Risk benefit analysis of treatments for general myasthenia gravis

MGFA Scientific Session 2022

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Disclosure

- Gordon Smith, MD: consulting relationships with Abalone, Alexion, Argenx, Disarm Therapeutics, Eidos, Lexicon and Sangamo; research funding from NIH.
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Background and objectives

- Myasthenia Gravis (MG) is a chronic autoimmune disease impairing neuromuscular junction transmission and resulting to injury to the post synaptic membrane
- Generalized Myasthenia Gravis (gMG) patients 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.[2,3]
- Approximately 85% of gMG patients have anti-acetylcholine receptor (AChR) antibodies.[1]
- FDA approved treatments include eculizumab (ECU), efgartigimod (EFG), and ravulizumab (RAV) with intravenous immunoglobulin (IVIg) frequently used off-label.

This study aims to

- assess clinical benefit and tolerability of ECU, EFG, RAV, and IVIg for patients with anti-AChR Ab+ generalized MG using the “number needed to treat (NNT)” for benefit and “number needed to harm (NNH)” for tolerability.

1. Lazaridis K et al. Frontiers in Immunology. 2020;11. doi:10.3389/fimmu.2020.00212
2. Muley S, et al. Patient burden of generalized myasthenia gravis. Poster presented at: 43rd Annual Carrell-Krusen Neuromuscular Symposium; February 18, 2021.
3. Centre for International Economics. The cost to patients and the community of Myasthenia Gravis. 2013.

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Methods

Numbers needed to treat (NNT)

NNT represents the number of patients who would need to be treated with an intervention to achieve one additional patient with a positive clinical outcome compared to placebo

$$\text{NNT} = \frac{1}{\text{Difference in clinical outcome of intervention vs. placebo}}$$

Clinical endpoints considered

- Minimally clinical important difference (≥ 3 points improvement) in quantitative myasthenia gravis (QMG) score
- Myasthenia Gravis Activities of Daily Living (MG-ADL) improvement of ≥ 3 points
- Minimal symptom expression (MG-ADL 0/1)

QMG is a quantitative assessment of patient function in 13 domains, based on the endurance of key muscle groups.

The **MG-ADL** score is an 8-item patient-reported outcome measure assessing MG symptoms and functional activities related to activities of daily living.

Numbers needed to harm (NNH)

NNH represents the numbers of patients treated with an intervention for one additional patient to experience an undesired adverse outcome compared to placebo

$$\text{NNH} = \frac{1}{\text{Difference in safety outcome of intervention vs. placebo}}$$

Safety endpoints considered

- Any serious adverse events
- Any treatment related adverse events
- Any adverse events leading to study discontinuation

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Summary of clinical trials

	ADAPT (NCT03669588)	NCT02473952	REGAIN (NCT01997229)	CHAMPION (NCT03920293)
Experimental Therapy	**EFG+CT**	**IVIG + CT**	**ECU + CT**	**RAV + CT**
Study design	Phase 3 1:1 EFG or placebo	Phase 2 1:1 IVIg or placebo	Phase 3 1:1 ECU or placebo	Phase 3 1:1 RAV or placebo
Study duration	26 weeks	24 weeks	26 weeks	26 weeks
Population	167 gMG • MGFA Class II, III, IV • Anti-AChR Ab+/- • MG-ADL ≥5 ***Data from 129 anti-AChR Ab+ patients analyzed***	62 gMG • MGFA Class II, III, IVa • Anti-AChR Ab+ • QMG ≥ 10	125 ***refractory*** gMG[1] • MGFA Class II, III, IV • Anti-AChR Ab+ • MG-ADL ≥ 6	175 gMG • MGFA Class II, III, IV • Anti-AChR Ab+ • MG-ADL ≥ 6
Dosing	***Individualized*** dosing	Fixed dosing	Fixed dosing	Fixed dosing

Note: All trials have background CT

1. Refractory is defined as receiving two or more immunosuppressive therapies or at least one IVIg without symptom control

Abbreviations: CT: conventional therapy; ECU, eculizumab; EFG, efgartigimod; IVIg, intravenous immunoglobulin; gMG, generalized myasthenia gravis; QMG, quantitative myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; RAV, ravulizumab

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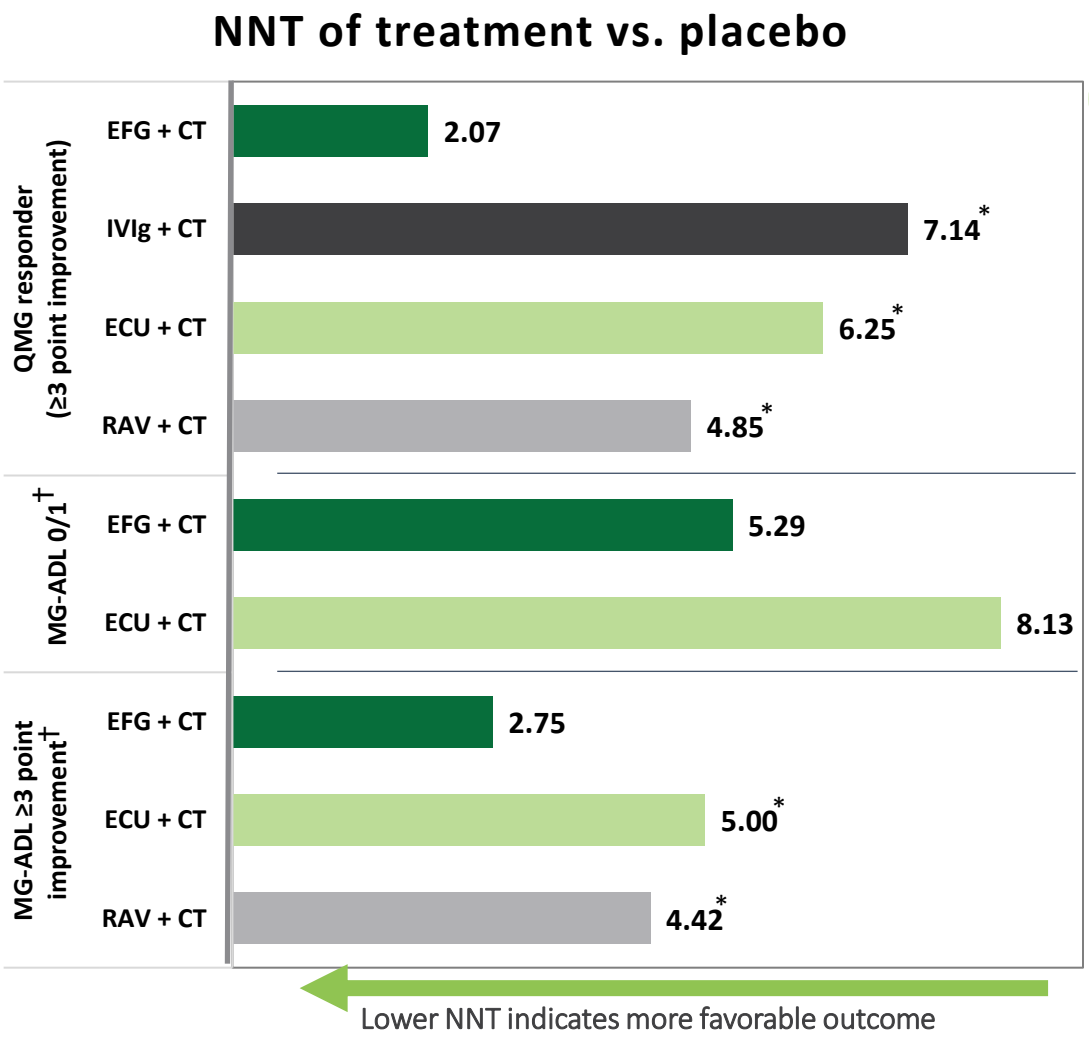
Results: NNT



INTERPRETATION

The lower the NNT, the more clinical benefit the intervention brings.
NNTs ≤ **10** are considered to represent a clinically relevant benefit.[1]

EFG was associated with the lowest NNT across all efficacy outcomes compared with IVIg, ECU, and RAV.

***Indicates the EFG has significantly better incremental NNT vs. comparators at the 0.05 level.**

† MG-ADL 0/1 and MG-ADL ≥ 3-point improvement outcomes are not evaluated in the IVIg trial (NCT02473952); MG-ADL 0/1 outcome is not evaluated in the RAV trial.

1. Citrome L, Ketter TA. Int J Clin Prac. 2013;67(5): 407-411

Abbreviations: CT: conventional therapy; ECU, eculizumab; EFG, efgartigimod; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; NNT, numbers needed to treat; QMG; Quantitative Myasthenia Gravis; RAV, ravulizumab

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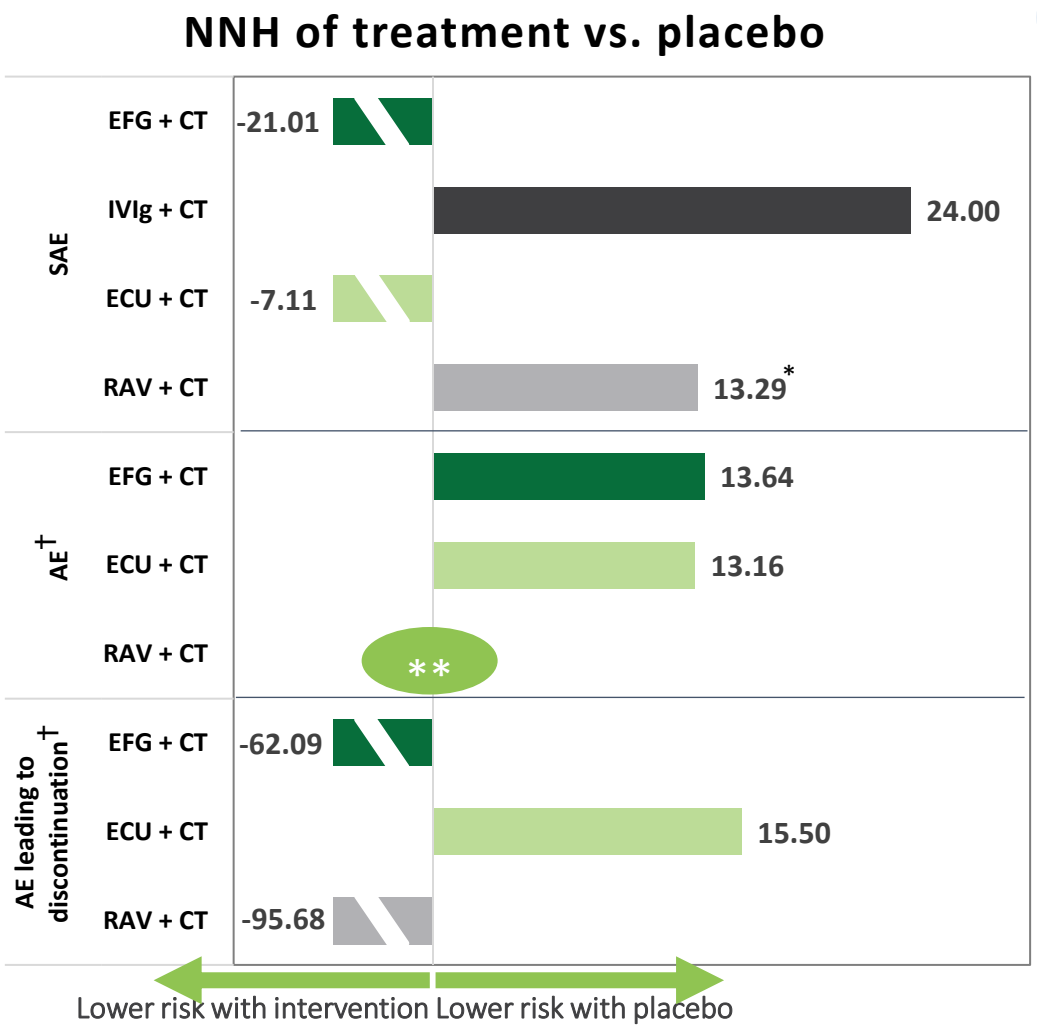
Results: NNH



INTERPRETATION

Negative NNH indicates the intervention has fewer AEs than placebo.
When NNH is positive, the intervention has more AEs than placebo. Acceptable safety profiles would be associated with an NNH in the **10-100** range or higher.[1]

Overall, EFG has a comparable safety profile compared with IVIg, ECU and RAV.

***Indicates the incremental NNH vs. EFG is statistically significant at the 0.05 level.**

† AE and AE leading to discontinuation outcomes are not reported in the IVIg trial (NCT02473952). **NNH not calculable due to the same AE rates between RAV + CT and CT

1. Citrome L, Ketter TA. Int J Clin Prac. 2013;67(5): 407-411

Abbreviations: AE: adverse event; CT: conventional therapy; ECU, eculizumab; EFG, efgartigimod; IVIg, intravenous immunoglobulin; NNH: numbers needed to harm; RAV, ravulizumab; SAE, serious adverse event

Discussion and conclusion

- In the absence of direct head-to-head clinical trials comparing all interventions together, individual clinical trials of each intervention vs. the same anchor arm (i.e., placebo) arms are the best available evidence.
- Efficacy and safety data from individual randomized clinical trials of EFG, ECU, IVIG and RAV (vs. placebo) were used for the current analysis.
- The applicability of the NNT values in clinical practice is limited to the specific comparator (i.e., CT alone) and the characteristics of the patient populations evaluated in the analyzed trials (i.e., anti-AChR Ab+) .
- These results suggest that EFG offers favorable clinical benefit with comparable or better safety profiles compared to ECU, IVIG and RAV in anti-AChR Ab+ gMG patients.