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Comparative Risk-Benefit Profiles of Immunomodulatory Therapies for Patients With Generalized Myasthenia Gravis

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BACKGROUND

- gMG is a chronic autoimmune neuromuscular condition that causes muscle weakness in different parts of the body.[1–3] Approximately 85% of these patients have anti-AChR Ab+ disease[4]
- Several novel immunomodulatory therapies have been approved in the United States for anti-AChR Ab+ gMG, including neonatal Fc receptor inhibitors (efgartigimod IV [VYVGART®] and PH20 SC [VYVGART Hytrulo®], rozanolixizumab [RYSTIGGO®]) and complement inhibitors (ravulizumab [ULTOMIRIS®], zilucoplan [ZILBRYSQ®]). In addition, 2 new treatments (inebilizumab, a CD19-targeting monoclonal antibody, and nipocalimab, an Fc receptor inhibitor) are either currently under regulatory review or will undergo evaluation for gMG
- With the availability of these new treatment options for gMG, it is important for health care providers, payers, and other stakeholders to understand their relative benefits, which have not yet been fully compared in the literature

OBJECTIVE

To compare efficacy outcomes of efgartigimod, inebilizumab, nipocalimab, ravulizumab, rozanolixizumab, and zilucoplan as treatments for anti-AChR Ab+ gMG

METHODS

Data Source

- Data from phase 3 placebo-controlled clinical trials of efgartigimod (ADAPT, NCT03669588),[5] inebilizumab (MINT, NCT04524273),[6] nipocalimab (VIVACITY-MG3, NCT04951622),[7] ravulizumab (CHAMPION, NCT01997229),[8] rozanolixizumab (MycarinG, NCT02473952),[9] and zilucoplan (RAISE, NCT04115293)[10] were used in this Bayesian NMA (**Table 1**)
  - Trial inclusion/exclusion criteria were generally similar
  - ADAPT, MINT, VIVACITY-MG3, and MycarinG trials included anti-AChR Ab+ and anti-AChR Ab- and/or anti-MuSK Ab+ and anti-LRP4 Ab+ patients. Data for anti-AChR Ab+ patients were used in this analysis where available
- Key baseline characteristics from the respective trials are presented in **Table 2**
- Efficacy outcomes including proportion of patients achieving ≥3- and ≥5-point reductions from baseline for MG-ADL, proportion of patients achieving ≥3- and ≥5-point reductions from baseline for QMG, and changes from baseline in QMG and MG-ADL scores. Primary time points of assessment in the respective clinical trials were assessed (**Table 2, 3**)
  - MG-ADL is an 8-item patient-recorded outcome measure assessing MG symptoms and their impact on daily living.[11] The total score ranges from 0 to 24, with higher score indicating more disability
  - QMG is a quantitative examiner assessment of patient function across 13 domains, based on strength and endurance of specific muscle groups. The total score ranges from 0 to 39, with higher score indicating more severe disease[12]

Statistical Analyses

- A **Bayesian NMA** was conducted using data from respective clinical trials based on the network (**Figure 1a, 1b**). Based on the NMA results, the NNT was estimated for each treatment
- 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 1 network
- Based on the NMA results, the NNT was estimated for each treatment versus placebo. For rozanolixizumab, the 10 mg/kg and 7 mg/kg arms were combined for the NNT analysis, as the product label specifies that dosing is weight-based rather than consisting of 2 distinct fixed doses. Since NNT is a population-level metric, the 2 dosing groups were combined using a sample size weighted average for the analysis

FIGURE 1A NMA Evidence Network (Continuous Outcomes)

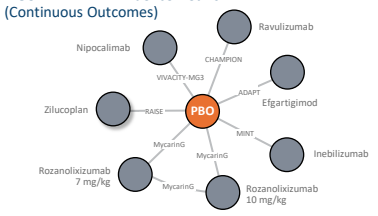
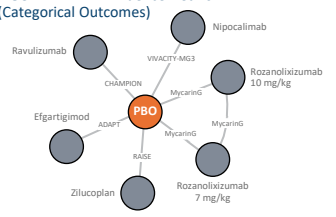


FIGURE 1B NMA Evidence Network (Categorical Outcomes)



- NNT represents the number of patients needed to treat to achieve 1 additional improved outcome relative to placebo[13]
- For example, an NNT of 3 means that 3 patients need to be treated with the active treatment vs placebo to achieve 1 additional responder

$$\text{NNT} = \frac{1}{\text{Clinical response rate of active treatment} - \text{Clinical response rate of placebo}}$$

TABLE 1 Phase 3 Clinical Trials of Efgartigimod, Inebilizumab, Nipocalimab, Ravulizumab, Rozanolixizumab, and Zilucoplan in gMG

	ADAPT (NCT03669588)[5]	MycarinG (NCT03971422)[9]	VIVACITY-MG3 (NCT04951622)[7]	CHAMPION (NCT03920293)[8]	RAISE (NCT04115293)[10]	MINT (NCT04524273)[6]
Study design	1:1 to efgartigimod IV or placebo	1:1:1 to rozanolixizumab 10 mg/kg SC or rozanolixizumab 7 mg/kg SC or placebo	1:1 to nipocalimab IV or placebo	1:1 to ravulizumab IV or placebo	1:1 to zilucoplan SC or placebo	1:1 to inebilizumab IV or placebo
Population	167 gMG patients ▪ MGFA class II to IV ▪ anti-AChR Ab+/- (N=129 anti-AChR Ab+ population was considered in this analysis) ▪ MG-ADL score ≥5 ▪ On a stable dose of ≥1 gMG treatment throughout the trial	200 gMG patients ▪ MGFA class II to IVa ▪ anti-AChR Ab+ or anti-MuSK Ab+ ▪ MG-ADL score ≥3 ▪ QMG ≥11 ▪ Stable-dose gMG treatments were permitted throughout the trial	196 gMG patients ▪ MGFA class II to IV ▪ anti-AChR Ab+ or anti-MuSK Ab+ or anti-LRP4 Ab+ or triple-antibody-negative (N=153 antibody-positive population was considered in this analysis) ▪ MG-ADL score ≥6 ▪ Stable-dose gMG treatments were permitted throughout the trial	175 gMG patients ▪ MGFA class II to IV ▪ anti-AChR Ab+ ▪ MG-ADL score ≥6 ▪ Stable-dose gMG treatments were permitted throughout the trial	175 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	238 gMG patients ▪ MGFA class II to IV ▪ anti-AChR Ab+ or anti-MuSK Ab+ ▪ MG-ADL score ≥6 ▪ QMG ≥11 ▪ On a stable dose of allowed gMG treatment
Dosing schedule	10 mg/kg at weekly intervals for 4 weeks followed by a 5-week period with no infusions in the initial cycle and individualized treatment schedule according to clinical evaluation	10 mg/kg or 7 mg/kg SC infusions once a week for 6 weeks	IV infusions with loading dose 30 mg/kg at Week 0, then 15 mg/kg every 2 weeks up to 24 weeks	Single loading dose on Day 1 followed by maintenance doses on Day 15 and every 8 weeks through Week 26	0.3 mg/kg SC injections administered daily for 12 weeks	300 mg IV infusions on Days 1, 15, 183
Primary time point of assessment	Week 4	Week 6	Week 24	Week 26	Week 12	Week 26

TABLE 2 Efficacy Inputs, Continuous Outcomes*

Study acronym	Change in QMG From Baseline, Mean (SE)		Change in MG-ADL From Baseline, Mean (SE)	
	Treatment	Placebo	Treatment	Placebo
ADAPT[5]	−6.20 (0.70)	−1.00 (0.40)	−4.60 (0.40)	−1.75 (0.30)
MycarinG[9]	10 mg/kg: −6.67 (0.69); 7 mg/kg: −5.40 (0.68)	−1.92 (0.68)	10 mg/kg: −3.40 (0.49); 7 mg/kg: −3.37 (0.49)	−0.78 (0.49)
VIVACITY-MG3[7]	−4.89 (0.54)	−2.01 (0.50)	−5.06 (0.37)	−3.44 (0.36)
CHAMPION[8]	−2.80 (0.46)	−0.80 (0.45)	−3.10 (0.38)	−1.40 (0.37)
RAISE[10]	−6.19 (0.56)	−3.25 (0.55)	−4.39 (0.45)	−2.30 (0.44)
MINT[6]	−4.40 (0.55)	−2.00 (0.58)	−4.20 (0.40)	−2.40 (0.41)

*Data among patients with anti-AChR Ab+ gMG were used for the ADAPT, CHAMPION, MINT, VIVACITY-MG3, and RAISE trials. Data among patients with anti-AChR Ab+ or anti-MuSK Ab+ gMG were used for the MycarinG trial.

TABLE 3 Efficacy Inputs, Categorical Outcomes*

Study acronym	≥3-Point Improvement in QMG Score		≥5-Point Improvement in QMG Score		≥3-Point Improvement in MG-ADL		≥5-Point Improvement in MG-ADL	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
ADAPT[5]	74%	26%	60%	12%	73%	37%	56%	12%
MycarinG[9]	10 mg/kg: 71%; 7 mg/kg: 51%	40%	10 mg/kg: 48%; 7 mg/kg: 45%	15%	10 mg/kg: 57%; 7 mg/kg: 55%	20%	10 mg/kg: 33%; 7 mg/kg: 31%	10%
VIVACITY-MG3[7]	45%	28%	43%	16%	60%	36%	44%	18%
CHAMPION[8]	45%	24%	30%	11%	57%	34%	32%	15%
RAISE[10]	77%	55%	62%	38%	78%	53%	54%	29%

*Data among patients with anti-AChR Ab+ gMG were used for the ADAPT, CHAMPION, and RAISE trials. Data among patients with anti-AChR Ab+ or anti-MuSK Ab+ gMG were used for the MycarinG trial. Data among patients with anti-AChR Ab+, anti-MuSK Ab+, or LRP4 Ab+ gMG were used for the VIVACITY-MG3 trial.

RESULTS

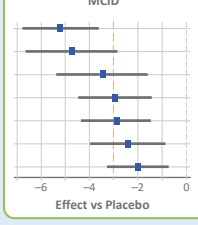
QMG Change From Baseline (Figure 2)

- Compared with placebo, all active treatments achieved significantly larger improvement in change from baseline in QMG
- Mean QMG improvement with efgartigimod and rozanolixizumab 10 mg/kg and 7 mg/kg had exceeded the commonly cited MCID value of ≥3-point improvement from baseline in QMG

MG-ADL Change From Baseline (Figure 3)

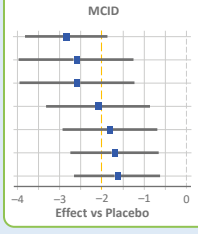
- Compared with placebo, all active treatments achieved significantly larger improvement in change from baseline in MG-ADL
- Mean MG-ADL improvement with efgartigimod, rozanolixizumab 10 mg/kg and 7 mg/kg, and zilucoplan had exceeded the commonly cited MCID value of ≥2-point improvement from baseline in MG-ADL

FIGURE 2 Effect of Treatments Compared With Placebo in QMG Change From Baseline



Treatment	Treatment Difference (Mean)	CrI (95%)
Efgartigimod	−5.20	(−6.77, −3.61)
Rozanolixizumab 10 mg/kg	−4.73	(−6.63, −2.81)
Rozanolixizumab 7 mg/kg	−3.45	(−5.37, −1.58)
Zilucoplan	−2.94	(−4.47, −1.41)
Nipocalimab	−2.89	(−4.36, −1.45)
Inebilizumab	−2.41	(−3.97, −0.83)
Ravulizumab	−2.00	(−3.26, −0.72)

FIGURE 3 Effect of Treatments Compared With Placebo in MG-ADL Change From Baseline



Treatment	Treatment Difference (Mean)	CrI (95%)
Efgartigimod	−2.85	(−3.82, −1.86)
Rozanolixizumab 10 mg/kg	−2.60	(−3.97, −1.24)
Rozanolixizumab 7 mg/kg	−2.57	(−3.95, −1.22)
Zilucoplan	−2.09	(−3.32, −0.86)
Inebilizumab	−1.81	(−2.93, −0.68)
Ravulizumab	−1.70	(−2.74, −0.64)
Nipocalimab	−1.63	(−2.65, −0.62)

≥3- and ≥5-Point Improvements in QMG, ≥3- and ≥5-Point Improvements in MG-ADL, Treatments Compared With Placebo (Table 4)

- All treatments demonstrated significantly greater improvements than placebo across all categorical efficacy outcomes, except for rozanolixizumab 7 mg/kg in the ≥3-point improvement in QMG outcome

Results of NNT, Categorical Outcomes (Figure 4)

- Efgartigimod IV had the lowest NNT for QMG ≥3- and ≥5-point improvements, as well as MG-ADL ≥5-point improvement. Its NNT was significantly lower than that of nipocalimab for QMG ≥3, ravulizumab for QMG ≥3 and MG-ADL ≥5, and zilucoplan for QMG ≥3, QMG ≥5, and MG-ADL ≥5
- Rozanolixizumab had the lowest NNT for MG-ADL ≥3-point improvement; however, the difference was not statistically significant compared with other treatments

LIMITATIONS

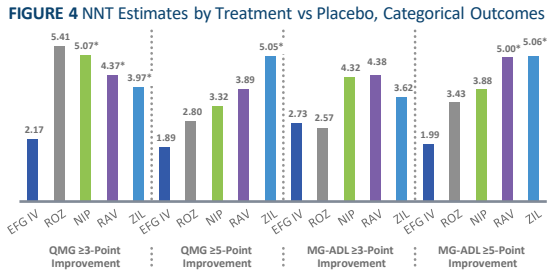
- Cross-trial differences were harmonized to the greatest extent possible. Whenever data were available, the anti-AChR Ab+ patient populations of trials were used for assessment of efficacy outcomes to maximize similarity with patients of ADAPT. However, residual differences may remain
- Differences in dosing schedules resulted in inherent variations in assessment time points across trials, which the current methodology cannot fully account for

TABLE 4 Effect of Treatments Compared With Placebo in Categorical Outcomes, Mean Differences (95% CrI)*

Treatment	≥3-Point Improvement in QMG	≥5-Point Improvement in QMG	≥3-Point Improvement in MG-ADL	≥5-Point Improvement in MG-ADL
Efgartigimod	0.45 (0.32, 0.56)	0.52 (0.33, 0.68)	0.36 (0.20, 0.49)	0.50 (0.29, 0.68)
Rozanolixizumab 10 mg/kg	0.31 (0.13, 0.47)	0.37 (0.17, 0.56)	0.39 (0.24, 0.51)	0.31 (0.10, 0.54)
Rozanolixizumab 7 mg/kg	0.11 (−0.07, 0.29)	0.35 (0.15, 0.54)	0.37 (0.22, 0.50)	0.28 (0.07, 0.52)
Nipocalimab	0.19 (0.03, 0.35)	0.30 (0.12, 0.49)	0.23 (0.07, 0.37)	0.26 (0.09, 0.44)
Ravulizumab	0.23 (0.06, 0.38)	0.26 (0.07, 0.48)	0.23 (0.07, 0.37)	0.20 (0.04, 0.41)
Zilucoplan	0.25 (0.09, 0.40)	0.20 (0.07, 0.36)	0.27 (0.12, 0.41)	0.20 (0.06, 0.36)

*Positive differences indicate greater improvement in treatment than placebo.

FIGURE 4 NNT Estimates by Treatment vs Placebo, Categorical Outcomes



*Indicates statistical significance compared with the treatment with the lowest NNT within each outcome.

KEY TAKEAWAYS

This analysis extends beyond published NMAs by incorporating phase 3 data for nipocalimab and inebilizumab, 2 novel agents that are currently under regulatory review or expected to undergo evaluation for treating gMG[14–16]

All novel therapies evaluated in this analysis demonstrated clinical benefit compared with placebo for both MG-ADL and QMG outcomes

Comparatively, efgartigimod exhibited a greater treatment effect in most efficacy outcomes compared with other therapies

In the absence of head-to-head comparisons and bearing the limitations stated above, this assessment may be used to inform treatment decision-making for patients with gMG

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ABBREVIATIONS

AChR Ab, acetylcholine receptor antibody; **CrI**, credible interval; **EFG**, efgartigimod; **gMG**, generalized myasthenia gravis; **IV**, intravenous; **LRP4 Ab**, low-density lipoprotein receptor-related protein 4 antibody; **MG-ADL**, Myasthenia Gravis-Activities of Daily Living; **MGFA**, Myasthenia Gravis Foundation of America; **MCID**, minimal clinically important difference; **MuSK Ab**, muscle-specific kinase antibody; **NIP**, nipocalimab; **NMA**, network meta-analysis; **NNT**, number needed to treat; **PBO**, placebo; **QMG**, Quantitative Myasthenia Gravis; **RAV**, ravulizumab; **ROZ**, rozanolixizumab; **SC**, subcutaneous; **ZIL**, zilucoplan.

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