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Comparative efficacy and acceptability of novel biologics in the treatment of myasthenia gravis: systematic review and network meta-analysis of randomized trials

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Abstract

Background Myasthenia gravis (MG) is a chronic autoimmune disorder affecting the neuromuscular junction. The emergence of molecular therapies, such as monoclonal antibodies, B-cell-depleting agents, and chimeric antigen receptor T-cell-based therapies, has the potential to transform the treatment landscape for myasthenia gravis. The clinical efficacy of novel biologics in the treatment of individuals with myasthenia gravis is still a subject of debate. The objective was to compare and rank the efficacy and acceptability of novel biologics in the treatment of individuals with MG through a network meta-analysis.

Methods This systematic review and network meta-analysis (NMA) involved a comprehensive search for published randomized controlled trials (RCTs) across several databases, including PubMed, Web of Science, Embase, Cochrane Library, SinoMed, CNKI, Wanfang, and VIP, covering articles published from inception until July 3, 2024. We included randomized controlled trials involving patients with myasthenia gravis. The main outcome was the overall symptomatology. Random-effects pairwise meta-analyses and network meta-analyses (NMAs) were conducted to compute standardized mean differences (SMDs) or risk ratios with 95% confidence intervals (CIs). The research process did not include individuals with lived experience. The studies' quality was evaluated utilizing the risk-of-bias assessment tool created by the Cochrane Collaboration. Network meta-analysis was performed utilizing Stata 16 and R4.2.3.

Results Eleven RCTs including 840 participants with myasthenia gravis were eligible. Belimumab improvement of the MG-ADL score is compared to placebo ($MD = -3.29$, 95% CI ($-5.78, -0.80$), $P < 0.05$). Compared to placebo, batoclimab enhanced the QMG score ($MD = -4.46$, 95% CI ($-7.57, -1.35$), $P < 0.05$) and the MGC score ($MD = -3.58$, 95% CI ($-6.68, -0.47$), $P < 0.05$). Eculizumab improvement of the MG-QoL 15r score is compared to placebo ($MD = -7.10$, 95% CI ($-12.20, -2.00$), $P < 0.05$). Regarding adverse reactions, we found no difference in the network

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comparison of novel biologics compared to placebo, but this conclusion requires further validation through rigorous research.

Conclusions This study provides an updated, relative rank-order efficacy of novel biologics therapies for myasthenia gravis. These data may help inform the design and sample size calculation of future clinical trials and assist selection of combination therapy.

Systematic review registration PROSPERO CRD42024559757.

Key points

- When compared to placebo, various novel biologics demonstrate distinct benefits in enhancing clinical outcomes.
- Batoclimab and eculizumab exhibit marginal advantages, with batoclimab effectively improving both QMG and MGC scores.
- Belimumab shows significant efficacy in enhancing the MG-ADL score while minimizing adverse reactions.
- Regarding adverse reactions, we found no difference in the network comparison of novel biologics compared to placebo, but this conclusion requires further validation through rigorous research.

Keywords Myasthenia gravis, Novel biologics, Efficacy and acceptability, Network meta-analysis

Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder characterized by prominent clinical manifestations of skeletal muscle weakness and significant fatigue, which are worsened by exertion and notably improved by rest. Contemporary therapeutic strategies for myasthenia gravis predominantly consist of the utilization of cholinesterase inhibitors, glucocorticoids, immunosuppressants, intravenous immunoglobulins, plasma exchange, and thymectomy [1].

Nonetheless, the heightened incidence of adverse effects, limited efficacy, and intolerance in certain individuals have sparked a growing interest in and utilization of novel biologic therapies [2]. These treatments can be categorized into three groups according to their distinct methods of action in the pathophysiological course of MG: complement inhibitors, FcRn antagonists, and B-cell-targeting therapies [3]. The FcRn, exhibiting structural similarities to the human major histocompatibility complex class I molecule (MHC-I) and expressed in several human cell types including epithelial, endothelial, and immune cells [4], plays a crucial role in the pathogenesis of MG. FcRn inhibitors exhibit superior binding affinity for FcRn relative to IgG in both acidic and neutral environments. These inhibitors competitively obstruct the attachment of pathogenic IgG to FcRn, resulting in the elimination of pathogenic IgG from the system [5, 6]. In the context of myasthenia gravis pathophysiology characterized by the presence of acetylcholine receptor antibodies, complement activation is recognized as the primary mechanism, substantiated by significant data from clinical investigations including myasthenia gravis patients and experimental autoimmune myasthenia gravis (EAMG). The main antibody subclasses involved in AChR-MG are IgG and IgG3. The interaction of antibodies with antigens activates the conventional complement system, resulting in the formation of the membrane attack complex C5b-9 (MAC) and the subsequent breakdown of the postsynaptic membrane structure [7]. Complement inhibitors exhibit considerable potential in modifying the progression of MG pathology. Monoclonal antibodies targeting B cells operate by decreasing CD20 + cells, obstructing B-cell activation and proliferation [8], or depleting CD19-expressing pre-B cells and mature B cells. Novel biologics are complex and have differing degrees of effectiveness, with insufficient direct comparison data among them. This study aimed to perform a network meta-analysis of randomized, placebo-controlled trials of novel therapeutics in MG with accessible efficacy data, to create a reference framework for the clinical use of MG treatments.

Methods

Search strategy and selection criteria

We included all randomized controlled trials (RCTs) that compared novel biologics and placebo interventions in adults diagnosed with generalized myasthenia gravis (gMG) with elevated autoantibodies (anti-acetylcholine receptor [AChR] or anti-muscle-specific kinase [MuSK]) prior to the screening process. No constraints regarding gender, race, language, nation, or context were imposed. Furthermore, participants had to demonstrate compromised activities of daily living, as evidenced by a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 5 or above at both screening and baseline, with over 50% of the score derived from non-ocular components.

Additionally, participants were required to fulfill a Myasthenia Gravis Foundation of America (MGFA) clinical categorization of class II to V during the screening phase [1]. Both open and blinded RCTs were included; however, open RCTs were eliminated in a sensitivity analysis. Cluster randomized studies were omitted due to their unique design, which might readily contravene the transitivity assumption in the NMA. We further rejected studies exhibiting a significant risk of bias in the randomization method. To ensure uniformity throughout the research, the control group was given a placebo intervention, while the experimental group got innovative biologics. Both groups maintained uniform baseline therapy protocols, and there were no restrictions on the treatment length. Furthermore, neither group received any supplementary Western medication or non-pharmacological therapies that may influence the treatment's efficacy.

The principal objective of this study was to evaluate the efficacy and acceptability of novel biologics in treating myasthenia gravis, with the primary outcome being the endpoint score on a validated myasthenia gravis rating scale, such as the quantitative myasthenia gravis (QMG) score, MG-ADL score, myasthenia gravis composite (MGC) score, or the 15-item revised version of the myasthenia gravis quality-of-life (MG-QoL 15r) score, as well as the difference between baseline and endpoint scores [9, 10]. In instances when endpoint scores were unreported, changes in scores were utilized instead. In instances where mean scores were unavailable, the proportion of subjects exhibiting treatment response was utilized. Supplementary outcome measures encompassed tolerability (treatment-related ill effects, quantified as the percentage of individuals encountering unpleasant events) and acceptance (treatment cessation, quantified as the percentage of participants who withdrew from the trial for any reason).

We identified suitable research by searching electronic databases, doing manual searches, and utilizing personal connections. A thorough database search was conducted in PubMed, Web of Science, Embase, Cochrane Library, SinoMed, CNKI, Wanfang, and VIP for publications published from inception to July 3, 2024. The search included a blend of topic phrases and free-text terms, with retrieval algorithms customized to the specific needs of each database. The comprehensive search technique for Embase is presented in Table 1. The collected papers were systematically sorted and analyzed using EndNote X9. Two reviewers, Peixi Zhao and Meijin Song, independently evaluated the identified references and chose the included articles based on the title and abstract. All disputes were settled through dialogue. In the presence of lingering uncertainty, we obtained the complete article for additional examination. If disputes could not be elucidated via dialogue, they were adjudicated by a third senior reviewer (Peng Xu). Upon acquisition of the complete papers, the two reviewers separately determined if the research satisfied the review's inclusion criteria and chose the final included articles. Two reviewers, Guan Chang and Xikang Ding, independently extracted relevant data. The dataset encompassed various parameters, including publication year, primary author, country of origin, publication timeline, subject demographics such as age and gender, sample size, comprehensive descriptions of the treatment, and control groups, along with meticulous documentation of outcomes and any adverse events. When data was insufficient or unclear, reviewer Tianying Chang proactively reached out to the primary or corresponding author via email or phone to solicit missing or supplementary data. The risk of bias was evaluated by two reviewers (Dongxu Li and Huijing Cui) utilizing the Cochrane Handbook for Systematic Reviews of Interventions and assessments for the primary outcome. In cases where inconsistencies could not be reconciled via conversation, a third reviewer, Peng Xu, adjudicated the disagreement.

Table 1 Search strategy of Embase

No	Query
#1	'myasthenia gravis'/exp
#2	'myasthenia gravis':ab,ti OR'myasthenia gravis, ocular':ab,ti OR'ocular myasthenia gravis':ab,ti OR'myasthenia gravis, generalized':ab,ti OR'generalized myasthenia gravis':ab,ti OR'muscle-specific receptor tyrosine kinase myasthenia gravis':ab,ti OR'muscle specific receptor tyrosine kinase myasthenia gravis':ab,ti OR'muscle-specific tyrosine kinase antibody positive myasthenia gravis':ab,ti OR'muscle specific tyrosine kinase antibody positive myasthenia gravis':ab,ti OR'musk mg':ab,ti OR'musk myasthenia gravis':ab,ti OR'myasthenia gravis, musk':ab,ti OR'anti-musk myasthenia gravis':ab,ti OR'anti musk myasthenia gravis':ab,ti OR'myasthenia gravis, anti-musk':ab,ti
#3	#1 OR #2
#4	'biological product'/exp
#5	'complement inactivating agents':ab,ti OR'agents, complement inactivating':ab,ti OR'inhibitor, complement':ab,ti OR'complement inhibiting agents':ab,ti OR'complement inhibitors':ab,ti OR eculizumab:ab,ti OR ravulizumab:ab,ti OR'fcrn inhibitor':ab,ti OR efgartigimod:ab,ti OR'efgartigimod alfa plus hyaluronidase':ab,ti OR rozanolixizumab:ab,ti OR nipocalimab:ab,ti OR batoclimab:ab,ti OR'b-cell inhibitors':ab,ti OR rituximab:ab,ti OR inebilizumab:ab,ti OR belimumab:ab,ti OR telitaciept:ab,ti OR zilucoplan:ab,ti
#6	#4 OR #5
#7	#3 AND #6

Data analysis

The research employed the mean difference (MD) for the analysis of quantitative data and the relative risk (RR) for the evaluation of count data. All effect sizes were reported alongside their respective 95% confidence intervals (CI). The evaluation of model fit and overall consistency was conducted using the deviance information criterion (DIC). The node-splitting method was utilized to evaluate local consistency in cases of a closed loop. Additionally, intervention measures were ranked based on the surface under the cumulative ranking curve (SUCRA) [11], and a league table was created to compare the effects of different interventions. Numerous original studies have been conducted to evaluate different dosages and treatment durations for a common intervention. Network meta-regression analysis was utilized to compare the efficacy of medications versus placebos, examining potential differences across various doses and treatment durations. Publication bias was assessed using a funnel plot when at least 10 studies reported the outcome measure. This study employed Stata 15.0 and R 4.2.0 as analytical tools. Funnel plots were generated and analyzed using Review Manager software (version 5.3) when more than 10 trials met the study criteria, with potential publication bias assessed through the evaluation of these plots. The study protocol has been registered with PROSPERO under the identifier CRD42024559757. The current study has been registered and designed without participant contact; therefore, ethical approval and patient consent were not necessary.

Role of the funding source

The study's funder did not participate in the design, data collection, analysis, interpretation, or report writing.

Results

Study characteristics, risk of bias, and certainty of evidence

A total of 3734 records were identified, with 1855 excluded through title and abstract screening. A total of 1879 full-text articles were evaluated for eligibility. Of these, 1868 were excluded for failing to meet the criteria, resulting in 11 reports from 11 studies being included in the qualitative synthesis. Figure 1 provides a visual representation of the entire screening process. Among these, there are 11 RCTs [12–22] involving 840 participants, with 431 in the experimental group and 409 in the control group. The studies included analyzed eight novel biologics. The listed formulas are batoclimab, efgartigimod, rozanolixizumab, eculizumab, zilucoplan, ravulizumab, belimumab, and rituximab. Table 2 provides comprehensive details on the characteristics of the included studies. Among the 11 studies included, 10 studies [12–20, 22] employed random number tables for group assignment, classified as "low risk"; 1 study merely stated "random" without detailing the grouping method. All studies reported on the use of allocation concealment and the implementation of blinding for participants, implementers, and outcome evaluators. Nine studies [12–16, 19–22] exhibited no selective reporting and were rated as "low risk." Two studies did not specify whether selective reporting occurred. The integrity of the study data was assessed as relatively high, characterized by complete and unbiased data. Figure 2 illustrates the assessment of bias.

Outcomes

MG-ADL score network

Eleven studies [12–22] have reported the MG-ADL score, specifically examining 8 types of novel biologics. Each study exclusively compared novel biologics to placebo, without conducting pairwise comparisons among the specific novel biologics. The batoclimab, efgartigimod, and rituximab were the most commonly reported interventions in the studies included. In the absence of closed loops, conducting an inconsistency test is unnecessary (Fig. 3). The network meta-analysis indicated that belimumab exhibited significantly greater efficacy compared to placebo ($MD = -3.29$, 95% CI (-5.78 to -0.80), $P < 0.05$) (Fig. 4). Variations exist in the efficacy of certain novel biologics (Table 3). The SUCRA probability rankings are as follows: belimumab ($SUCRA = 88.5\%$) is ranked higher than zilucoplan ($SUCRA = 71.7\%$), followed by eculizumab ($SUCRA = 64\%$), ravulizumab ($SUCRA = 62.5\%$), rozanolixizumab ($SUCRA = 54.5\%$), rituximab ($SUCRA = 43.9\%$), efgartigimod ($SUCRA = 41.8\%$), and placebo ($SUCRA = 18.1\%$) (Table 4).

QMG score network

Eleven studies [12–22] have reported the QMG score, specifically examining 8 types of novel biologics. Each study exclusively compared novel biologics to placebo, without conducting pairwise comparisons among the specific novel biologics themselves. The batoclimab, efgartigimod, and rituximab were the most commonly reported interventions in the studies included. In the absence of closed loops, conducting an inconsistency test is unnecessary (Fig. 5). The network meta-analysis indicated that batoclimab exhibited significantly greater efficacy compared to placebo ($MD = -4.46$, 95% CI (-7.57, -1.35), $P < 0.05$) (Fig. 6). Variations exist in the efficacy of certain novel biologics (Table 5). The SUCRA probability rankings are as follows: batoclimab ($SUCRA = 83.4\%$) is superior to eculizumab ($SUCRA = 62.2\%$), followed by zilucoplan ($SUCRA = 57.4\%$), belimumab ($SUCRA = 53.8\%$), ravulizumab ($SUCRA = 49.7\%$), rituximab ($SUCRA = 47.3\%$), efgartigimod ($SUCRA =$

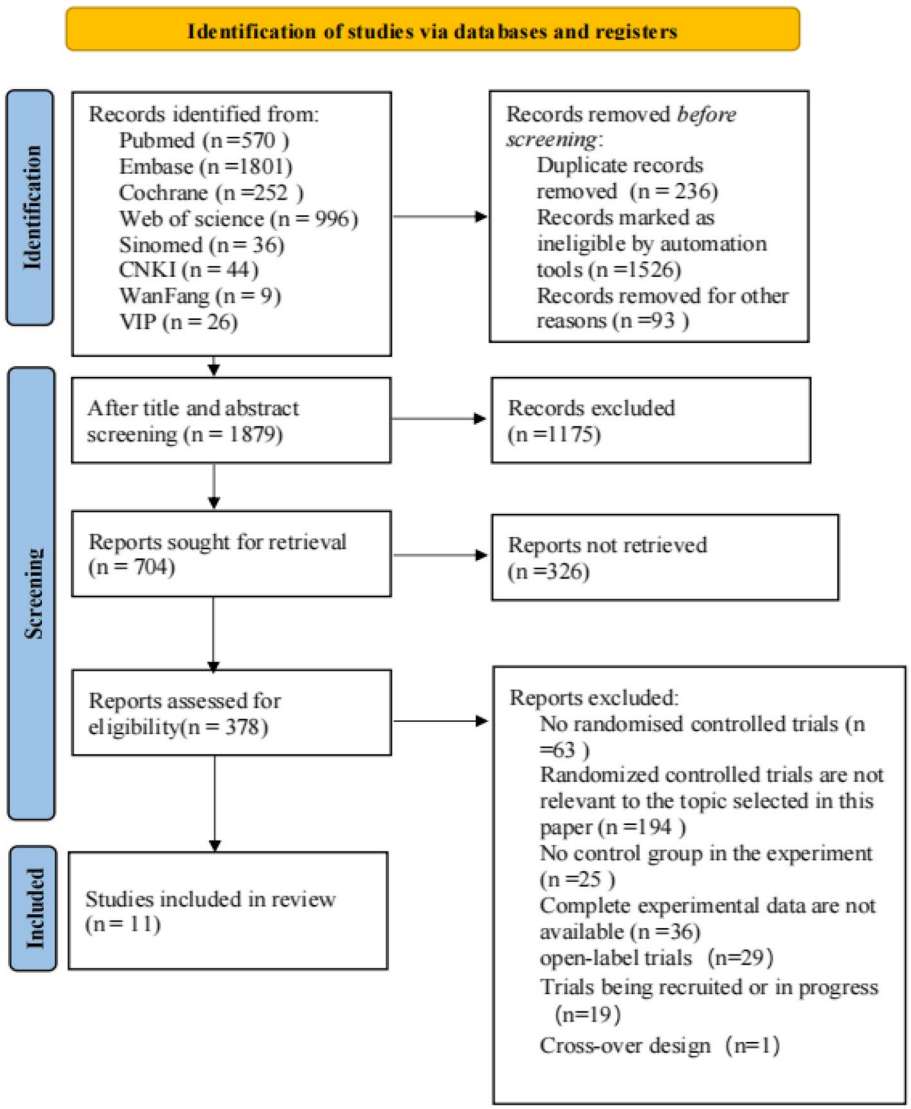

Fig. 1 Flow diagram of the study selection process

46.9%), rozanolixizumab (*SUCRA* = 31.8%), and placebo (*SUCRA* = 17.4%) (Table 4).

MGC score network

Nine studies [12–18, 20, 22] have reported the MGC score, specifically examining seven types of novel biologics. Each study exclusively compared novel biologics to placebo, without conducting pairwise comparisons among the specific novel biologics. The batoclimab and efgartigimod were the most commonly reported interventions in the studies included. In the absence of closed loops, conducting an inconsistency test is unnecessary (Fig. 7). The network meta-analysis indicated that batoclimab exhibited significantly greater efficacy compared to placebo (*MD* = −3.58, 95% *CI* (− 6.68, −0.47), $P < 0.05$) (Fig. 8). Variations exist in the efficacy of certain novel biologics (Table 6). The SUCRA probability rankings are as follows: Batoclimab (*SUCRA* = 74.5%) > eculizumab (SUCRA = 69.1%) > zilucoplan (*SUCRA* = 62.7%) > rozanolixizumab (*SUCRA* = 51.4%) > rituximab (*SUCRA* = 48%) > efgartigimod (*SUCRA* = 42.5) > belimumab (*SUCRA* = 31.4%) > placebo (*SUCRA* = 20.5%) (Table 4).

MG-QoL 15r score network

Nine studies [12–15, 17–19, 21, 22] have reported the MG-QoL 15r score, specifically examining six types of novel biologics. Each study exclusively compared novel biologics to placebo, without conducting pairwise comparisons among the specific novel biologics.

Table 2 Characteristics of the included studies

First author and year of publication	Intervention measures in the control group	Intervention measures in the observation group	The number of cases in the control group	The number of cases in the observation group	Gender (female/male)	Ages in the control group	Ages in the observation group	Course of treatment	Follow-up time	Outcome indicators
Chong Yan (2022) [12]	Placebo	Batoclimab 340 mg/ batoclimab 680 mg	9	340 mg: 10 680 mg: 11	24/6	40.2 ± 9.3	340 mg: 36.4 ± 9.8 680 mg: 40.6 ± 16.8	43 days	120 days	abcde
Chong Yan (2024) [13]	Placebo	Batoclimab	65	67	88/43	43.7 ± 13.5	43.8 ± 13.9	6 weeks	4 weeks	abcde
James F. Howard Jr. (2019) [14]	Placebo	Efgartigimod	12	12	15/9	43.5 ± 19.3	55.3 ± 13.6	78 days	2 weeks	abcde
James F. Howard Jr. (2021) [15]	Placebo	Efgartigimod	64	65	118/49	48.2 ± 15.0	45.9 ± 14.4	8 weeks	5 weeks	abcde
Vera Bri (2021) [16]	Placebo	Rozanolixizumab	22	21	27/16	53.3 ± 15.7	50.5 ± 14.7	29 days	70 days	abce
James F. Howard Jr. (2017) [17]	Placebo	Eculizumab	63	62	82/43	46.9 ± 18.0	47.5 ± 15.7	26 weeks	8 weeks	abcde
James F. Howard Jr. (2020)[18]	Placebo	Zilucoplan 0.1 mg/kg Zilucoplan 0.3 mg/kg	15	0.1 mg/kg: 15 0.3 mg/kg: 14	21/23	48.4 ± 15.7	0.1 mg/kg: 45.5 ± 15.7 0.3 mg/kg: 54.6 ± 15.5	12 weeks	60 weeks	abcde
Tuan Vu (2022) [19]	Placebo	Ravulizumab	89	86	89/86	53.3 ± 16.1	62.6 ± 11.2	26 weeks	4 years	abde
Karen Hewett (2018) [20]	Placebo	Belimumab 10 mg/kg	21	18	24/15	59.0 ± 13.88	52.7 ± 17.32	20 weeks	24 weeks	abce
Fredrik Piehl (2022) [21]	Placebo	Rituximab 500 mg	22	25	14/33	58 ± 18.6	67.4 ± 13.4	1 day	24 weeks	abde
Richard J. Nowak (2022) [22]	Placebo	Rituximab	27	25	23/29	56.8 ± 17	53.2 ± 17.5	4 weeks	24 weeks	abcde

Notes: [a]Myasthenia Gravis Activities of Daily Living (*MG-ADL*) score. [b]Quantitative myasthenia gravis (*QMG*) score. [c]Myasthenia gravis composite (MGC) score. [d]15-item revised version of the myasthenia gravis quality-of-life (*MG-QoL 15r*) score. [e]Adverse effects (*AEs*)

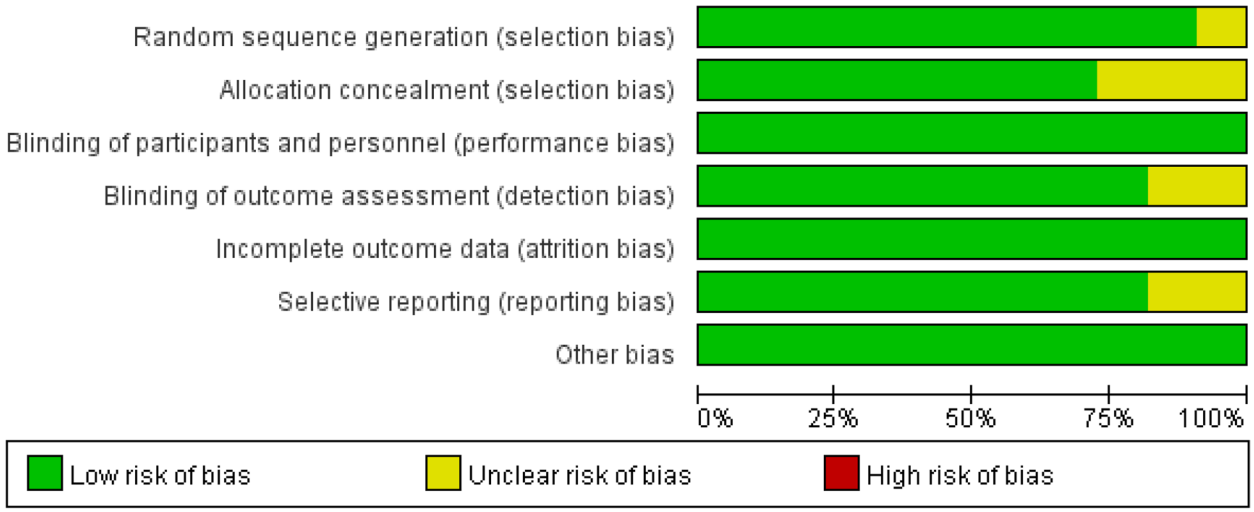

Fig. 2 Assessment of bias

The batoclimab, efgartigimod, and rituximab were the most commonly reported interventions in the studies included. In the absence of closed loops, conducting an inconsistency test is unnecessary (Fig. 9). The network meta-analysis indicated that eculizumab exhibited significantly greater efficacy compared to placebo (*MD* = −7.10, 95% *CI* (− 12.20, −2.00), *P* < 0.05) (Fig. 10). Variations exist in the efficacy of certain novel biologics (Table 7). The SUCRA probability rankings are as follows: Eculizumab (*SUCRA* = 93.7%) > zilucoplan (*SUCRA* = 77.6%) > batoclimab (*SUCRA* = 67.1%) > ravulizumab (*SUCRA* = 47.2%) > efgartigimod (*SUCRA* = 32.4%) > placebo (*SUCRA* = 17.8%) (Table 4).

Adverse reactions

A total of 10 studies [12, 14–22] have documented adverse reactions, specifically examining 8 types of novel biologics. The reactions encompassed hormone-induced obesity, gastrointestinal complications including nausea, vomiting, abdominal pain, and diarrhea, and gastrointestinal ulcers. Moreover, symptoms indicative of autonomic nervous dysfunction, including dizziness and palpitations, as well as other general symptoms such as rash, fever, and abnormalities in renal and liver function, were observed and documented in these studies (Table 8).

Publication bias

This study's two outcomes are represented in the literature comprising at least 10 articles, leading to the construction of comparative and corrected funnel plots for both the MG-ADL score and the QMG score. The literature reviewed is predominantly symmetrically distributed around the zero line; however, a minor portion exhibits relative discreteness and a slope, suggesting the potential presence of publication bias and small sample effects (Figs. 11, 12).

Discussion

Summary of findings

This study represents the first network meta-analysis evaluating novel biologic interventions for the treatment of myasthenia gravis. We examined 8 interventions documented in 11 randomized controlled trials involving 840 participants. These agents were subject to categorical discussions and ranked based on their treatment efficacy and acceptability for MG. The network meta-analysis results indicated that the novel biologics for treating myasthenia gravis demonstrated significant efficacy and safety overall. Belimumab demonstrated the most significant improvement in MG-ADL score among the eight novel biologics, with a mean difference of −3.29 (95% *CI*: −5.78, −0.80; *P* < 0.05). In enhancing the QMG score, all eight novel biologics outperformed placebo, with batoclimab demonstrating the most significant effect (*MD* = −4.46, 95% *CI* (− 7.57, −1.35), *P* < 0.05). In enhancing the MGC score, all eight novel biologics outperformed placebo, with batoclimab demonstrating the most significant effect (*MD* = −3.58, 95% *CI* (− 6.68, −0.47), *P* < 0.05). Eculizumab demonstrated the most significant impact on improving the MG-QoL 15r score among six novel biologics (*MD* = −7.10, 95% *CI* (− 12.20, −2.00), *P* < 0.05). No single novel biologic demonstrates an efficacy advantage across all outcome indicators. Various novel biologics demonstrate distinct benefits in enhancing clinical outcomes. Notably, batoclimab and eculizumab exhibit marginal

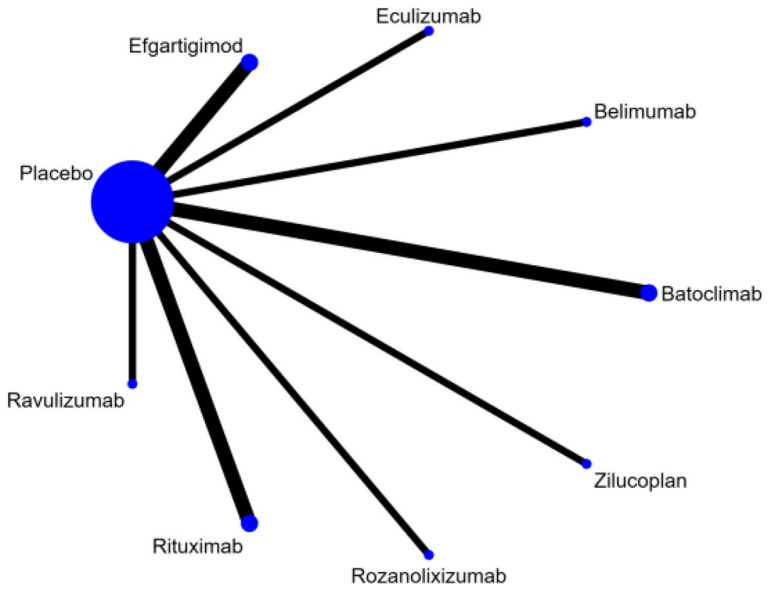

Fig. 3 Inconsistency test

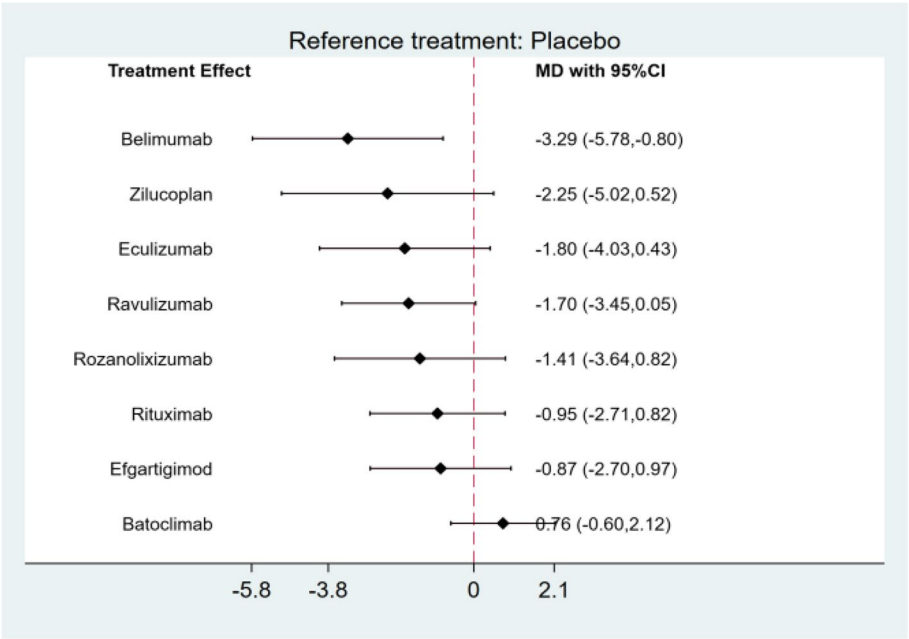

Fig. 4 Belimumab exhibiting significantly greater efficacy compared to placebo (*MD* = − 3.29, 95% *CI* (− 5.78 to − 0.80), *P* < 0.05)

advantages, with batoclimab effectively improving both QMG and MGC scores. Additionally, belimumab shows significant efficacy in enhancing the MG-ADL score while minimizing adverse reactions. The SUCRA rankings indicated that eculizumab achieved the highest comprehensive ranking, suggesting that this novel biologic demonstrates significant clinical efficacy in the treatment of myasthenia gravis. A total of 11 studies addressed drug safety, with 10 randomized controlled trials reporting adverse events. These reactions included hormone-induced obesity, gastrointestinal issues such as nausea, vomiting, abdominal pain, and diarrhea, and gastrointestinal ulcers. Furthermore, symptoms indicative of autonomic nervous dysfunction

Table 3 Variations existing in the efficacy of certain novel biologics

Belimumab								
− 1.04 (− 4.76, 2.68)	Zilucoplan							
− 1.49 (− 4.83, 1.85)	− 0.45 (− 4.00, 3.10)	Eculizumab						
− 1.88 (− 5.22, 1.46)	− 0.84 (− 4.40, 2.71)	− 0.39 (− 3.54, 2.76)	Rozanolixizumab					
− 1.59 (− 4.63, 1.45)	− 0.55 (− 3.82, 2.72)	− 0.10 (− 2.93, 2.73)	0.29 (− 2.54, 3.13)	Ravulizumab				
− 2.34 (− 5.39, 0.71)	− 1.30 (− 4.58, 1.98)	− 0.85 (− 3.69, 1.99)	− 0.46 (− 3.30, 2.38)	− 0.75 (− 3.23, 1.73)	Rituximab			
− 2.42 (− 5.52, 0.67)	− 1.38 (− 4.71, 1.94)	− 0.93 (− 3.82, 1.95)	− 0.54 (− 3.43, 2.35)	− 0.83 (− 3.37, 1.70)	− 0.08 (− 2.63, 2.46)	Efgartigimod		
− 4.05 (− 6.89, − 1.22)	− 3.01 (− 6.10, 0.07)	− 2.56 (− 5.17, 0.05)	− 2.17 (− 4.78, 0.44)	**− 2.46 (− 4.68, − 0.25)**	− 1.71 (− 3.94, 0.52)	− 1.63 (− 3.91, 0.65)	Batoclimab	
− 3.29 (− 5.78, − 0.80)	− 2.25 (− 5.02, 0.52)	− 1.80 (− 4.03, 0.43)	− 1.41 (− 3.64, 0.82)	− 1.70 (− 3.45, 0.05)	− 0.95 (− 2.71, 0.82)	− 0.87 (− 2.70, 0.97)	0.76 (− 0.60, 2.12)	Placebo

Table 4 Variations existing in the efficacy of nine novel biologics

Batoclimab								
− 1.56 (− 7.06, 3.94)	Eculizumab							
− 1.92 (− 7.89, 4.05)	− 0.36 (− 7.19, 6.47)	Zilucoplan						
− 2.17 (− 7.97, 3.63)	− 0.61 (− 7.28, 6.06)	− 0.25 (− 7.32, 6.82)	Belimumab					
− 2.46 (− 7.70, 2.78)	− 0.90 (− 7.10, 5.30)	− 0.54 (− 7.16, 6.08)	− 0.29 (− 6.76, 6.18)	Ravulizumab				
− 2.77 (− 7.67, 2.14)	− 1.20 (− 7.11, 4.70)	− 0.84 (− 7.19, 5.51)	− 0.59 (− 6.78, 5.59)	− 0.30 (− 5.97, 5.36)	Efgartigimod			
− 2.74 (− 7.46, 1.99)	− 1.18 (− 6.95, 4.59)	− 0.82 (− 7.04, 5.40)	− 0.57 (− 6.62, 5.49)	− 0.28 (− 5.80, 5.25)	0.03 (− 5.17, 5.22)	Rituximab		
− 3.84 (− 9.34, 1.66)	− 2.28 (− 8.70, 4.14)	− 1.92 (− 8.75, 4.91)	− 1.67 (− 8.35, 5.01)	− 1.38 (− 7.58, 4.82)	− 1.08 (− 6.98, 4.83)	− 1.10 (− 6.87, 4.67)	Rozanolixizumab	
− 4.46 (− 7.57, − 1.35)	− 2.90 (− 7.44, 1.64)	− 2.54 (− 7.64, 2.56)	− 2.29 (− 7.19, 2.61)	− 2.00 (− 6.22, 2.22)	− 1.70 (− 5.48, 2.09)	− 1.72 (− 5.28, 1.84)	− 0.62 (− 5.16, 3.92)	Placebo

include dizziness and palpitations, in addition to general symptoms such as rash, fever, and abnormalities in renal and liver function.

Mechanism of novel biologics

Batoclimab is a monoclonal antibody targeting the neonatal Fc receptor (FcRn), initially identified in rodent models, where FcRn facilitates the transport of IgG from maternal milk to neonates in the intestine. Subsequent findings indicate that under physiological conditions, FcRn regulates the half-life of antibodies and is crucial for maintaining the levels of IgG and albumin in the body [2, 23]. It primarily binds to the Fc portion of antibodies and albumin, thereby inhibiting their degradation in lysosomes. Patients with autoimmune diseases often exhibit elevated levels of IgG, which may inadvertently harm tissues and organs. The mechanism of action of batoclimab involves competitive binding to FcRn with IgG, which diminishes FcRn's protective role for IgG. This process leads to the degradation of excess IgG and enhances the clearance and metabolism of IgG antibodies in the body, ultimately alleviating symptoms and progression of pathogenic IgG-mediated autoimmune diseases. Batoclimab, engineered with an Fc segment, incorporates multiple amino acid mutations and optimized glycosylation patterns, which significantly enhance its affinity for FcRn compared to other anti-FcRn antibodies like efgartigimod. This increased affinity effectively inhibits the interaction between endogenous IgG and FcRn, resulting in reduced IgG levels in the body [24].

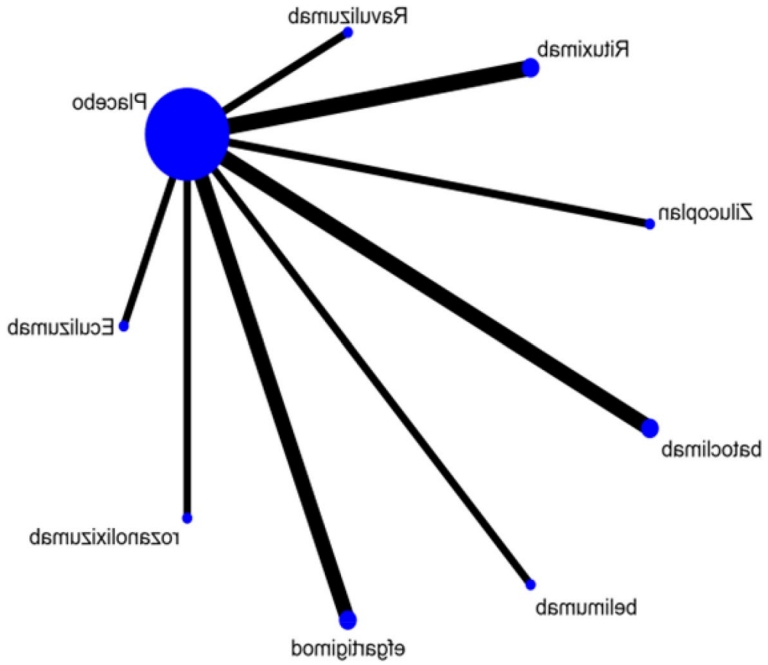

Fig. 5 The batoclimab, efgartigimod, and rituximab as the most commonly reported interventions in the studies included

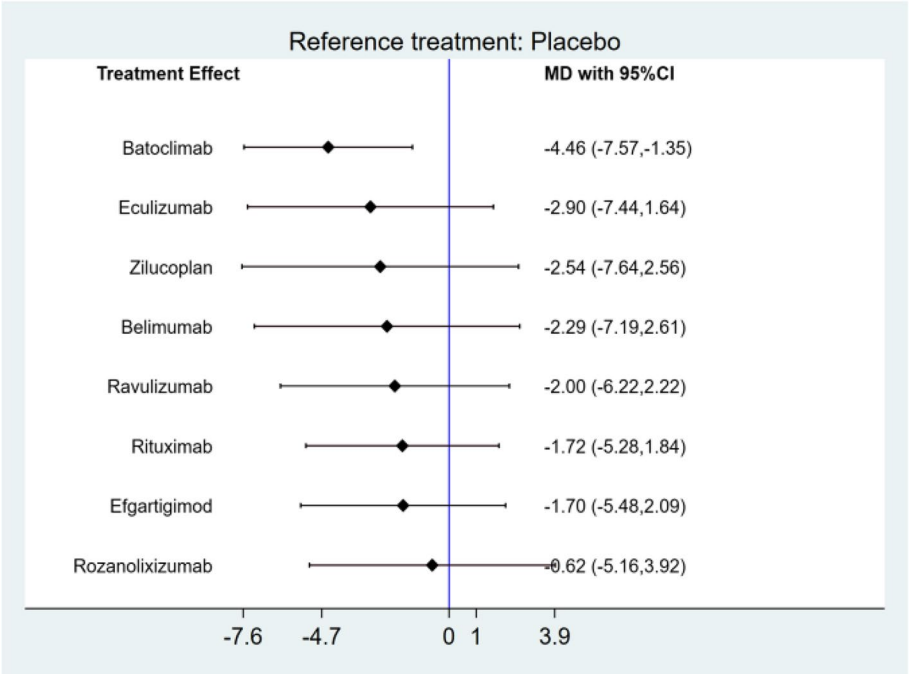

Fig. 6 Batoclimab exhibiting significantly greater efficacy compared to placebo (*MD* = −4.46, 95% *CI* (− 7.57, − 1.35), *P* < 0.05)

The complement system constitutes a significant element of the innate immune system, featuring activation pathways such as the classical, lectin, and alternative pathways, culminating in the formation of the membrane attack complex (MAC). The dysregulation of the complement system results in the abnormal activation of both innate and adaptive immune responses. In individuals with myasthenia gravis, acetylcholine receptor antibodies

Table 5 Variations existing in the efficacy of eight novel biologics

Eculizumab							
− 0.29 (− 7.56, 6.98)	Zilucoplan						
0.28 (− 5.44, 6.00)	0.57 (− 5.71, 6.85)	Batoclimab					
− 1.60 (− 8.60, 5.40)	− 1.31 (− 8.78, 6.16)	− 1.88 (− 7.84, 4.09)	Rituximab				
− 1.39 (− 8.09, 5.30)	− 1.10 (− 8.28, 6.08)	− 1.67 (− 7.27, 3.93)	0.21 (− 6.70, 7.11)	Rozanolixizumab			
− 2.03 (− 8.29, 4.23)	− 1.74 (− 8.51, 5.04)	− 2.30 (− 7.43, 2.83)	− 0.43 (− 6.91, 6.06)	− 0.63 (− 6.78, 5.52)	Efgartigimod		
− 3.03 (− 9.83, 3.77)	− 2.74 (− 10.02, 4.54)	− 3.31 (− 9.04, 2.43)	− 1.43 (− 8.44, 5.58)	− 1.64 (− 8.34, 5.07)	− 1.00 (− 7.28, 5.27)	Belimumab	
− 3.30 (− 8.10, 1.50)	− 3.01 (− 8.47, 2.45)	**− 3.58 (− 6.68, − 0.47)**	− 1.70 (− 6.80, 3.40)	− 1.91 (− 6.57, 2.75)	− 1.27 (− 5.29, 2.74)	− 0.27 (− 5.09, 4.55)	Placebo

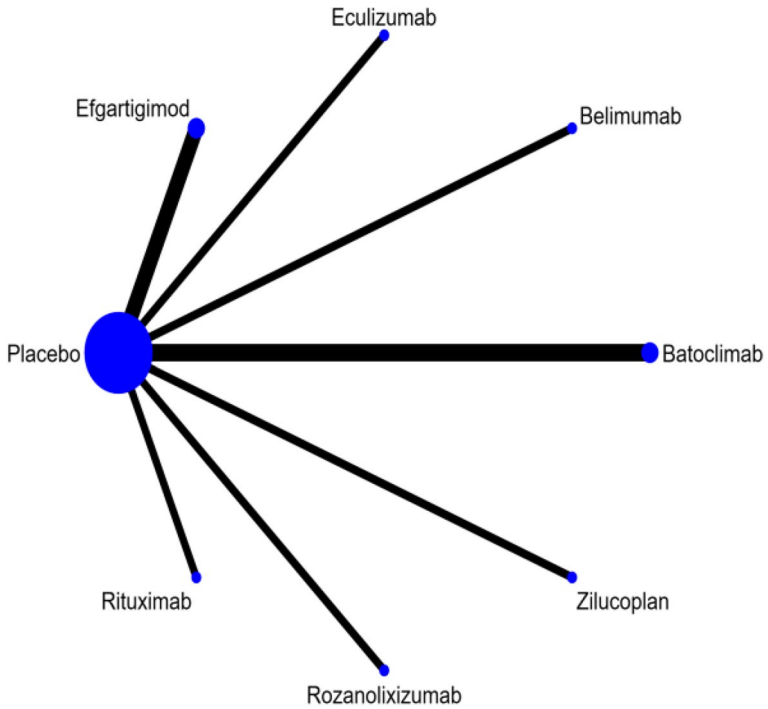

Fig. 7 The batoclimab and efgartigimod as the most commonly reported interventions in the studies included

initiate the classical complement pathway through antigen binding, resulting in the production of terminal complement components. The development of TCC pores induces localized dissolution on the postsynaptic surface, causing a reduction in AChR, sodium channels, and postsynaptic folds. One key step involves the activation of C5 convertase. Strategies aimed at inhibiting the activation of the complement component C5 have significantly enhanced clinical outcomes in complement-related diseases [25]. Eculizumab is a humanized chimeric monoclonal antibody that exhibits high affinity for human C5, preventing its cleavage. This action inhibits the formation of C5a and the terminal C5b-9 complex, thereby obstructing the C5 convertase and limiting the formation of the terminal complement complex (TCC). Eculizumab operates downstream of C3 activation, indicating its therapeutic potential for conditions associated with the overactivation of all three complement pathways [26]. Research indicates that eculizumab can enhance symptoms and quality of life in patients with MG. In the chronic phase, achieving sustained remission and early identification of exacerbations to avert myasthenic crises

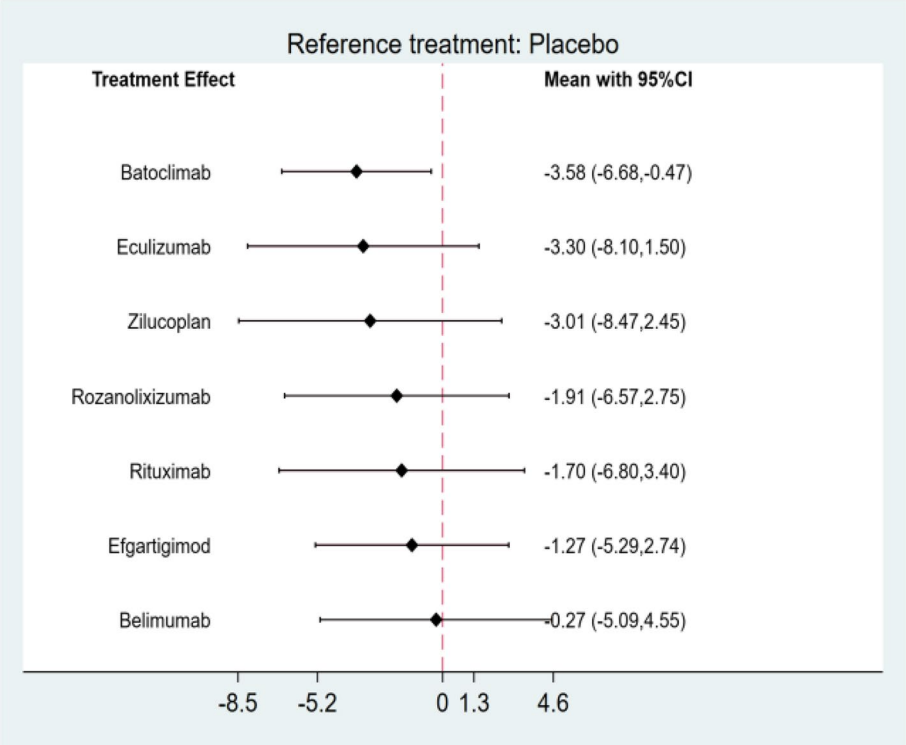

Fig. 8 Batoclimab exhibiting significantly greater efficacy compared to placebo (*MD* = − 3.58, 95% *CI* (− 6.68, − 0.47), *P* < 0.05)

Table 6 Variations existing in the efficacy of seven novel biologics

Eculizumab						
− 2.52 (− 9.51, 4.47)	Zilucoplan					
− 4.02 (− 9.51, 1.48)	− 1.50 (− 6.70, 3.70)	Batoclimab				
− 5.40 (− 11.08, 0.28)	− 2.88 (− 8.28, 2.52)	− 1.38 (− 4.63, 1.87)	Ravulizumab			
− 7.89 (− 14.40, − 1.38)	− 5.37 (− 11.63, 0.90)	− 3.87 (− 8.41, 0.67)	− 2.49 (− 7.26, 2.28)	Rituximab		
− 6.36 (− 12.12, − 0.61)	− 3.84 (− 9.32, 1.63)	− 2.34 (− 5.72, 1.03)	− 0.96 (− 4.63, 2.71)	1.53 (− 3.33, 6.38)	Efgartigimod	
− 7.10 (− 12.20, − 2.00)	− 4.58 (− 9.36, 0.20)	**− 3.08 (− 5.14, − 1.03)**	− 1.70 (− 4.22, 0.82)	0.79 (− 3.26, 4.84)	− 0.74 (− 3.41, 1.94)	Placebo

and respiratory failure is deemed essential. The rapid onset of action, enhanced tolerance, and capacity to slow disease progression and extend survival are critical for the treatment of refractory patients. A consensus among Italian experts indicates that eculizumab may address the treatment requirements of numerous refractory gMG patients; however, further research and evaluation are necessary to assess its treatment effects and side effects.

The TNF family B-cell activation factor (BAFF), or Blys, is regarded as a logical therapeutic target for MG [27]. Elevated serum BAFF levels are observed in patients with MG and thymoma, and a polymorphism in the BAFF gene is linked to susceptibility to MG. Belimumab is a humanized immunoglobulin G1 antibody that inhibits BAFF activity. It is the first specific inhibitor of BLyS, effectively blocking the interaction between soluble BLyS and its receptors on B cells. Approval has been granted for the treatment of systemic lupus erythematosus. Research indicates that belimumab can markedly enhance the symptoms in patients with MG and demonstrates a favorable safety profile. In contrast to rituximab, a chimeric antibody that targets CD20, belimumab

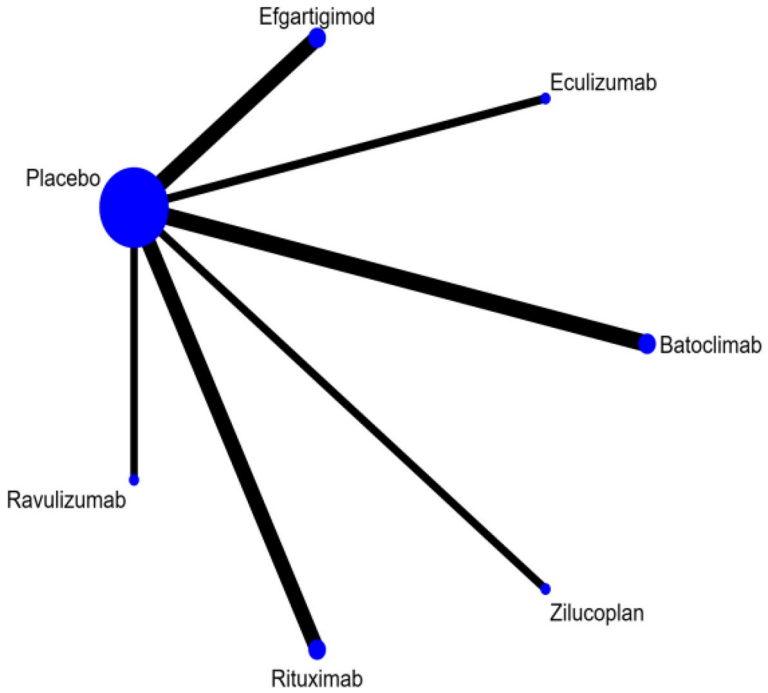

Fig. 9 Unnecessary conductions of an inconsistency test in the absence of closed loops

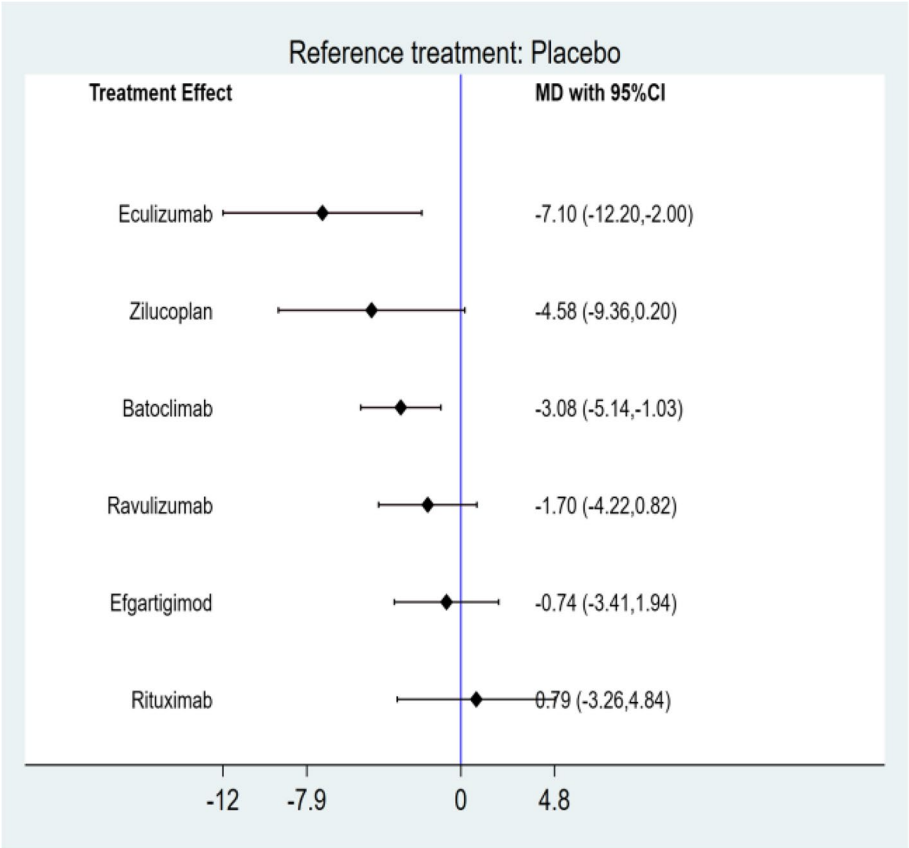

Fig. 10 Eculizumab exhibiting significantly greater efficacy compared to placebo (*MD* = − 7.10, 95% *CI* (− 12.20, − 2.00), *P* < 0.05)

Table 7 Symptoms indicative of autonomic nervous dysfunction

Literature	Intervention measures	Experimental group	Control group
Chong Yan (2022) [12]	Batoclimab 340 mg/ batoclimab 680 mg	Five cases of hyponatremia, two cases of hypomagnesemia, one case of hypoproteinemia, two cases of hyperuricemia, one case of hypokalemia, three cases of dropsy, seven cases of injection site reactions, one case of nausea, one case of toothache, two cases of diarrhea, one case of sore gums, one case of abdominal pain, two cases of muscle twitching, one case of diseases of the skin and subcutaneous tissues, one case of pruritus, one case of rash, one case of sweating at night, one case of cough, one case of sleep disturbances, one case of anxiety, four cases of dizziness, one case of headache, one case of palpitations, one case of blurred vision, one case of frequent urination	Four cases of hyponatremia, three cases of hypomagnesemia, one case of hypokalemia, two cases of injection site reactions, two cases of hypercholesterolemia, four cases of urinary tract infection, one case of upper respiratory tract infections, one case of herpes simplex, one case of folliculitis, one case of blepharitis, one case of weight gain, one case of decreased albumin, one case of increased blood cholesterol, four cases of dizziness, one case of headache
James F. Howard Jr. (2019) [14]	Efgartigimod	Four cases of headache, one case of nausea, one case of diarrhea, one case of abdominal pain, four cases of decreased lymphocyte count, two cases of decreased monocyte count, two cases of increased neutrophil count, two cases of muscle pain, one case of pruritus, one case of runny nose	Three cases of headache, one case of nausea, one case of diarrhea, one case of abdominal pain, two cases of arthralgia, two cases of pruritus, one case of runny nose, two cases of tooth abscess, two cases of toothache
James F. Howard Jr. (2021) [15]	Efgartigimod	Thirty-nine cases of infection, three cases of infusion-related reaction events, twenty-four cases of headache, ten cases of nasopharyngitis, seven cases of nausea, six cases of diarrhea	Thirty-one cases of infection, eight cases of infusion-related reaction events, twenty-three cases of headache, fifteen cases of nasopharyngitis, nine cases of nausea, nine cases of diarrhea
Vera Bri (2021) [16]	Rozanolixizumab	Twelve cases of headache, one case of fatigue, one case of nasopharyngitis, one case of upper respiratory tract infections, one case of muscle twitching, two cases of muscle weakness, one case of dizziness	Two cases of headache, two cases of diarrhea, three cases of fatigue,3 three cases of nasopharyngitis, one case of upper respiratory tract infections, one case of muscle twitching, three cases of dizziness, one case of nausea, one case of vomiting, one case of dyspnea
James F. Howard Jr. (2017) [17]	Eculizumab	Six cases of myasthenia gravis worsens, ten cases of headache, ten cases of upper respiratory tract infections, nine cases of nasopharyngitis, eight cases of nausea, eight cases of diarrhea, six cases of muscle weakness	Fifteen cases of myasthenia gravis worsens, two cases, twelve cases of headache, twelve cases of upper respiratory tract infections, ten cases of nasopharyngitis, nine cases of nausea, eight cases of diarrhea, eleven cases of muscle weakness
James F. Howard Jr. (2020) [18]	Zilucoplan 0.1 mg/kg Zilucoplan 0.3 mg/kg	Two cases of nausea, five cases of injection site reactions, one case of bruising, six cases of headache	One case of injection site reactions, one case of headache
Tuan Vu (2022) [19]	Ravulizumab	Sixteen cases of headache, thirteen cases of diarrhea, nine cases of nausea, one case of myasthenic gravis crisis, two cases of death, one case of difficulty swallowing, one case of tendonitis	Twenty-three cases of headache, eleven cases of diarrhea, nine cases of nausea, two cases of cellulitis, one case of herpes zoster, one case of injection site reactions
Karen Hewett (2018) [20]	Belimumab 10 mg/kg	Three cases of influenza, three cases of nausea, four cases of diarrhea, three cases of headache, three cases of back pain	Six cases of hormonal obesity, ten cases of gastrointestinal reactions. The exact number of other adverse events is not listed
Fredrik Piehl (2022) [21]	Rituximab 500 mg	Seven cases of upper respiratory tract infections, eight cases of musculoskeletal pain, six cases of diarrhea, four cases of nausea, three cases of rash	Eight cases of upper respiratory tract infections, five cases of musculoskeletal pain, two cases of diarrhea, one case of nausea
Richard J. Nowak (2022) [22]	Rituximab	Six cases of arthralgia, eleven cases of headache, twelve cases of upper respiratory tract infections, three cases of fatigue, two cases of back pain, three cases of nausea, four cases of muscle weakness	Thirteen cases of headache, five cases of upper respiratory tract infections, nine cases of fatigue, eleven cases of back pain, ten cases of nausea, four cases of muscle weakness, seven cases of paresthesia

Table 8 SUCRA

Interventions	QMG		MGC		MG-ADL		MG-QoL 15r	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Placebo	17.4	9	20.5	8	18.1	8	17.8	6
Batoclimab	83.4	1	74.5	1	5	9	67.1	3
Efgartigimod	46.9	7	42.5	6	41.8	7	32.4	5
Rituximab	47.3	6	48	5	43.9	6	14.1	7
Rozanolixizumab	31.8	8	51.4	4	54.5	5		
Belimumab	53.8	4	31.4	7	88.5	1		
Zilucoplan	57.4	3	62.7	3	71.7	2	77.6	2
Eculizumab	62.2	2	69.1	2	64	3	93.7	1
Ravulizumab	49.7	5			62.5	4	47.2	4

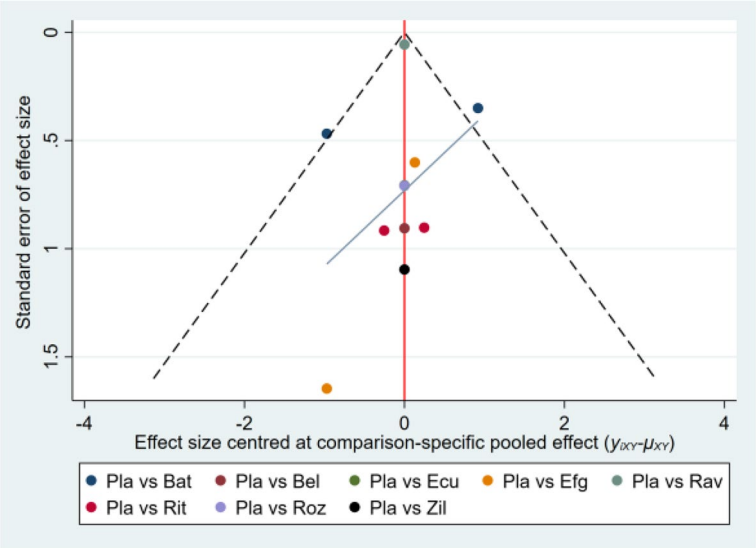

Fig. 11 MG-ADL score

does not directly interact with B cells. Instead, it binds to BLyS, thereby diminishing the differentiation of B cells into plasma cells [28]. Belimumab decreases the quantity of abnormal B cells in patients with myasthenia gravis and facilitates B-cell apoptosis [29, 30].

The strengths and limitations of this study

The research titled "Efficacy of innovative therapies in myasthenia gravis: A systematic review, meta-analysis and network meta-analysis" [31] examined the effectiveness of FcRn blockers and complement inhibitors. In contrast, our study incorporated monoclonal antibodies targeting B cells and addressed both efficacy and acceptability. The diversity of novel biologics and their varying effectiveness highlight a deficiency in direct comparative evidence among these treatments. Consequently, our study employed a network meta-analysis to evaluate the efficacy and safety differences of various novel biologics in the treatment of MG and to rank them, with the objective of offering guidance for clinical decision-making regarding MG treatment.

This study has several limitations that warrant consideration. The quality of the included studies is inadequate. Ten studies employed random number tables for grouping; one study merely stated "random" without detailing the grouping method, and two studies did not address the occurrence of selective reporting, and this may lead to uncertainty in evaluating selection bias. According to the Cochrane Handbook for Systematic Reviews of Interventions, insufficient randomization descriptions may

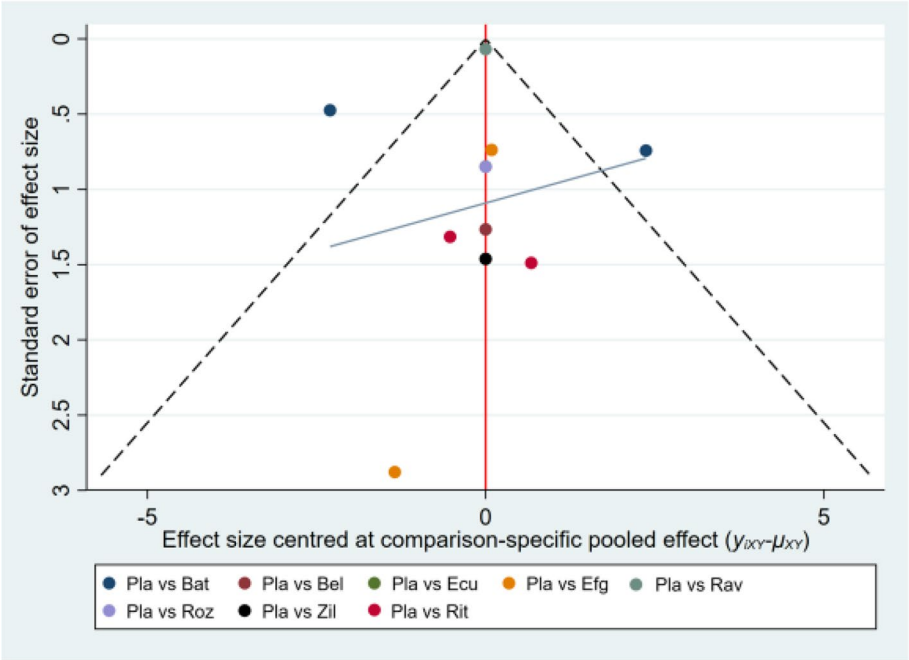

Fig. 12 QMG score

mask systematic errors in the allocation sequence generation process, such as human intervention in grouping leading to baseline imbalance. Future studies must focus on designing research protocols that clearly define the use of randomization methods, implement allocation concealment, and incorporate blinding to improve reporting quality and reduce bias risks. Secondly, the statistical power of this study may be limited because of the prevalence of small-sample studies. Thirdly, the studies reviewed did not detail the methods employed for sample size estimation, potentially affecting the validity of the research outcomes. Therefore, developing accurate methods for determining sample sizes is essential for conducting robust, large-sample clinical studies and producing high-quality evidence. A fourth limitation of our study is the absence of individuals with lived experience of myasthenia gravis at any stage of the research process. Additionally, we did not intend to conduct sex-based or gender-based analyses of the primary outcome. The lack of direct comparative evidence among novel biologics represents a significant limitation, potentially affecting the reliability of the research findings.

Future research should investigate the effects of various novel biologics on serum AChR-Ab levels and daily life abilities to enhance clinical practice guidance. The efficacy of novel biologics in treating myasthenia gravis is established. Nevertheless, the studies included exhibit low methodological quality; thus, these conclusions require further validation through high-quality research.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02859-3.

Supplementary Material 1. Appendix 1. PRISMA-NMA checklist. Appendix 2. Search strategy. Appendix 3. Study protocol. Appendix 4. Excluded articles and reasons for exclusion. Appendix 5. Network plots of acceptability outcome and safety outcomes in myasthenia gravis population. Appendix 6. Included trials for each outcome. Appendix 7. P-scores. Appendix 8. Results of pairwise meta-analyses. Appendix 9. Risk of bias assessment for efficacy outcomes. Appendix 10. Comparison-adjusted funnel plots with Egger's test. Appendix 11. SUCRA Score. Appendix 12. Adverse reactions

Authors' contributions

CG, PZ, and MS designed this study with oversight by PX. CG drafted the manuscript, and the draft was modified by PZ and MS. PZ and MS searched, selected, and identified studies independently, while CG and XD finished data extraction. DL and HC assessed the risk of bias in each included article. PX was responsible for the methodology. All authors have approved the publication of this manuscript.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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