eNeurologicalSci 37 (2024) 100541

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Myasthenia gravis: The evolving therapeutic landscape☆

Gil I. Wolfe *, Jonathan E. Hanson, Nicholas J. Silvestri

From the Dept. of Neurology, Jacobs School of Medicine and Biomedical Sciences, Univ. at Buffalo, State University of New York, Buffalo, NY, USA

ARTICLE INFO

Keywords:
Myasthenia gravis
Therapeutics
Neonatal Fc receptor
Complement

ABSTRACT

Pharmacological options in the management of generalized myasthenia gravis (gMG) have expanded rapidly in the last 7 years. There are now several complement inhibitors and neonatal Fc receptor antagonists on the market in many countries for patient management, following the successful completion of Phase 3 studies. In open-label extensions, these agents have proven to be effective over the longer term extending several years, with benefits such as reduction of corticosteroid requirements being observed. In the communication below, we will briefly summarize recent pharmacologic advancements in the management of gMG and outline how these agents are currently being used and may be used in the future.

1. Introduction

Conventional therapy for generalized myasthenia gravis (gMG) until the last decade has primarily included anticholinesterase inhibitors, corticosteroids and other oral immunosuppressants, thymectomy, and in settings of severe exacerbations or myasthenic crisis, plasma exchange and intravenous immunoglobulin therapy [1]. Since 2017, directed pharmacological therapies have been approved that offer advantages including rapidity of clinical improvement and favorable adverse event profiles.

2. Material and methods

Clinical investigations of recently approved pharmacological agents for gMG were summarized, with a focus on Phase 3 trials. In addition, trials of related agents still under investigation for gMG were reviewed.

3. Results

In 2017, eculizumab, an intravenous monoclonal antibody that inhibits C5 cleavage, was the first of the novel directed therapies to receive FDA approval for treatment of gMG. These agents prevent formation of C5a and C5b, inhibiting downstream formation of the membrane attack complex, an important pathophysiologic mechanism resulting in muscle membrane damage in acetylcholine receptor-antibody (AChR-Ab) positive gMG populations. In the phase 3 trial, eculizumab demonstrated significant benefit over placebo in the vast majority of prespecified outcomes including the change in Quantitative MG score (QMG) from baseline and the responder analysis for both the QMG and MG Activities of Daily Living scale (MG-ADL) [2]. The primary outcome, a worst-rank analysis of the change in MG-ADL from baseline, did not reach significance. Since 2017, two other terminal complement inhibitors with similar action have received regulatory approval following Phase 3 trials that used the MG-ADL change from baseline as the primary efficacy measure. Ravulizumab, a slightly modified version of eculizumab with a longer half-life that allows for every 8 week instead of every 2 week intravenous infusion, demonstrated significant benefit versus placebo for both the change in MG-ADL and QMG from baseline [3]. Most recently, zilucoplan, a macrocyclic peptide delivered as a daily subcutaneous injection, received approval for management in this population of AChR-Ab positive gMG patients based on significant reductions from baseline in both MG-ADL and QMG versus placebo [4]. Of note, quality of life measures also improved significantly on zilucoplan versus placebo. In open-label extension studies, these agents have demonstrated the ability to reduce exacerbations, hospital admissions and both corticosteroid and other immunosuppressive agent requirements [5,6]. Importantly, vaccination against *N. meningitidis* is mandatory before starting complement inhibitor therapy, and prophylactic antibiotics may

☆ Detailed disclosures are noted as part of a separate Declaration of Interest form, which forms part of the journal's official records. Gil Wolfe has served as a consultant/advisor for Alexion, Argenx, BPL, UCB, and Cartesian and has received research support from Argenx, Ra/UCB, Immunovant, Roche, Alexion, NINDS/NIH, and MGFA. Nicholas Silvestri has served as a consultant/advisor for Argenx, Amgen, Alexion, Annexon, Immunovant, Janssen, Takeda and UCB. Jonathan Hanson has no nothing to disclose.No AI-assisted technologies were used in preparation of this manuscript.

* Corresponding author at: Dept. of Neurology, Univ. at Buffalo, 1010 Main St., Buffalo, NY 14202, USA.
E-mail address: gilwolfe@buffalo.edu (G.I. Wolfe).

https://doi.org/10.1016/j.ensci.2024.100541
Received 27 August 2024; Received in revised form 11 November 2024; Accepted 17 November 2024
Available online 19 November 2024

be required.

The other mechanism of action recently approved in management of gMG is antagonism of the neonatal Fc receptor (FcRn). FcRn plays a critical role in maintaining both IgG and albumin levels in circulation by rescuing them from degradation in lysosomes [7]. As a result, IgG has a longer half-life when compared to other immunoglobulin classes. Molecules with strong affinity to FcRn will disrupt this recycling, leading to marked reductions in disease-mediating IgG and overall IgG levels. Efgartigimod, an IgG1 Fc fragment with strong affinity for FcRn, was found to be superior to placebo when delivered cyclically in four weekly intravenous infusions [8]. Statistically significant higher responder rates for both the MG-ADL and QMG persisting at least four weeks were observed on efgartigimod. Quality of life measures also improved significantly. One-third of patients receiving efgartigimod maintained responder status for at least 12 weeks after the initial cycle. Delivered via 6 weekly subcutaneous infusions, rozanolixizumab, an IgG4 monoclonal antibody that also targets FcRn, produced significant improvement versus placebo on MG-ADL, QMG, and patient reported outcomes for fatigue and bulbar weakness [9]. In addition to AChR-Ab positive gMG, rozanolixizumab received FDA approval for management of MuSK-antibody positive gMG. Ongoing open-label extension studies of efgartigimod demonstrate sustained clinically meaningful improvements in clinical outcomes as well as total IgG and auto-antibody reductions [10]. Other FcRn antagonists and several agents with primary action against B cells have completed or shortly will complete Phase 3 investigations.

The approved targeted therapies have been well tolerated with few notable differences between actively treated and placebo groups. Most adverse events have been mild to moderate, and only marginal increases in upper respiratory and urinary tract infection rates have been observed with FcRn antagonists.

4. Conclusions

The treatment of gMG has historically relied on agents providing relatively broad immunosuppression to reduce antibody-mediated destruction of the neuromuscular junction. While effective, these agents often lead to both short- and long-term side effects, the most serious of which include increased risk of infection and certain malignancies. Theoretically, use of more targeted agents such as FcRn antagonists and complement inhibitors should reduce the risk of these potential adverse effects. Based on available data, these highly efficacious agents appear to be generally safe and well-tolerated in the majority of patients. However, it is important to remember that the recently approved targeted therapies do not directly impact plasma cells or their precursors, and that autoreactive antibody production will not cease. Therefore, a sustained remission may not be observed. Nevertheless, the availability of these agents has modified the treatment paradigm for various gMG patient populations over the past decade. Their use in refractory disease, as maintenance or bridging therapy, and even in the setting of acute exacerbations and myasthenic crisis are being reported. Management strategies will continue to evolve as targeted therapies still under investigation – some of which directly inhibit B-cell activity – receive approval.

CRediT authorship contribution statement

Gil I. Wolfe: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Jonathan E. Hanson:** Writing – review & editing, Writing – original draft. **Nicholas J. Silvestri:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

None.

References

[1] N.E. Gilhus, Myasthenia gravis, N. Engl. J. Med. 375 (2016) 2570–2581, https://doi.org/10.1056/NEJMra1602678.
[2] J.F. Howard, K. Utsugisawa, M. Benatar, et al., Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase 3 randomised, double-blind, placebo-controlled multicentre study, Lancet Neurol. 16 (2017) 976–986, https://doi.org/10.1016/S1474-4422(17)30369-1.
[3] T. Vu, A. Meisel, R. Mantegazza, et al., Terminal complement inhibitor ravulizumab in generalized myasthenia gravis, NEJM Evid. 1 (2022) 1–11, https://doi.org/10.1056/EVIDoa2100066.
[4] J.F. Howard, S. Bresch, A. Genge, et al., Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study, Lancet Neurol. 22 (2023) 395–406.
[5] S. Muppidi, K. Utsugisawa, M. Benatar, et al., Long-term safety and efficacy of eculizumab in generalized myasthenia gravis, Muscle Nerve 60 (2019) 14–24, https://doi.org/10.1002/mus.26447.
[6] R.J. Nowak, S. Muppidi, S.R. Beydoun, et al., Concomitant immunosuppressive therapy use in eculizumab-treated adults with generalized myasthenia gravis during the REGAIN open-label extension study, Front. Neurol. 11 (2020), https://doi.org/10.3389/fneur.2020.556104.
[7] G.I. Wolfe, E.S. Ward, H. de Haard, et al., IgG regulation through FcRn blocking: a novel mechanism for the treatment of myasthenia gravis, J. Neurol. Sci. 430 (2021) 118074, https://doi.org/10.1016/j.jns.2021.118074.
[8] J.F. Howard, V. Bril, T. Vu, et al., Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, ramdomised, placebo-controlled, phase 3 trial, Lancet Neurol. 20 (2021) 526–536, https://doi.org/10.1016/S1474-4422(21)00159-9.
[9] V. Bril, J. Grosskreutz, A.A. Habib, et al., Safety and efficacy of rozanolixizumab in patients with generlised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study, Lancet Neurol. 22 (2023) 383–394, https://doi.org/10.1016/S1474-4422(23)00077-7.
[10] J.F. Howard, V. Bril, T. Vu, et al., Long-term safety, tolerability, and efficacy of efgartigimod (ADAPT+): interim results from a phase 3 open-label extension study in participants with generalized myasthenia gravis, Front. Neurol. 14 (2023) 1284444, https://doi.org/10.3389/fneur.2023.1284444.