NETWORK META-ANALYSIS OF TREATMENT OPTIONS IN GENERALIZED MYASTHENIA GRAVIS: IMPACT ON HEALTH-RELATED QUALITY OF LIFE OUTCOME

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Introduction

- Generalized myasthenia gravis (gMG) is a chronic autoimmune neuromuscular condition that causes muscle weakness in different parts of the body.[1,2,3] Approximately 85% of these patients have anti-acetylcholine receptor antibody-positive (anti-AChR Ab+) disease.[4]
- Patients with gMG may experience debilitating and potentially life-threatening symptoms, which can have a profound negative impact on activities of daily living, physical functioning and quality of life (QoL).[5,6]
- Patient-centric outcomes including EuroQol-5 Dimension visual analog scale (EQ-5D VAS) and Myasthenia Gravis-Quality of Life 15-item revised scale (MG-QoL15r) can help guide treatment decisions for gMG.
- Conventional therapies (CT) are commonly used as initial treatments, however, a proportion of patients with gMG are inadequately managed with CT.[7]
- The US Food and Drug Administration (FDA) has approved several new agents for gMG in recent years, including eculizumab, efgartigimod, ravulizumab and rozanolixizumab. The FDA also accepted a new drug application for zilucoplan.
- Despite the availability of these new treatment options, there is limited evidence comparing their effects on health-related quality of life (HRQoL) outcomes in gMG patients.

Objective

- To compare HRQoL outcomes of efgartigimod, ravulizumab, rozanolixizumab and zilucoplan for anti-AChR Ab+ gMG.

Methods

Data source

- A targeted literature review (TLR) was performed to identify clinical trials assessing HRQoL outcomes in patients with gMG.
- Data from phase III clinical trials of efgartigimod (ADAPT, NCT03669588)[8], ravulizumab (CHAMPION, NCT01997229)[9], rozanolixizumab (MycarinG, NCT02473952)[10] and zilucoplan (RAISE, NCT04115293)[11] were used in this Bayesian network meta-analysis (NMA) (**Table 1**). The phase III trial of eculizumab (REGAIN, NCT01997229)[12] was not included in this analysis due to lack of commonly assessed HRQoL outcomes.
- Key baseline characteristics from respective trials are presented in **Table 2**.
- Change from baseline values of EQ-5D VAS and MG-QoL15r measures at the primary timepoint of assessment in the respective clinical trial were assessed
  - **EQ-5D VAS** records the patient's current self-rated health on a vertical visual analogue scale. EQ-5D VAS ranges from 0 to 100, with higher scores indicating better HRQoL.
  - **MG-QoL15r** is a 15-item disease-specific HRQoL scale designed to assess the patient's experience related to MG. MG-QoL15r ranges from 0 to 30, with lower scores indicating better HRQoL.

Table 1. Clinical trials of efgartigimod, ravulizumab, rozanolixizumab and zilucoplan in gMG

	ADAPT (NCT03669588)[8]	CHAMPION (NCT03920293)[9]	MycarinG (NCT03971422)[10]	RAISE (NCT04115293)[11]
Study design	Phase 3, 1:1 to efgartigimod intravenous (IV) or placebo	Phase 3, 1:1 to ravulizumab IV or placebo	Phase 3, 1:1:1 to rozanolixizumab 10mg/kg subcutaneous (SC) or rozanolixizumab 7mg/kg SC or placebo	Phase 3, 1:1 to zilucoplan SC or placebo
Population	167 gMG patients ▪ Myasthenia Gravis Foundation of America (MGFA) Class II to IV ▪ anti-AChR Ab+/- * ▪ Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 ▪ On a stable dose of at least one gMG treatment throughout the trial	75 gMG patients ▪ MGFA Class II to IV ▪ anti-AChR Ab+ ▪ MG-ADL score ≥6 ▪ Stable-dose gMG treatments were permitted throughout the trial	200 gMG patients ▪ MGFA Class II to IVa ▪ anti-AChR Ab+ or anti-MuSK Ab+ ▪ MG-ADL score ≥3 (non-ocular symptoms) ▪ Quantitative Myasthenia Gravis (QMG) ≥11 ▪ Stable-dose gMG treatments were permitted throughout the trial	174 gMG patients ▪ MGFA Class II to IV ▪ anti-AChR Ab+ ▪ MG-ADL score ≥6 ▪ QMG ≥12 ▪ Stable-dose gMG treatments were permitted throughout the trial
Dosing schedule	10mg/kg at weekly intervals for 4 weeks followed by a 5-week period with no infusions and individualized treatment schedule.	Single loading dose on day 1 followed by maintenance doses on day 15 and every 8 weeks through week 26.	10mg/kg or 7mg/kg SC infusions once a week for 6 weeks	0.3mg/kg SC injections administered daily for 12 weeks
Primary timepoint of assessment	Week 4	Week 26	Week 6	Week 12

*Anti-AChR Ab+ population (N=129) was used in this analysis.

Table 2. Baseline characteristics of clinical trials included

Study acronym (NCT #)		ADAPT (NCT03669588)*,*		CHAMPION (NCT03920293)[9]		MycarinG (NCT03971422)[10]			RAISE (NCT04115293)[11]	
Treatment		Efgartigimod (n=65)	Placebo (n=64)	Ravulizumab (n=86)	Placebo (n=89)	Rozanolixizumab 7mg/kg (n=66)	Rozanolixizumab 10mg/kg (n=67)	Placebo (n=67)	Zilucoplan (n=86)	Placebo (n=88)
Age, years (standard deviation [SD])		44.7 (15.0)	49.2 (15.5)	58.0 (13.8)	53.3 (16.1)	53.2 (14.7)	51.9 (16.5)	50.4 (17.7)	52.6 (14.6)	53.3 (15.7)
Sex, female (%)		46 (71%)	40 (63%)	44 (51%)	45 (51%)	39 (59%)	35 (52%)	47 (70%)	52 (60%)	47 (53%)
Race (%)	White	54 (83%)	56 (88%)	67 (78%)	61 (69%)	41 (62%)	49 (73%)	46 (69%)	66 (77%)	62 (70%)
	Non-white and not reported	11 (17%)	8 (12%)	19 (22%)	28 (31%)	25 (38%)	18 (27%)	21 (31%)	20 (23%)	26 (30%)
MGFA class (%)	II	28 (43%)	25 (39%)	39 (45%)	39 (44%)	29 (44%)	26 (39%)	23 (34%)	22 (26%)	27 (31%)
	III	35 (54%)	36 (56%)	41 (48%)	45 (51%)	34 (52%)	39 (58%)	41 (61%)	60 (70%)	57 (65%)
	IV	2 (3%)	3 (5%)	6 (7%)	5 (6%)	3 (5%)	2 (3%)	3 (4%)	4 (5%)	4 (5%)
MG-ADL score (SD)		9.0 (2.5)	8·6 (2.1)	9.1 (2.6)	8.9 (2.3)	8.4 (3.8)	8.1 (2.9)	8.4 (3.4)	10.3 (2.5)	10.9 (3.4)
QMG score (SD)		16.0 (5.1)	15.2 (4.4)	14.8 (5.2)	14.5 (5.3)	15.4 (3.7)	15.6 (3.7)	15.8 (3.5)	18.7 (3.6)	19.4 (4.5)

* ADAPT trial baseline characteristics reflective of the anti-AChR Ab+ population.

Table 3. Efficacy inputs

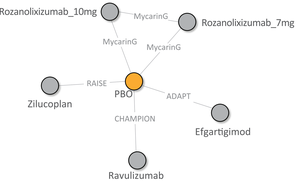
Study acronym	Treatment	Sample Size*	Mean change from baseline	Standard Error†
EQ-5D VAS				
ADAPT	Placebo	60	4.10	1.64
	Efgartigimod	63	15.80	2.20
CHAMPION	Placebo	89	2.70	2.07
	Ravulizumab	86	4.00	2.12
MycarinG	Placebo	67	6.10	2.22
	Rozanolixizumab 10 mg/kg	67	11.40	2.05
	Rozanolixizumab 7mg/kg	66	12.20	2.45
RAISE	Placebo	88	5.81	2.11
	Zilucoplan	86	8.97	2.11
MG-QoL15r				
ADAPT	Placebo	60	-2.30	0.51
	Efgartigimod	63	-7.30	0.79
CHAMPION	Placebo	82	-1.60	0.70
	Ravulizumab	78	-3.30	0.71
MycarinG	Placebo	67	-1.30	0.53
	Rozanolixizumab 10 mg/kg	67	-5.30	0.72
	Rozanolixizumab 7mg/kg	66	-4.00	0.75
RAISE	Placebo	88	-3.16	0.76
	Zilucoplan	86	-5.65	0.78

* Sample sizes reflective of available data at the primary timepoint of assessment of each trial.
† Standard errors were not reported in the RAISE trial for the EQ-5D VAS outcome and were imputed using the average of available standard errors from other trials.

Statistical analyses

- A Bayesian NMA was conducted using data from four trials. (**Figure 1**)
- NMA is the most commonly used indirect treatment comparison approach in the absence of head-to-head clinical trials comparing multiple treatments simultaneously as long as they can be connected in one network.
- Due to lack of established minimal clinically important difference (MCID) in EQ-5D VAS and MG-QoL15r measures in gMG, MCIDs were calculated using distribution-based approach as half of the average standard deviation from all treatment arms. This approximation is a commonly accepted MCID value for patient-reported outcomes in literatures.[13]

Figure 1. NMA evidence network

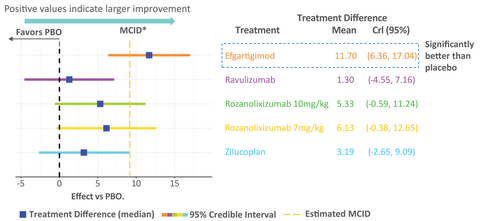


Results

EQ-5D VAS, comparing interventions to placebo (Figure 2)

- Compared to placebo, efgartigimod had significantly larger improvement in EQ-5D VAS.
- Median EQ-5D VAS improvement with efgartigimod exceeded the estimated MCID value of 9.09.

Figure 2. Effect of treatments compared to placebo in EQ-5D VAS



* MCID of EQ-5D VAS was 9.09 and was calculated as half of the average standard deviation from all treatment arms.

EQ-5D VAS and MG-QoL15r, comparing interventions with efgartigimod as reference (Table 4)

- In EQ-5D VAS, efgartigimod demonstrated significantly greater improvement compared to ravulizumab and zilucoplan.
- In MG-QoL15r, efgartigimod demonstrated significantly greater improvement compared to ravulizumab.

Table 4. Effect of efgartigimod compared with other treatments in EQ-5D VAS and MG-QoL15r outcomes, median differences (95% CrI)

For EQ-5D VAS, positive differences indicate more improved HRQoL by efgartigimod; for MG-QoL15r, negative differences indicate more improved HRQoL by efgartigimod.

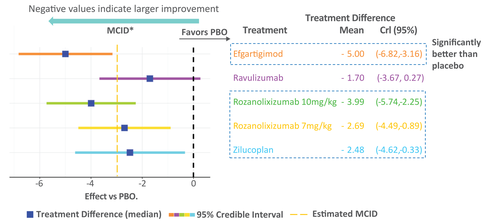
Treatment	EQ-5D VAS	MG-QoL15r
Ravulizumab	**10.39 (2.39, 18.31)***	**-3.29 (-6.01, -0.61)***
Rozanolixizumab 10 mg/kg	6.39 (-1.52, 14.31)	-1.00 (-3.52, 1.51)
Rozanolixizumab 7 mg/kg	5.57 (-2.98, 13.91)	-2.31 (-4.90, 0.26)
Zilucoplan	**8.50 (0.68, 16.46)***	-2.52 (-5.29, 0.31)

* indicates the difference between efgartigimod and comparator is significant

MG-QoL15r, comparing interventions to placebo (Figure 3)

- Compared to placebo, efgartigimod, rozanolixizumab 7mg/kg, 10mg/kg and zilucoplan had significantly larger improvement in MG-QoL15r.
- Median MG-QoL15r improvement with efgartigimod and rozanolixizumab 10mg/kg exceeded the estimated MCID value of -2.97.

Figure 3. Effect of treatments compared to placebo in MG-QoL15r

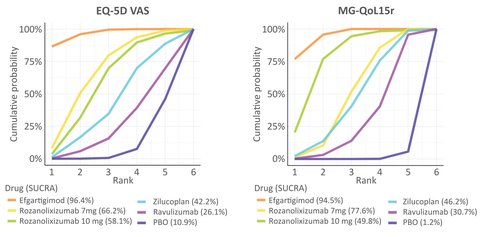


* MCID of MG-QoL15r was -2.97 and was calculated as half of the average standard deviation from all treatment arms.

Ranking probabilities of treatments

- Efgartigimod had the highest probabilities of being ranked first in both EQ-5D VAS and MG-QoL15r, and the highest cumulative probabilities of being the best in any position per surface under the cumulative ranking curve (SUCRA). (**Figure 4**).

Figure 4. SUCRA plots for EQ-5D VAS and MG-QoL15r



Limitations

- The inclusion and exclusion criteria and baseline patient characteristics looked similar across trials, however, NMA comparisons could be biased by differences in unobserved effect modifiers. Meta-regression, however, is not feasible due to the sparsity of the networks.
- The MCIDs of the HRQoL outcomes were estimated using distribution-based approach in the absence of established MCIDs for these two outcomes in gMG. Future studies using anchor-based approaches would be valuable to validate these MCID values.
- The HRQoL outcomes were measured at the primary timepoints of assessment in respective trials, which were different across trials and had varying places in the dosing schedules. This inconsistency could not be addressed in meta-analysis relying on existing data.

Discussion and Conclusions

- **The results suggested efgartigimod was associated with greater degree of improvement in EQ-5D VAS (compared to ravulizumab and zilucoplan) and MG-QoL15r (compared to ravulizumab) among patients with gMG.**
- **The findings were consistent with the results from Saccà 2023 et al., where they concluded that anti-neonatal Fc receptor (FcRn) inhibitors (efgartigimod and rozanolixizumab) were more effective than anti-complement inhibitors (eculizumab, ravulizumab and zilucoplan) on the MG-QoL15r outcome (the MG-QoL15 was used in the REGAIN study for eculizumab).[14]**
- **The primary endpoint measurement time was used to compare efficacy measures across trials. The same approach was used by Saccà et al. in NMA.[14] This allows a comparison of treatments at a time where patients were consistently receiving treatment.**

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Abbreviations

anti-AChR Ab+, anti-acetylcholine receptor antibody-positive; CrI, credible interval; CT, conventional therapy; EQ-5D VAS; EuroQol-5 Dimension visual analog scale; FcRn, neonatal Fc receptor; FDA, Food and Drug Administration; gMG, generalized myasthenia gravis; HRQoL, health-related QoL; IV, intravenous; MCID, minimal clinically important difference; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Myasthenia Gravis-Quality of Life 15-item revised scale; NMA, network meta-analysis; QMG, Quantitative Myasthenia Gravis; QoL, quality of life; SC, subcutaneous; SD, standard deviation; SUCRA, surface under the cumulative ranking curve; TLR, targeted literature review.

References

1. Behin A et al. J Neuromusc Dis. 2018;5(3):265-277.
2. Grob D et al. Muscle Nerve. 2008;37(2):141-149.
3. National Institutes of Health (NIH). Myasthenia gravis information page. National Institute of Neurological Disorders and Stroke. Accessed April 4, 2022. https://www.ninds.nih.gov/Disorders/All-Disorders/Myasthenia-Gravis-Information-Page#disorders-r1
4. Lazaridis K et al. Frontiers in Immunology. 2020;11. doi:10.3389/fimmu.2020.00212
5. Muley S et al. Carrell-Krusen Neuromuscular Symposium. 2021.
6. Centre for International Economics. The cost to patients and the community of Myasthenia Gravis. 2013.
7. Dalakas MC. Curr Opin Neurol. 2020;33(5):545-52.
8. Howard Jr JF et al. Lancet Neurol. 2021;20(7):526-36.
9. Vu et al. NEJM Evid 2022;1(5).
10. Bril et al. Lancet Neurol. 2023;22:383-94.
11. Howard Jr JL et al. Lancet Neurol. 2023;22:395-406.
12. Howard Jr JF et al. Lancet Neurol. 2017;16(12):976-986.
13. Norman et al. Medical care. 2003; 582-92.
14. Saccà et al. Eur J Neurol. 2023; 10.1111