Early Network Meta-Analysis in Generalized Myasthenia Gravis Using Time-Course Adjustment Through Model-Based Network Meta-Analysis

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RESEARCH IN CONTEXT

1. **Conventional NMA methods assume time-invariant effects at a single timepoint, but a prior feasibility assessment found substantial heterogeneity, including time-varying treatment response, across trials, limiting standard NMA validity for this analysis**
2. **A time-course MBNMA accounted for longitudinal efficacy trends to generate time-matched Week 24 estimates across interventions, offering a more robust framework than conventional NMA while flagging key assumptions and evidence gaps**

OBJECTIVE

To estimate the relative efficacy of available treatments for gMG using time-course MBNMA

INTRODUCTION

gMG is a rare, chronic autoimmune neuromuscular disorder marked by unpredictable muscle weakness and fatigue[1,2]

With an evolving treatment landscape and multiple therapies available, comparative evidence on efficacy, safety, and overall value is needed

In the absence of head-to-head trials, NMA[3] enables indirect comparisons; however, heterogeneity in follow-up duration, assessment timepoints and treatment-response trajectories may limit conventional NMA approaches

An MBNMA[4] was therefore conducted to account for differences in follow-up time and estimate comparative treatment effects and response trajectories over time

METHODS

Data sources

- An existing literature review of pharmacological treatments for gMG provided the evidence base for the NMA[5]

Efficacy outcomes included:

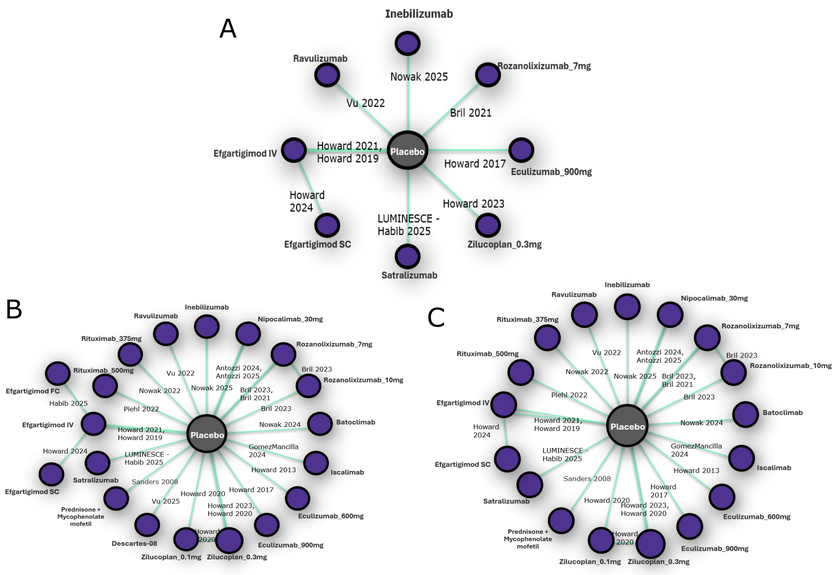
• MG-ADL • QMG • MGC	**≥3-point improvement at Week 24**
• MG-ADL • QMG and MGC scores • Rescue medication use	**CFB at Week 24**
• MG-QoL15r	**Health-related quality of life at Week 24**

- Treatment nodes were defined by treatment, dose and route of administration, with clinically distinct doses or routes modelled separately
- Bayesian estimation was conducted by using MCMC simulations in R
- Details of the statistical methodology are available in the Supplementary Materials via the QR code.

RESULTS

- A total of 21 studies evaluating 14 distinct treatments contributed to the NMA
- The evidence networks (MG-ADL ≥3-point improvement [9 studies], MG-ADL CFB [21 studies], and QMG CFB [19 studies]) were predominantly star-shaped, with limited or no direct head-to-head evidence between active treatments **(Figure 1)**

Figure 1. Evidence networks for (A) MG-ADL ≥3-point improvement, (B) MG-ADL CFB, and (C) QMG CFB at Week 24

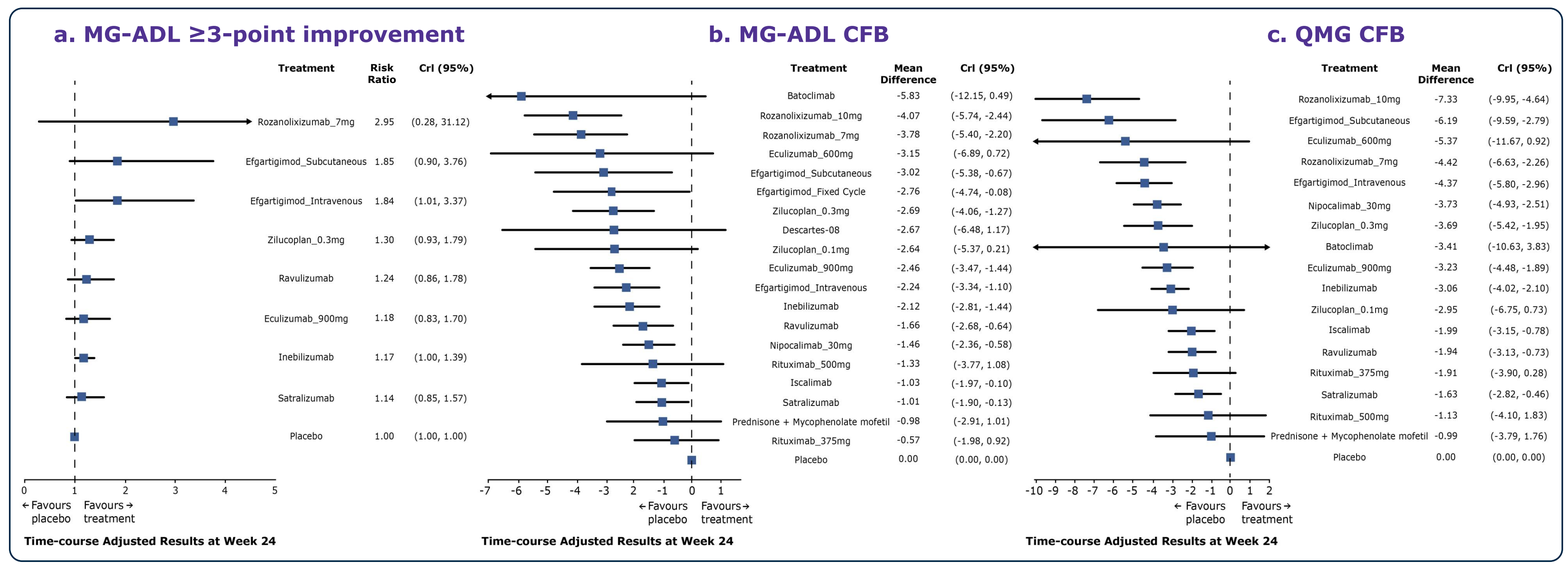


- Further details of the network diagrams and subsequent MBNMA results for MG-ADL ≥2-point responders, MG-ADL 0-1, QMG ≥3-point responders, MGC ≥3-point responders, rescue medication, MGC CFB and MG-QoL15r CFB are available in the **Supplementary Materials**

Summary of relative efficacy of available treatments for gMG at Week 24 using MBNMA

- **MG-ADL ≥3-point improvement:** All treatments showed numerically higher response versus placebo, with clear evidence of benefit for efgartigimod IV and inebilizumab (95% CrI excluded the null; **Figure 2a**)
- **MG-ADL and QMG score CFB:** All treatments showed greater reductions versus placebo; with clear evidence of benefit for rozanolixizumab (7 and 10 mg/kg), efgartigimod (SC, and IV) (95% CrI excluded the null; **Figures 2b and 2c**)

Figure 2. Comparative treatment effect for MG-ADL ≥3-point improvement, MG-ADL CFB, and QMG CFB at Week 24



- Similar favorable treatment effects versus placebo were observed for the remaining outcomes (MGC, MG-QoL15r, rescue therapy); full results are presented in **Table 1**

Table 1. Summary of NMA adjusted at Week 24 using MBNMA

Treatment	MG-ADL				QMG		MGC		Rescue therapy	MG-QoL15r
	0/1 (MSE)	≥2 Point	≥3 Point	CFB	≥3 Point	CFB	≥3 Point	CFB		CFB
BATO	—	—	—	↑	—	↑	—	↑↑	—	—
Descartes-08	↑	—	—	↑	—	—	—	↑	—	—
ECU 600mg	—	↑	—	↑	↑	↑	—	—	—	—
ECU 900mg	↑	—	~	↑↑	—	↑↑	—	↑↑	↑	↑↑
EFG FC	↑	—	—	↑↑	—	—	—	—	—	—
EFG IV	↑	↑↑	↑↑	↑↑	↑↑	↑↑	—	↑↑	—	↑↑
EFG SC	↑	↑↑	↑	↑↑	↑↑	↑↑	—	—	—	—
INEB	—	—	↑↑	↑↑	~	↑↑	—	—	↑	↑↑
ISC	—	—	—	↑↑	~	↑↑	—	↑↑	↓	↑
NIPO 30mg	↑	~	—	↑↑	↑↑	↑↑	—	—	~	↑↑
PD + MMF	—	—	—	↑	—	↑	—	—	—	—
RAVU	—	~	↑	↑↑	↑	↑↑	—	—	~	↑
ROZA 7mg	↑	↑↑	↑	↑↑	↑	↑↑	↑	↑↑	↑	↑↑
ROZA 10mg	↑	↑↑	—	↑↑	↑	↑↑	↑	↑↑	↑	↑↑
RTX 375mg	—	—	—	↑	~	↑	~	↑	↑	↑
RTX 500mg	—	—	—	↑	—	↑	—	—	↑	↑
SATR	~	~	~	↑↑	↑	↑↑	—	↑↑	↑	↑
ZILU 0.3mg	↑	~	↑	↑↑	~	↑↑	~	↑↑	↑	↑↑
ZILU 0.1mg	↑	—	—	↑	~	↑	—	↑	↑	↑↑

↑Favourable results compared to placebo; ↑↑statistically significant ($p<0.05$) results in favour of intervention; ↓lower efficacy compared to placebo; ~ Comparable efficacy of intervention and placebo; —, analysis was not feasible for comparisons

Summary of SUCRA-based treatment rankings for efficacy outcomes at Week 24

- Rozanolixizumab (7 and 10 mg/kg) and efgartigimod (SC, fixed-cycle, and IV) consistently ranked among the top-performing treatments across efficacy outcomes **(Table 2)**
- Eculizumab ranked favorably for MG-QoL15r; batoclimab ranked favorably for MG-ADL and MGC; zilucoplan showed favorable but less consistent rankings across endpoints **(Table 2)**

Table 2. Summary of SUCRA-based Treatment Rankings for Efficacy Outcomes at Week 24

Treatment ranks	MG-ADL				QMG		MGC		Rescue therapy	MG-QoL15r
	0/1 (MSE)	≥2 Point improvement	≥3 Point improvement	CFB	≥3 Point improvement	CFB	≥3 Point improvement	CFB		CFB
1	ROZA 10 mg	ROZA 7 mg	EFG IV	ROZA 10 mg	EFG SC	ROZA 10 mg	ROZA10 mg	ROZA 10 mg	RTX 500 mg	ECU 900 mg
2	ROZA 7 mg	ROZA 10 mg	EFG SC	BATO	EFG IV	EFG SC	ROZA 7 mg	BATO	ROZA 7 mg	ROZA 10 mg
3	ECU 900 mg	EFG IV	ROZA 7 mg	ROZA 7 mg	ROZA 10 mg	EFG IV	ZILU 0.3 mg	ROZA 7 mg	INEB	NIPO 30 mg
4	EFG FC	EFG SC	RAVU	EFG SC	NIPO 30 mg	ECU 600 mg	RTX 375 mg	EFG IV	ZILU 0.3 mg	EFG IV
5	EFG IV	ECU 600 mg	ZILU 0.3 mg	ECU 600 mg	RAVU	ROZA 7 mg	Pla	ECU 900 mg	ZILU 0.1 mg	ZILU 0.1 mg
6	EFG SC	NIPO 30 mg	ECU 900 mg	ZILU 0.3 mg	ROZA 7 mg	NIPO 30 mg		ZILU 0.3 mg	ROZA 10 mg	ROZA 7 mg
7	ZILU 0.3 mg	SATR	INEB	EFG FC	SATR	ZILU 0.3 mg		Descartes-08	RTX 375 mg	ISC
8	NIPO 30 mg	ZILU 0.3 mg	SATR	ECU 900 mg	ECU 600 mg	ECU 900 mg		SATR	SATR	ZILU 0.3 mg
9	Descartes-08	RAVU	Pla	ZILU 0.1 mg	INEB	BATO		ISC	ECU 900 mg	RTX 500 mg
10	ZILU 0.1 mg	Pla		Descartes-08	ZILU 0.3 mg	INEB		ZILU 0.1 mg	RAVU	INEB
11	SATR			EFG IV	RTX 375 mg	ZILU 0.1 mg		RTX 375 mg	NIPO 30 mg	RAVU
12	Pla			INEB	ZILU 0.1 mg	ISC		Pla	Pla	SATR
13				RAVU	ISC	RTX 375 mg			ISC	RTX 375 mg
14				NIPO 30 mg	Pla	RAVU				Pla
15				RTX 500 mg		SATR				
16				PD + MMF		RTX 500 mg				
17				ISC		PD+MMF				
18				SATR		Pla				
19				RTX 375 mg						
20				Pla						

CONCLUSIONS

- **Time-course adjusted MBNMA provided a valuable framework for synthesizing comparative evidence across targeted therapies, identifying clinically relevant improvements in MG-ADL and QMG versus placebo at Week 24 and highlighting potential differences in treatment effects across interventions**
- **Despite the challenges of a predominantly placebo-controlled network and the inability to adjust for key cross-trial effect modifiers (including antibody status, baseline disease severity, and prior treatment), these findings offer useful insights into the comparative efficacy landscape. Population-adjusted indirect comparisons, such as ML-NMR or MAICs, could further strengthen the evidence by accounting for differences in trial populations**

Abbreviations: **BATO**, batoclimab; **CFB**, change from baseline; **CrI**, credible interval; **ECU**, eculizumab; **EFG**, efgartigimod; **FA**, feasibility assessment; **FC**, fixed cycle; **gMG**, generalized myasthenia gravis; **INEB**, inebilizumab; **ISC**, iscalimab; **IV**, intravenous; **MAICs**, matching-adjusted indirect comparisons; **MBNMA**, model-based network meta-analysis; **MCMC**, Markov chain Monte Carlo; **MG-ADL**, myasthenia gravis activities of daily living; **MGC**, myasthenia gravis composite; **MG-QoL15r**, myasthenia gravis quality of life – 15-item revised; **ML-NMR**, multilevel network meta-regression; **MMF**, mycophenolate mofetil; **MSE**, minimal symptom expression; **NIPO**, nipocalimab; **NMA**, network meta-analysis; **PD**, prednisone; **Pla**, placebo; **QMG**, quantitative myasthenia gravis; **RAVU**, ravulizumab; **ROZA**, rozanolixizumab; **RTX**, rituximab; **SATR**, satralizumab; **SC**, subcutaneous; **SUCRA**, surface under the cumulative ranking curve; **ZILU**, zilucoplan

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