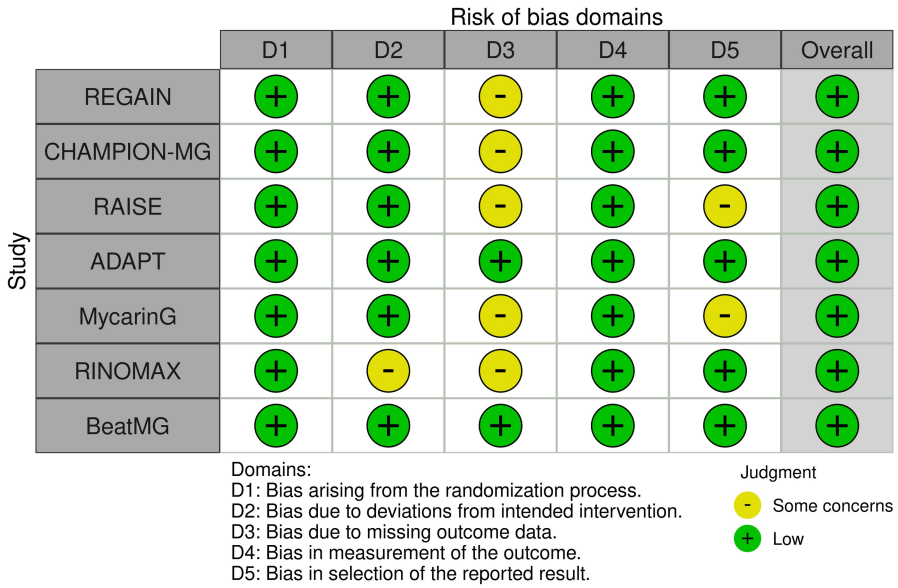

FIGURE 2 Risk of bias for selected studies. ADAPT, efgartigimod trial; BeatMG, rituximab trial; CHAMPION-MG, ravulizumab trial; mycarinG, rozanolixizumab trial; RAISE, zilucoplan trial; REGAIN, eculizumab trial; RINOMAX, rituximab trial.

is often low and disease evaluation with modern scales is lacking. Approximately 15% of gMG patients could be defined as non-responders to standard therapy and experience a high burden of the disease [10]. Of the remaining patients, many have side effects and comorbidities that are the result of year-long standard therapy, thus limiting their quality of life.

For this reason, there is a huge unmet need for innovative gMG therapies that can achieve a deeper response, that are more selective in their mechanism of action, that have a short latency of response, and cause a limited number of side effects and comorbidities [41, 42].

If disability improvement is the primary goal, as well as quality of life, all new treatments should be tested using common primary and secondary endpoints aimed at this. A certain degree of flexibility should always occur, for example, to fit a trial design based on a specific mechanism of action or administration scheme, but there is a high agreement between Food and Drug Administration and European Medicinal Agency that the MG-ADL should be the primary endpoint of every trial. Other endpoints, namely, QMG, MGC and MGQoL-15 scores, are usual secondary endpoints, and add important information to the primary finding.

In our meta-analysis all trials met this general design, with the exception of the rituximab trial in which the primary endpoints were: (i) 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, for the BEAT-MG trial [14] and (ii) minimal disease manifestations at 16 weeks defined as a QMG score of 4 or less with prednisolone, 10 mg or less daily, and no rescue treatment, for the RINOMAX trial [15]. Both trials captured the MG-ADL and QMG scores, making comparison feasible, but it is our opinion that future trials should be designed in a way that at least the primary endpoint, and the resulting sample size calculations, should be the same. Also, baseline characteristics are very important and should be considered when reporting clinical trial results. A minimal set of data should include: mean steroid dose, proportion of patients with bulbar involvement, proportion of patients under long-term treatment with NSISTs, and proportion of thymectomized patients.

The most important finding of our meta-analysis was that innovative treatments are effective, and results seem to be homogeneous within each class. The complement inhibitors eculizumab, ravulizumab and zilucoplan all seem to have similar efficacy. The FcRn active treatments efgartigimod and rozanolixizumab also showed similar effects.

Rituximab did not show any significant effect on MG-ADL score after pooling data from the two trials. The sample size was a total of 47 patients, which is lower than the number involved in anti-complement ($n = 234$) or anti-FcRn therapies ($n = 217$). This could be responsible for the large CI seen for the MG-ADL (−2.34, 0.39), but still the mean effect of rituximab compared to placebo was −0.92, which is less than half of that which was observed with innovative treatments. It should be noted that the aim of the RINOMAX trial was to demonstrate that early treatment with rituximab after diagnosis was able to stop disease progression. The trial reached this endpoint, but it failed all secondary endpoints regarding MG-ADL, QMG and MG-QoL15, meaning that its effect does not translate into quality of life or daily living improvement.

Another difference between the rituximab and other trials was disease severity, with mean baseline MG-ADL scores of <5 versus approximately 9 (range 8–10). Also, disease duration was widely different, 5.5 years or less than 6 months for rituximab trials versus more than 9 years for all other trials. Whether or not this is an advantage as it allows for a higher treatment effect, we should consider that dealing with patients with a longer disease duration and higher disease burden is a clear disadvantage.

Our analysis showed a difference favoring anti-FcRn over anti-complement treatments for their ability to improve QMG score (−4.78 vs. −2.6; net difference 2.18). In our opinion, this is a non-negligible

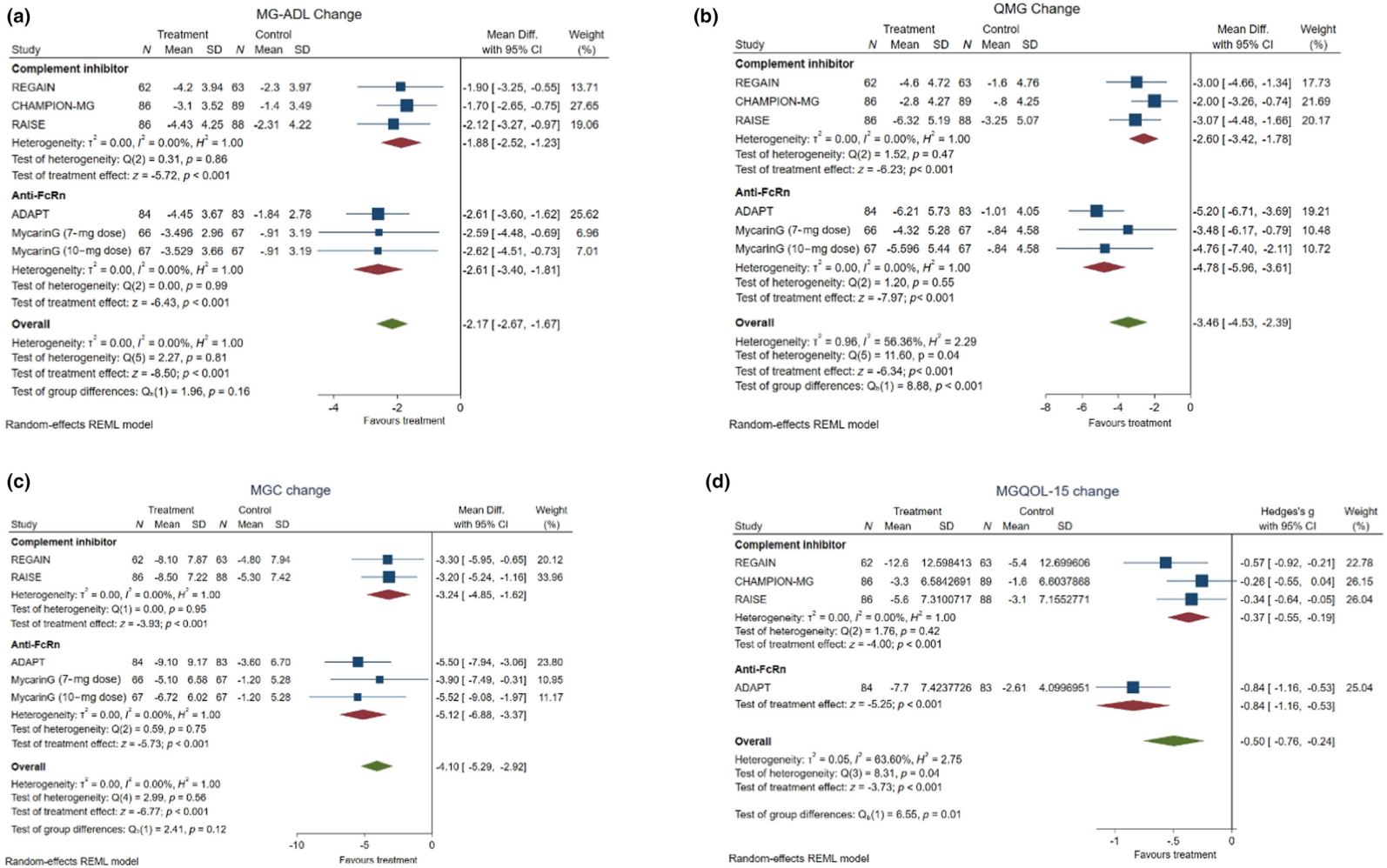

FIGURE 3 Meta-analysis forest plot. ADAPT, efgartigimod trial; CHAMPION-MG, ravulizumab trial; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis–Composite; MG-QoL15, Myasthenia Gravis Quality of Life 15-item scale; MycarinG, rozanolixizumab trial; QMG, Quantitative Myasthenia Gravis scale; RAISE, zilucoplan trial; REGAIN, eculizumab trial; REML, restricted maximum likelihood approach; SD, standard deviation.

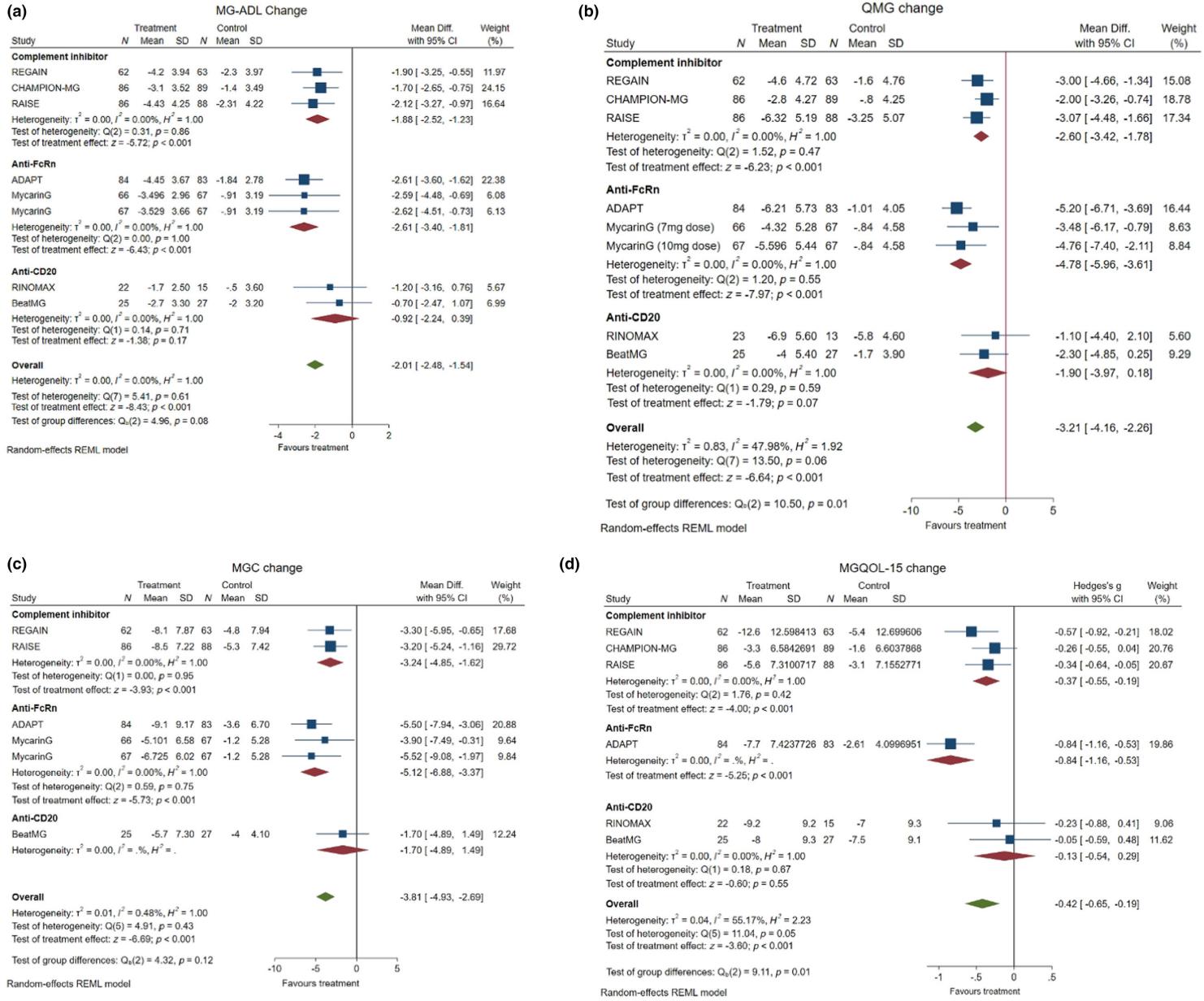

FIGURE 4 Meta-analysis forest plot including anti-CD-20 therapies. ADAPT, efgartigimod trial; BeatMG, rituximab trial; CHAMPION-MG, ravulizumab trial; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis–Composite; MG-QoL15, Myasthenia Gravis Quality of Life 15-item scale; MycarinG, rozanolixizumab trial; QMG, Quantitative Myasthenia Gravis scale; RAISE, zilucoplan trial; REGAIN, eculizumab trial; REML, restricted maximum likelihood approach; RINOMAX, rituximab trial; SD, standard deviation.

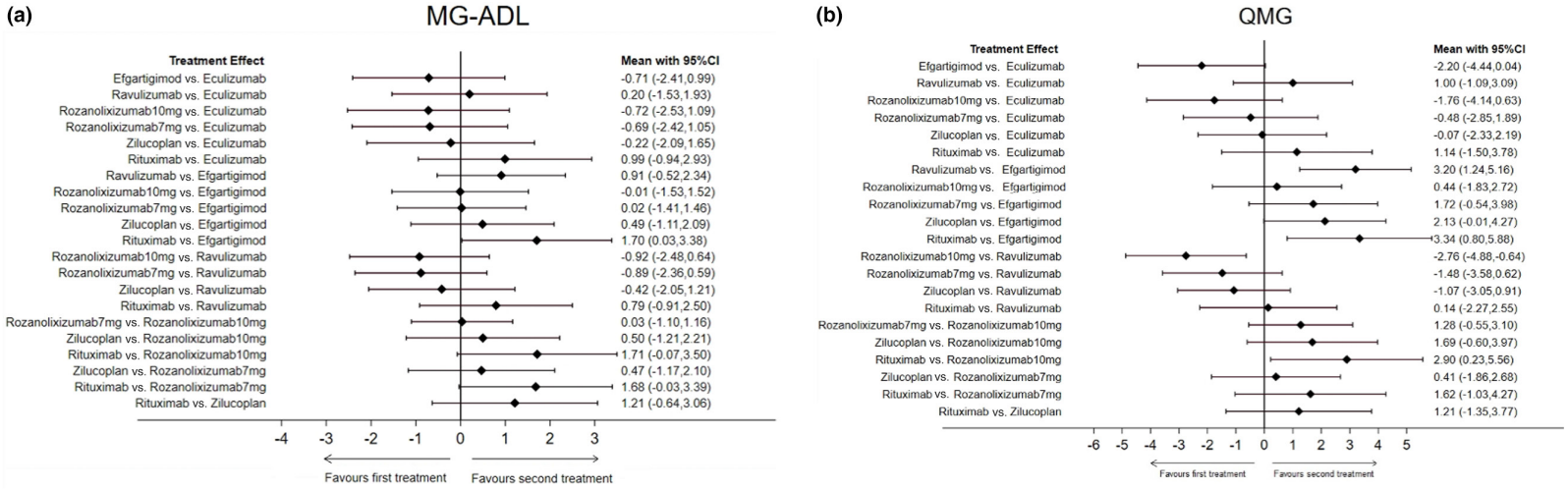

FIGURE 5 Network meta-analysis for Myasthenia Gravis Activities of Daily Living scale (MG-ADL) and Quantitative Myasthenia Gravis scale (QMG). CI, confidence interval.MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale.

TABLE 3 Surface under the cumulative ranking curve and rank probability for each treatment for the Myasthenia Gravis Activities of Daily Living and Quantitative Myasthenia Gravis scales derived from the network meta-analysis.

	MG-ADL		QMG	
Treatment	SUCRA	Probability to be the best (%)	SUCRA	Probability to be the best
Eculizumab	50.5	7.6	51.4	1.1
Efgartigimod	77.4	31.5	93.2	62.6
Ravulizumab	41.9	2.4	28.3	0.0
Rozanolixizumab 7 mg	75.2	20.6	59.9	1.3
Rozanolixizumab 10 mg	76.5	28.1	87.1	34.0
Zilucoplan	56.7	9.5	51.7	1.0
Rituximab	20.5	0.3	27.9	0.0
Placebo	1.2	0.0	0.5	0.0

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis scale; SUCRA, surface under the cumulative ranking curve.

difference; although it is less than a 3-point difference, this is considered a meaningful QMG response in clinical trials. This was also confirmed at the network meta-analysis where efgartigimod and rozanolixizumab had the highest probability of being the most effective treatment.

For a balanced comparison, we would also like to point out that anti-complement therapies achieved stable and prolonged improvement on both the MG-ADL and QMG during the core and extension phase of their trials. In contrast, we set a cut-off point for anti-FcRn treatments after 28 and 43 days from treatment start as they were meant to be administered as treatment cycles. This reduces the generalizability of our findings as longer-term treatment strategies in real life will probably be different compared to clinical trials. Clinicians could use anti-FcRn treatments in different ways. They could be more aggressive and try to maintain peak efficacy as long as possible with frequent re-infusions or let patients fluctuate more and wait for a re-treatment. The result is that a mean reduction in MG-ADL/QMG score, or area under the curve, may be different as captured at the response peak. This issue cannot be resolved in the setting of a meta-analysis, and real-life studies with long-term measurement of MG-ADL and QMG scores will provide useful results.

To our knowledge, this is the first meta-analysis of innovative treatments for gMG, collecting data from placebo-controlled studies. Limitations of this analysis are the different cut-off points for anti-FcRn versus anti-complement treatments for efficacy assessment, the differences in the inclusion/exclusion criteria between studies (i.e., serological data and pre-treatments), the overall limited number of patients, and lack of proper head-to-head studies. We show that all treatments, except for rituximab, have a significant effect on gMG and the depth of their response compared to placebo was −2.2 for the MG-ADL and −3.5 for the QMG. We found a greater response for anti-FcRn treatment at the QMG, but since this is the first report in this direction, the findings should be prudently interpreted and confirmed in larger cohorts or through real-life comparisons.

AUTHOR CONTRIBUTIONS

Francesco Saccà: Conceptualization; validation; writing – review and editing; writing – original draft; supervision. **Chiara Pane:** Writing – review and editing; investigation; data curation; validation. **Pablo Ezequiel Espinosa:** Data curation; methodology; investigation. **Maria Pia Sormani:** Supervision; data curation; writing – review and editing. **Alessio Signori:** Conceptualization; investigation; writing – review and editing; methodology; validation; formal analysis; data curation.

ACKNOWLEDGMENTS

This study did not receive any financial support.

CONFLICT OF INTEREST STATEMENT

Francesco Saccà received public speaking honoraria from Alexion, argenx, Novartis; he also received compensation for Advisory boards or consultation fees from Alexion, argenx, Lexeo Therapeutics, Novartis, Reata; he acted as principal investigator in trials sponsored by Alexion, argenx, Immunovant, Novartis, Sanofi.

DATA AVAILABILITY STATEMENT

Research data are not shared as they are part of previous publications.

ORCID

Francesco Saccà https://orcid.org/0000-0002-1323-6317

REFERENCES

1. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016;375:2570-2581.
2. Verschuuren JJ, Huijbers MG, Plomp JJ, et al. Pathophysiology of myasthenia gravis with antibodies to the acetylcholine receptor, muscle-specific kinase and low-density lipoprotein receptor-related protein 4. *Autoimmun Rev*. 2013;12:918-923.
3. Engel AG, Arahata K. The membrane attack complex of complement at the endplate in myasthenia gravis. *Ann N Y Acad Sci*. 1987;505:326-332.
4. Drachman DB, Adams RN, Josifek LF, Self SG. Functional activities of autoantibodies to acetylcholine receptors and the clinical severity of myasthenia gravis. *N Engl J Med*. 1982;307:769-775.
5. Cole RN, Ghazanfari N, Ngo ST, Gervasio OL, Reddel SW, Phillips WD. Patient autoantibodies deplete postsynaptic muscle-specific kinase leading to disassembly of the ACh receptor scaffold and myasthenia gravis in mice. *J Physiol*. 2010;588:3217-3229.
6. Bacchi S, Kramer P, Chalk C. Autoantibodies to low-density lipoprotein receptor-related protein 4 in double seronegative myasthenia gravis: a systematic review. *Can J Neurol Sci*. 2018;45:62-67.

7. Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol*. 2022;21:163-175.
8. Evoli A, Spagni G, Monte G, Damato V. Heterogeneity in myasthenia gravis: considerations for disease management. *Expert Rev Clin Immunol*. 2021;17:761-771.
9. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375:511-522.
10. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015;14:1023-1036.
11. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. *Yale J Biol Med*. 2013;86:255-260.
12. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12:1756286419832242.
13. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. *J Neurol*. 2015;262:1115-1119.
14. Nowak RJ, Coffey CS, Goldstein JM, et al. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized myasthenia gravis: the BeatMG study. *Neurology*. 2021;98:e376-e389.
15. Piehl F, Eriksson-Dufva A, Budzianowska A, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: the RINOMAX randomized clinical trial. *JAMA Neurol*. 2022;79:1105-1112.
16. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Pract Neurol*. 2015;15:199-206.
17. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. *Muscle Nerve*. 2017;56:185-196.
18. Diaz-Manera J, Martinez-Hernandez E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology*. 2012;78:189-193.
19. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: multicenter blinded prospective review. *Neurology*. 2017;89:1069-1077.
20. 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;16:976-986.
21. Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. 2019;60:14-24.
22. Vu T, Meisel A, Mantegazza R, et al. Efficacy and safety of Ravulizumab, a long-acting terminal complement inhibitor, in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG study. *Neurology*. 2022;98(18 Suppl):791.
23. Howard JF, Genge A, Hussain Y, et al. Outcomes from RAISE: a randomized, placebo-controlled, double-blind, phase 3 trial of zilucoplan in generalized myasthenia gravis. *Muscle Nerve*. 2022;65:S34.
24. Howard JF, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology*. 2019;92:e2661-e2673.
25. Howard JF Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalized myasthenia gravis (ADAPT): a multicentre, randomized, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2021;20:526-536.
26. Bril V, Druzdz A, Grosskreutz J, et al. Efficacy and safety of rozanolixizumab in patients with generalized myasthenia gravis: a randomized, multicenter, double-blind, placebo-controlled phase 3 study (mycaring). *Muscle Nerve*. 2022;65:S35.
27. Nowak RJ, Benatar M, Ari B, Isaacman DJ, Bril V. A randomized, double-blind, placebo-controlled phase 2 study of subcutaneous batoclimab in patients with generalized myasthenia gravis. *Muscle Nerve*. 2022;65:S21.
28. Guptill J, Antozzi C, Bril V, et al. Serum autoantibody lowering by the anti-FcRn monoclonal antibody, nipocalimab, correlates with clinical improvement in generalized myasthenia gravis patients. *Muscle Nerve*. 2022;65:S4.
29. NCT04963270: Satralizumab trial. Accessed February 14, 2023. https://clinicaltrials.gov/ct2/show/NCT04963270
30. NCT04524273: Inebilizumab trial. Accessed February 14, 2023. https://clinicaltrials.gov/ct2/show/NCT04524273
31. NCT03920293: Gefurulimab trial. Accessed February 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03920293
32. NCT05218096: Vemircopan trial. Accessed February 14, 2023. https://clinicaltrials.gov/ct2/show/NCT05218096
33. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology*. 1999;52:1487-1489.
34. Barohn RJ. *The Quantitative Myasthenia Gravis (QMG) Test: the Manual*. Myasthenia Gravis Foundation of America; 2000.
35. Burns TM, Conaway MR, Sanders DB, MG Composite and MG-QOL15 Study Group. The MG composite: a valid and reliable outcome measure for myasthenia gravis. *Neurology*. 2010;74:1434-1440.
36. Burns TM, Sadjadi R, Utsugisawa K, et al. International clinicometric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve*. 2016;54:1015-1022.
37. Higgins JP, Savović J, Page MJ, et al. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane Collaboration; 2019:205-228.
38. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth*. 2020;12:1-7.
39. Signori A, Gallo F, Bovis F, Di Tullio N, Maietta I, Sormani MP. Long-term impact of interferon or glatiramer acetate in multiple sclerosis: a systematic review and meta-analysis. *Mult Scler Relat Disord*. 2016;6:57-63.
40. Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol*. 2009;65:268-275.
41. Wendell LC, Levine JM. Myasthenic crisis. *Neurohospitalist*. 2011;1:16-22.
42. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve*. 2008;37:141-149.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Saccà F, Pane C, Espinosa PE, Sormani MP, Signori A. Efficacy of innovative therapies in myasthenia gravis: A systematic review, meta-analysis and network meta-analysis. *Eur J Neurol*. 2023;30:3854-3867. doi:10.1111/ene.15872