NUMBERS NEEDED TO TREAT AND COSTS PER IMPROVED OUTCOME OF TREATMENTS FOR GENERAL MYASTHENIA GRAVIS

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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]
- Conventional therapies (CT) including acetylcholinesterase inhibitors, steroids, and non-steroidal immunosuppressants are used as initial treatments to eliminate gMG symptoms or functional limitations. However, many patients are inadequately managed by CT due to suboptimal effectiveness and safety concerns.[5]
- For anti-AChR Ab+ gMG patients inadequately managed by CT and plasma exchange, eculizumab or intravenous immunoglobulin (IVIg) can be considered. However, these options are typically reserved for a small subset of gMG population due to the high-cost profile (eculizumab) or off-label use (IVIg).[6,7,8]
  - Eculizumab has a label indication for anti-AChR Ab+ gMG, and is mainly used in severe, refractory gMG[9]
  - IVIg does not have a label indication for gMG, but is recommended by treatment guidelines as a potential option for MG exacerbation/crisis or for patients not responding to other treatments[7]
- Efgartigimod, a human IgG1 antibody Fc fragment, is a novel treatment approved by US FDA in 2021 for anti-AChR Ab+ gMG with demonstrated clinical efficacy and safety profile.[10] It has the potential to provide enhanced clinical benefits and address an unmet need for patients with anti-AChR Ab+ gMG.

Objective

- This study estimated and compared the numbers needed to treat (NNT) and costs per improved outcome of efgartigimod, eculizumab, and IVIg for AChR Ab+ gMG.

Methods

Data source

- Data from phase 3 clinical trials of efgartigimod (ADAPT, NCT03669588)[10], eculizumab (REGAIN, NCT01997229)[11], and IVIg (NCT02473952)[12] were used in this analysis **(Table 1)**.
- NNT and cost per improved outcomes were estimated based on the following efficacy endpoints **(Table 2)**:
  - Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 4
  - Proportion of patients achieving minimal clinically importance difference (MCID) in QMG (patients with ≥ 3-point reduction in QMG score) at week 4
  - Proportion of patients achieving Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 0 or 1 at week 4
- Cost per improved outcomes considered wholesale acquisition costs and administration costs of each treatment **(Table 3)**:
  - Dosing schedule and treatment duration are based on evidence from respective clinical trial studies and supplemented by real-world data
  - Drug acquisition and administration costs were obtained from IBM Micromedex REDBOOK and Magellan Rx Management Medical Pharmacy Trend Report (9th ed., 2018)

Table 1. Clinical trials of efgartigimod, eculizumab, and IVIg in gMG

	ADAPT (NCT03669588)[10]	NCT02473952[12]	REGAIN (NCT01997229)[11]
Study design	Phase 3 trial randomizing patients 1:1 to efgartigimod or placebo for 26 weeks.	Phase 2 trial randomizing patients 1:1 to IVIg or placebo for 24 weeks.	Phase 3 trial randomizing patients 1:1 to eculizumab or placebo for 26 weeks.
Population	167 gMG patients (129 were anti-AChR Ab+) ▪ MGFA Class II, III, IV ▪ AChR-antibody positive or negative ▪ MG-ADL score ≥5 ▪ On a stable dose of at least one CT for gMG	62 gMG (anti-AChR Ab+) patients ▪ MGFA Class II, III, IVa ▪ AChR-antibody positive ▪ QMG score ≥ 10 ▪ On a stable dose of at least one CT for gMG	125 gMG (anti-AChR Ab+) patients ▪ MGFA Class II, III, IV ▪ AChR-antibody positive ▪ MG-ADL score ≥ 6 ▪ Received two or more prior immuno-suppressive therapies or at least one IVIg without symptom control
Dosing schedule	10mg/kg as 4 IV infusions at weekly intervals, followed by a 5-week period with no infusions in the initial cycle. After cycle 1, the time between each TC was individualized according to clinical evaluation	Initial loading dose of 2000mg/kg at baseline followed by 1000mg/kg maintenance doses every third week through week 21	3 vials weekly for 4 doses followed by 4 vials for the fifth dose during induction phase, 4 vials every 2 weeks through week 26 during maintenance phase

Table 2. Efficacy inputs

	ADAPT (NCT03669588)[10,13]			NCT02473952[8,12]			REGAIN (NCT01997229)[8,11]		
Efficacy endpoints	Efgartigimod + CT N=65	Placebo + CT N=64	Difference -	IVIg + CT N=30	Placebo + CT N=32	Difference -	Eculizumab + CT N=62	Placebo + CT N=63	Difference -
Change in QMG from baseline at week 4, points[§]	-6.2	-1.0	5.2	-4.6	-2.7	1.9	-3.3	-1.5	1.8
% achieving MCID in QMG at week 4[†]	74%	25%	49%	62%	48%	14%	53%	37%	16%
% achieving MG-ADL 0/1 at week 4[‡]	40%	11%	29%	N/A	N/A	N/A	12%	0%	12%

[§]QMG is a 13-item direct physician assessment scoring system that quantifies disease severity based on impairments of body functions and structures. Total QMG score ranges from 0 (least severe) to 39 (most severe).

[†]MCID in QMG was defined as improvement in QMG score ≥ 3 points (i.e., the minimally clinical importance difference).

[‡]MG-ADL is an 8-item patient-reported outcome measure assessing myasthenia gravis symptoms and the impact of myasthenia gravis on daily functional activities. Total MG-ADL score ranges from 0 (no impact) to 24 (worst impact).

Table 3. Cost inputs

	Annual Costs[14]	Dosing Schedule and Courses
CT	$5,326	A mix of acetylcholine inhibitors, steroids, and non-steroidal immunosuppressants. Dosing schedule and strength varied by regimen[7,15]
Efgartigimod + CT	$289,304	4 infusions of 2.3 vials/infusion per course for 5.2 courses, 20.6 infusions in total[13,16]
IVIg + CT	$178,752	2000 mg/kg loading dose followed by 1000 mg/kg maintenance dose for 12 infusions in total[17]
Eculizumab + CT	$711,872	900 mg induction dose weekly for 4 weeks followed by 1200 mg maintenance dose every 2 weeks[18]

Statistical analyses

- NNT offers a measurement of the treatment effect by estimating the number of patients that need to be treated to achieve one more patient with clinical benefit, or one unit of improvement in a clinical outcome, if receiving treatment A vs. treatment B.
- NNT is an interpretable and clinically applicable measure of treatment efficacy and enables comparisons of treatments that have not been directly compared in a clinical trial.
- NNT was calculated as the inverse of the difference in efficacy outcome between each treatment and their respective placebo arm (i.e., CT alone).

$$NNT\ to\ achieve\ one\ additional\ responder = \frac{1}{Response\ rate_{Treatment\ X+CT} - Response\ rate_{CT\ alone}}$$

$$NNT\ to\ achieve\ one\ point\ improvement\ in\ outcome = \frac{1}{Change\ from\ baseline\ in\ outcome_{Treatment\ X+CT} - Change\ from\ baseline\ in\ outcome_{CT\ alone}}$$

- A lower NNT value indicates greater benefit of the combination treatment (efgartigimod, eculizumab, or IVIg) with CT.
- Cost per improved outcome analysis is a way to evaluate and compare costs and effectiveness across different treatment, leveraging the concept of NNT.
- Cost per improved outcome was calculated as the ratio of cost difference and clinical improvement / response rate difference between each treatment and their respective placebo arm.

$$Cost\ to\ one\ additional\ responder = \frac{Cost_{Treatment\ X+CT} - Cost_{CT\ alone}}{Response\ rate_{Treatment\ X+CT} - Response\ rate_{CT\ alone}}$$

$$Cost\ to\ achieve\ one\ point\ improvement\ in\ outcome = \frac{Cost_{Treatment\ X+CT} - Cost_{CT\ alone}}{Change\ in\ outcome_{Treatment\ X+CT} - Change\ in\ outcome_{CT\ alone}}$$

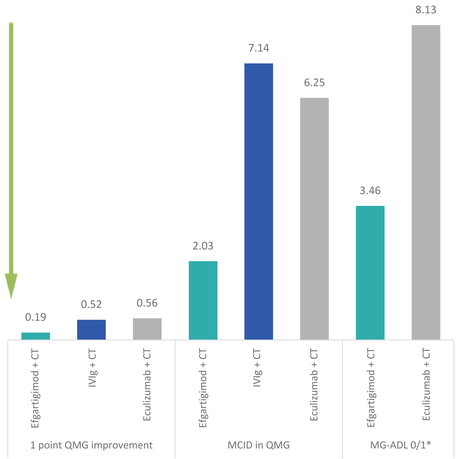
- NNT and cost per improved outcome were compared between efgartigimod + CT and comparators (IVIg + CT and eculizumab + CT) using Wald tests.

Results

Numbers needed to treat

- Among the treatments assessed in this study, efgartigimod + CT was associated with the lowest NNT to achieve one point of QMG improvement, an additional patient achieving MCID in QMG, or an additional patient achieving MG-ADL of 0 or 1 **(Figure 1)**.
- The incremental NNT were significantly lower for efgartigimod + CT vs. comparators across all efficacy outcomes, except for the NNT to achieve one additional patient achieving MCID in QMG vs. eculizumab + CT **(Table 4)**.

Figure 1. NNT for combination treatment with CT vs CT alone

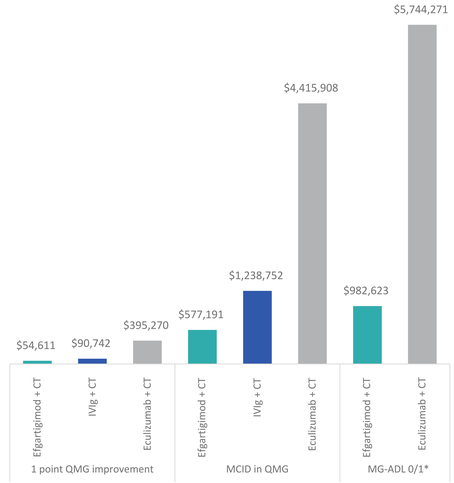


* MG-ADL 0/1 outcome is not evaluated in the IVIg trial (NCT02473952)

Cost per improved outcome

- Among the treatments assessed in this study, efgartigimod + CT was associated with the lowest costs to achieve one point of QMG improvement ($54,611), an additional patient achieving MCID in QMG ($577,191), and an additional patient achieving MG-ADL 0/1 ($982,623) **(Figure 2)**.
- The incremental costs associated with achieving improved outcomes were significantly lower for efgartigimod + CT vs. comparators across all efficacy outcomes, except for the cost per additional patient achieving MCID in QMG vs. IVIg + CT **(Table 5)**.

Figure 2. Cost per improved outcome for combination treatment with CT vs CT alone



* MG-ADL 0/1 outcome was not evaluated in the IVIg trial (NCT02473952)

Table 4. Comparison of NNT between combination treatment with CT

Outcome	Efgartigimod vs.	Mean difference	95% CI	p-value
1 point QMG improvement	IVIg + CT	0.33	(0.21,0.45)	<0.001
	Eculizumab + CT	0.37	(0.11,0.63)	0.006
% achieving MCID in QMG	IVIg + CT	5.11	(0.03,10.19)	0.049
	Eculizumab + CT	4.22	(0.00,9.74)	0.134
% achieving MG-ADL 0/1*	Eculizumab + CT	4.67	(1.87,7.47)	0.001

* MG-ADL 0/1 outcome was not evaluated in the IVIg trial (NCT02473952)

Table 5. Comparison of cost per improved outcome between combination treatment with CT

Outcome	Efgartigimod vs.	Mean difference	95% CI	p-value
1 point QMG improvement	IVIg + CT	$36,130	($14,024, $58,237)	0.001
	Eculizumab + CT	$340,659	($158,038, $523,280)	<0.001
% achieving MCID in QMG	IVIg + CT	$661,561	($0, $1,546,275)	0.143
	Eculizumab + CT	$3,838,718	($1,470,740, $6,206,695)	0.001
% achieving MG-ADL 0/1*	Eculizumab + CT	$4,761,649	($2,859,671, $6,663,626)	<0.001

* MG-ADL 0/1 outcome was not evaluated in the IVIg trial (NCT02473952)

Abbreviations

CI, confidence interval; CT, conventional therapy; gMG, generalized myasthenia gravis; IVIg, intravenous immunoglobulin; N/A, not available; NNT, number needed to treat; QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; TC: treatment cycle.

Limitations

- The applicability of NNT values in clinical practice is limited to the specific comparator (i.e., CT alone) and the characteristics of the patient populations (e.g., Anti-acetylcholine receptor antibody positive) evaluated in the trials used in this study. Population differences between trials were not adjusted and future research on indirect treatment comparison is warranted.
- Clinical endpoints were evaluated at different time points across trials of efgartigimod, eculizumab, and IVIg. Specifically, the efficacy of IVIg at week 4 was assumed to be the same as the efficacy evaluated at week 24 given the rapid therapeutic onset reported for IVIg.[19]
- The clinical and economic benefits estimated in this study may not be representative of the benefits in real-world practice given the differences between well-controlled trial and real-world clinical settings.

Discussion and Conclusions

- **The current estimates of the NNTs and costs for improved outcomes help inform the comparative clinical efficacy and cost-effectiveness of gMG treatments.**
- **While consensus has not reached upon a threshold for NNT, Citrome and Ketter suggested that NNTs that are equal to or less than 10 could demonstrate clinically relevant benefits.[20] The NNT findings from the current study for efgartigimod, eculizumab, and IVIg are all below this threshold, suggesting clinical benefit for these treatments in gMG.**
- **Among the therapies evaluated in this study, efgartigimod + CT had the lowest NNT to achieve one unit improvement in QMG and one additional patient with MCID in QMG compared to IVIg and eculizumab, and one additional patient with MG-ADL score of 0/1 at 4 weeks compared to eculizumab. Efgartigimod + CT also demonstrated the lowest cost per efficacy response for each outcome of interest.**
- **This evidence indicates more favorable treatment benefits and economic value for efgartigimod + CT, with lower NNT and costs estimated to achieve improved outcomes compared to other treatments.**

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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. Dalakas MC. *Curr Opin Neurol.* 2020;33(5):545-52.
6. Narayanaswami P et al. *Neurology.* 2021 96(3):114-122.
7. Sanders DB et al. *Neurology.* 2016;87(4):419-425.
8. Institute for Clinical and Economic Review. Eculizumab and efgartigimod for the treatment of myasthenia gravis: Effectiveness and value. 2021. Available from: https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Final-Report_102021-1.pdf. Accessed on: January 25, 2022.
9. US Food and Drug Administration. Highlights of prescribing information: SOLIRIS (eculizumab). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125166s434lbl.pdf. Accessed on: April 4, 2022.
10. Howard Jr JF et al. *Lancet Neurol.* 2021;20(7):526-36.
11. Howard Jr JF et al. *Lancet Neurol.* 2017;16(12):976-986.
12. ClinicalTrials.gov. A study to evaluate the efficacy and safety of IGIV-C in symptomatic subjects With generalized myasthenia gravis. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02473952. Accessed on: January 25, 2022.
13. argenx, Inc. (data on file).
14. IBM Micromedex RED BOOK. Available from: https://www.ibm.com/products/micromedex-red-book. Accessed on: January 31, 2021.
15. Bird S. Overview of the treatment of myasthenia gravis. Available from UpToDate: https://iso.uptodate.com/contents/overview-of-the-treatment-of-myasthenia-gravis. Accessed on: January 31, 2021.
16. Howard Jr JF et al. AAN Annual Meeting 2022, Seattle, WA, United States.
17. Qi C et al. (2022 May 15-18) ISPOR, Washington, DC., United States and Virtual.
18. Vissing et al. J Neurol. 2020; 267:1991–2001.
19. Alhaidar MK et al. J Clin Med. 2022;11(6):1597.
20. Citrome L, Ketter TA. Int J Clin Prac. 2013;67(5): 407-411.