4-1-2022

Immunomodulatory effects and clinical benefits of intravenous immunoglobulin in myasthenia gravis.

Marinos C Dalakas
Department of Neurology, Thomas Jefferson University, Philadelphia, PA, United States

Andreas Meisel
Department of Neurology, Integrated Center for Myasthenia Gravis, Charité - University Medicine Berlin, Berlin, Germany

Taylor & Francis
Taylor & Francis Group

Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Immunomodulatory effects and clinical benefits of intravenous immunoglobulin in myasthenia gravis

Marinos C Dalakas & Andreas Meisel

To cite this article: Marinos C Dalakas & Andreas Meisel (2022) Immunomodulatory effects and clinical benefits of intravenous immunoglobulin in myasthenia gravis, Expert Review of Neurotherapeutics, 22:4, 313-318, DOI: 10.1080/14737175.2022.2057223

To link to this article: https://doi.org/10.1080/14737175.2022.2057223

Published online: 05 Apr 2022.

EXPERT REVIEW OF NEUROTHERAPEUTICS
2022, VOL. 22, NO. 4, 313–318
https://doi.org/10.1080/14737175.2022.2057223

Taylor & Francis
Taylor & Francis Group

REVIEW

Immunomodulatory effects and clinical benefits of intravenous immunoglobulin in myasthenia gravis

Marinos C Dalakas[a] and Andreas Meisel[b]

[a]Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [b]Department of Neurology, Integrated Center for Myasthenia Gravis, Charité - University Medicine Berlin, Berlin, Germany

ABSTRACT

Introduction: Myasthenia gravis (MG) is an antibody-mediated disease that develops in the majority of patients mainly as a result of acetylcholine receptor (AChR) autoantibodies. This process is mediated by a series of immunoregulatory events. Therapeutic targets for MG include suppression of circulating antibodies or antibody production, suppression of complement activation, and immunomodulation of cytokines or T cells. Intravenous immunoglobulin (IVIg) has an effect on all of these mechanisms.

Areas covered: This narrative review explores the broad immunomodulatory effects of IVIg in MG and provides an update on IVIg treatment for MG.

Expert opinion: IVIg has a range of immunomodulatory effects on therapeutic targets relevant to the immunopathogenesis of MG. An emerging area of research is the pharmacogenomics of IVIg in MG related to FcRn and IgG catabolism. New data suggest that the FcRn *VNTR3* genotype can affect the efficacy of IVIg in certain MG patients and may have an impact on IgG kinetics and selected dosing. Immune globulin 10% caprylate/chromatography purified (IVIg-C) has been shown to reverse the symptoms of severe acute exacerbation in patients with MG supporting its use for this severely ill subgroup of patients during a relapse.

ARTICLE HISTORY
Received 14 September2021
Accepted 21 March2022

KEYWORDS
Immunomodulation; intravenous immunoglobulin; myasthenia gravis

1. Introduction

Myasthenia gravis (MG) is a prototypic antibody-mediated disease that, in the majority of cases, occurs due to development of autoantibodies against acetylcholine receptors (AChR). The antibodies block AChR-binding sites at the end-plate region; they cross-link and internalize the receptors, and initiate the membrane attack complex via complement activation, thereby destroying AChRs at the end-plate region of the neuromuscular junction.

This process is mediated by a series of immunoregulatory events. The main immune factors involved in the pathogenesis of MG include: antibodies against AChR; B cells and B cell trophic factors; complement, which fixes antibodies at the end-plate region; CD4 + T cells and associated cytokines, which facilitate antibody production by B cells and plasma cells; regulatory T cells (Treg) and T helper cells (e.g. Th17+) that affect antibody production via Th1/Th2 cytokine balance; and cytokines, such as interleukin (IL)-6, that affect the induction of Treg to pathogenic Th1 (anti-IL6 suppresses experimental autoimmune MG [EAMG]) [1].

Therapeutic targets for MG include suppression of circulating antibodies or antibody production, suppression of complement activation, and immunomodulation of cytokines or T cells. Intravenous immunoglobulin (IVIg) has effects on all these mechanisms.

This narrative review, which is based on proceedings of a symposium held in May 2021 during the 16th International Congress on Neuromuscular Diseases (ICNMD 2021) virtual congress, explores the broad immunomodulatory effects of IVIg in MG and provides an update on IVIg treatment for MG.

2. Intravenous immunoglobulin in myasthenia gravis

IVIg works by multiple mechanisms that restore immune balance. Main factors involved the pathogenesis of MG that are relevant to the immunomodulatory actions of IVIg include antibodies, complement, cytokines, FcγRIIb, T cells and antigen-presenting cells (APC), and immunoregulatory genes [2].

2.1. Effect of IVIg on antibodies

IVIg affects antibodies in several ways (Figure 1) [2]. First, IVIg provides idiotypic antibodies that can neutralize pathogenic autoantibodies. Immunoglobulins have idiotypes which can form monomers or dimers. Because IVIg is derived from thousands of donors, up to 40% of the immunoglobulins in IVIg are in dimeric pairs. These idiotypes form dimers with circulating pathogenic autoantibodies, leading to destruction of some pathogenic antibodies.

Second, IVIg can affect B-cell trophic factors such as B-cell activating factor (BAFF) and its close relative APRIL (A Proliferation-Inducing Ligand) [3]. BAFF is known to be

CONTACT Marinos C Dalakas marinos.dalakas@jefferson.edu Department of Neurology, Thomas Jefferson University, 901 Walnut Street, Philadelphia, Pennsylvania, PA 19107, USA; Neuroimmunology Unit, National and Kapodistrian University of Athens, Athens, Greece

Article highlights

- Intravenous immunoglobulin (IVIg) has a range of immunomodulatory effects on relevant therapeutic targets for myasthenia gravis (MG), such as suppression of circulating antibodies or antibody production, suppression of complement activation, and immunomodulation of cytokines or T cells.
- An emerging area of research is the pharmacogenomics of IVIg in MG. It has recently been shown that polymorphisms in the *VNTR3* gene that encodes the FcRn receptor can affect IVIg kinetics and patient outcomes.
- A phase 3 clinical trial showed that immune globulin (human) 10% caprylate/chromatography purified (IVIg-C) reversed the symptoms of severe acute exacerbation in patients with MG and was well tolerated. Clinically meaningful improvements in efficacy measures were seen as early as day 7 and continued to the end of the study (day 28).

increased in patients with MG, and can be suppressed by IVIg [4].

Third, IVIg can saturate FcRn transport receptors leading to accelerated catabolism of pathogenic immunoglobulin G (IgG), thus reducing circulating antibody titers. FcRn is found on the surface of many cells and is involved in the recycling of IgG through endosomes and back into the circulation [5]. Upon saturation of FcRn receptors by infused IVIg, excess immunoglobulin, including anti-AChR autoantibodies will be transferred to lysosomes for degradation, rather than being recycled into the circulation. In an experimental model of MG (EAMG), levels of all IgG types decreased after IVIg infusion. Over the subsequent weeks, a significant reduction in mean clinical score was seen compared with control animals, with evidence of a dose-related effect [3].

2.2. Effect of IVIg on complement

Complement is bound by pathogenic antibodies in the endplate region (Figure 1) [2]. In MG, complement C3b is increased, with one study finding a geometric mean uptake value for C3 of 10,570 counts/minute in patients compared with 3459 in healthy individuals [6]. The complement activation pathway leads to the formation of the C3a and C3b products, which are then involved in the formation of the membranolytic attack complex (MAC), which leads to lysis of target cells.

IVIg can suppress the complement activation process by suppressing C3a and C3b, thereby interfering with the formation of MAC. IVIg has been shown to have a marked effect on inhibition of complement consumption from 2 days after infusion in patients with dermatomyositis, with C3b and MAC deposits disappearing from muscle biopsy samples after therapy [7]. Microvasculopathy and perifascicular atrophy due to complement were reversed after complement inhibition by IVIg, leading to neovascularization and restoration of the muscle fiber architecture, which correlated with clinical improvement. The effect of IVIg on C3 is dose-dependent.

2.3. Effect of IVIg on cytokines

IVIg has effects on various cytokines (Figure 1) [2]. In the EMAG model, IVIg downregulated pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα), and upregulated anti-inflammatory cytokines such as IL-4 and IL-10 [3]. IVIg also has an effect on IL-1; *in vitro* research showed that IL-1 caused destruction of cultured human myotubes, which were rescued by the addition of IVIg (Dalakas MC unpublished data 1998)

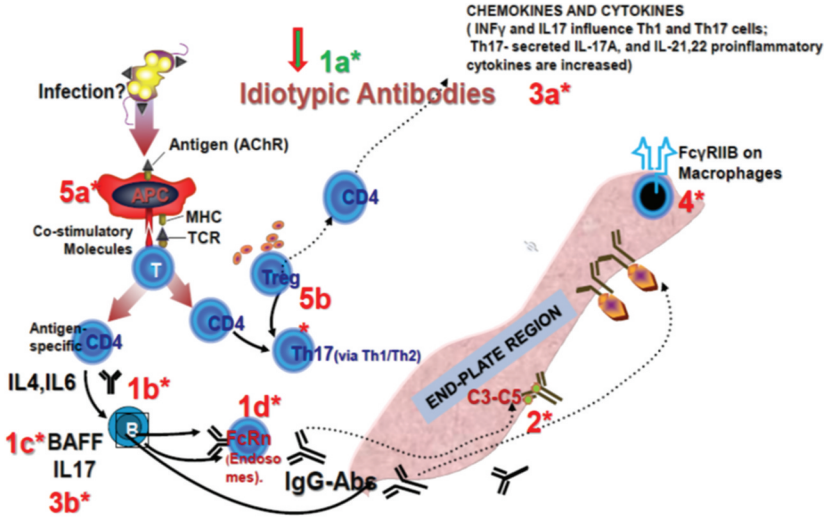

Figure 1. Main factors involved in the immunopathogenesis of myasthenia gravis that are relevant to the actions of intravenous immunoglobulin. Reproduced with permission from [2]. IVIg has effects on antibodies (1a,b,c,d), complement (2), cytokines (3a,b), FcγRIIB (4), and T-cell and APC functions (5a,b). It affects antibodies by providing idiotypic antibodies, facilitating neutralization of pathogenic autoantibodies (1a), by affecting related cytokines (1b), by suppressing B-cell trophic factors, such as B-cell activating factor (BAFF) (1c), and by accelerating the catabolism of pathogenic immunoglobulin G (IgG) by saturating the FcRn transport receptors (1d). IVIg also: inhibits complement binding (2) and prevents membranolytic attack complex (MAC) formation; suppresses pathogenic cytokines (3a,b); upregulates FcγRIIb inhibitory receptors (4), intercepting antibody-dependent cell-mediated cytotoxicity; has effects on antigen presenting cells, T-cell modulatory functions and antigen recognition (5a,b); and affects immunoregulatory genes. AChR, acetylcholine receptor; APC, antigen-presenting cell; BAFF, B-cell activating factor; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; Treg, regulatory T cell.

2.4. Effect of IVIg on FcγRIIb

FcγRIIb inhibitory receptors are found on B cells and macrophages. FcγRIIb on B cells transduce inhibitory signals on the B cells and prevent their transformation into IgG-producing plasma cells. Mice that lack FcγRIIb inhibitory receptors are known to develop autoimmune diseases.

IVIg upregulates FcγRIIb inhibitory receptors, which intercepts antibody-dependent cell-mediated cytotoxicity, and enhances its therapeutic efficacy. This has been shown in chronic inflammatory demyelinating polyneuropathy (CIDP) [8]. Patients with active CIDP have decreased FcγRIIb inhibitory receptors in memory B cells and monocytes. Administration of IVIg leads to upregulation of FcγRIIb in monocytes, naïve and memory B cells, which correlates with clinical benefit. The same process can be assumed in MG and other autoimmune diseases.

2.5. Effect of IVIg on T-cell and APC function

IVIg has effects on various T-cell factors and co-stimulatory molecules. In the EAMG model, IVIg-induced reduction in the co-stimulatory molecule CD40 ligand in treated animals compared with controls correlated with clinical benefit [3]. MHC class 1 is upregulated in muscle biopsies from patients with inflammatory myopathies but is substantially downregulated after IVIg administration.

Preliminary data have suggested that a subset of Treg cells associated with cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is functionally defective in patients with MG, but after IVIg therapy these cells were expanded, suggesting that IVIg may also affect the function of Tregs [9].

2.6. Pharmacogenomics of IVIg in MG

The pharmacogenomics of IVIg in MG is a novel area of research which may have important implications. IVIg is known to be highly effective in some patients, but not in others with clinically similar disease states. It is possible that various biologically relevant genes that are modulated by IVIg directly at the respective tissues may play a role in this variation.

There are data indicating that polymorphisms in the *VNTR3* gene that encodes the FcRn receptor can affect IVIg kinetics and patient outcomes [5,10]. Individuals who are homozygous for *VNTR3* (i.e. *VNTR3/3*), the most common allele, have increased FcRn function. Patients who have heterozygous *VNTR2/3* genotypes have reduced FcRn saturation, meaning that less IVIg is returned to the circulation and more is sent to the lysosomes, which results in enhanced catabolism of infused IVIg and lower serum IgG levels. Patients with MG who were homozygous for *VNTR3* had higher IgG concentrations after IVIg infusion and were more likely to be responders compared with those who were heterozygous [9]. This suggests that *VNTR3* genotype matters with respect to the efficacy of IVIg in MG. It is possible that the *VNTR2/3* genotype could serve as a predictive marker for a poor response to IVIg in some MG patients.

VNTR3 gene polymorphisms may also explain the lack of response in 20–30% of patients treated with IVIg, which is relevant not only in MG but also in other disorders such as CIDP, Guillain–Barré syndrome and multifocal motor neuropathy. Patients who are heterozygous for *VNTR3* are likely to require higher IVIg doses (such as super-high IVIg at 3–4 g/kg per month) or more frequent administrations if 2 g/kg is not effective. This warrants further study in the future.

3. New clinical data on IVIg treatment of MG

3.1. Clinical presentation of MG

Half of patients with MG have ocular onset, with symptoms such as diplopia and ptosis [11–13]. Of these, 50–70% progress to generalized MG [11]. A generalized onset is seen in 40% of patients. Muscle fatigability is the key feature of MG [12,13]. Many patients have pronounced facial muscle involvement. The muscle weakness in the extremities tends to affect more the proximal than the distal muscle groups [12]. The maximum severity of MG is usually reached within 3 years from onset in 80–90% of patients [13].

The Myasthenia Gravis Foundation of America (MGFA) clinical classification can be summarized as follows: Class I covers pure ocular muscle weakness; Classes II–IV cover different severities of muscle weakness (from mild to severe), with subclasses based on whether the weakness predominantly affects (a) limb/axial muscles or (b) oropharyngeal/respiratory muscles; and Class V is myasthenic crisis, defined by the need for intubation [14].

3.2. Exacerbation of MG and myasthenic crisis

Clinical red flags for MG exacerbation and crisis include: febrile bacterial infections within the last 2 weeks (this can trigger MG and may be associated with a more severe disease course); inverse aspiration of food and drink into the nose when swallowing; inadequate swallowing (causing coughing or throat clearing); aphonic dysarthria (increasing phonation weakness with hypernasal speech); dropped head (head tips forward due to fixed paresis of the head extensor muscles); dropped chin (i.e. the lower jaw drops after extended chewing); and, most importantly, a reduced vital capacity to <1500 mL (men)/<1000 mL (women) or estimated 20 mL/kg bodyweight [15,16]. The dynamics of a change in vital capacity is also important, with a rapid decrease (over a matter of days) posing the greatest concern.

3.3. Treatment of MG

Standard symptomatic treatment of MG is pyridostigmine, usually with the addition of corticosteroids (or steroid-sparing immunosuppressive therapy) in the case of moderate severity disease [17]. With increasing disease severity, treatment escalation to include IVIg, plasmapheresis or immunoadsorption therapies may be indicated. An exacerbation may necessitate intensive care [18].

All patients diagnosed with MG should be screened for thymoma; if found, the patient should undergo thymectomy. If a thymoma is not identified by computed tomography, AChR antibody–positive patients, aged 18–60 years, with

generalized disease and a disease course of <5 years may be considered for thymectomy as immunosuppressive-sparing treatment [19,20].

The latency period until an effect is observed varies according to type of therapy. Pyridostigmine can produce an effect within hours, whereas corticosteroids take 3–4 weeks, and extended therapy with steroid-sparing treatments can take 2–18 months. For example, azathioprine generally takes 12–18 months to produce an adequate effect in terms of stabilizing the patient's condition. Eculizumab is now available as an option for AChR antibody-positive patients with treatment-refractory MG, and takes 3–4 weeks to produce an effect [21].

Treatments used for exacerbations or myasthenic crisis, such as IVIg, plasmapheresis and immunoadsorption therapies, are faster acting, producing an effect within a few days to a couple of weeks [18].

3.4. Clinical trial of IVIg-C in subjects with severe acute MG exacerbations

The efficacy and safety of immune globulin (human) 10% caprylate/chromatography purified (IVIg-C) (Gamunex®-C, Grifols Inc., Clayton, NC, USA) were evaluated in a study of patients with MG exacerbations [22]. This phase 3, multicenter, prospective, open-label, non-controlled clinical trial was conducted in 15 centers in 10 countries. Participants received a 2 g/kg bodyweight infusion of IVIg-C administered as a 1 g/kg/day dose over 2 consecutive days. Key outcome measures were the Quantitative Myasthenia Gravis (QMG) test score, the Myasthenia Gravis composite (MG Composite) score, and the Myasthenia Gravis Activities of Daily Living (MG-ADL) profile.

The study included patients aged ≥18 years who had MG exacerbation, defined as worsening of symptoms with MGFA classification IVb or V; i.e. affecting the respiratory muscles, while receiving long-term (≥8 weeks) corticosteroid treatment for MG. Key exclusion criteria were: treatment with IVIg or plasmapheresis within 30 days, modification of corticosteroid treatment within the previous 2 weeks, positivity for anti-MuSK antibodies, or MG exacerbation attributable to a change in medication or an infection (with fever, positive blood culture, leukocytosis, or pulmonary infiltrates on x-ray).

The primary efficacy endpoint was the change in QMG score from baseline to day 14. Secondary endpoints included the percentage of participants with clinical improvement from baseline to day 14 (QMG decrease ≥3 points; MG Composite decrease ≥3 points; MG-ADL decrease ≥2 points). Change from baseline and percentage of participants with clinical improvement in QMG, MG Composite, and MG-ADL at other time-points (days 7, 21 and 28) were evaluated as exploratory endpoints. Safety measures included laboratory parameters and evaluation of adverse events. Changes in routine MG therapy were not permitted until after the primary endpoint assessment on day 14 (unless required for safety reasons).

Among 49 enrolled patients, 43 were evaluable for efficacy. The majority of participants (69.4%) were female, and median age was 47 years. All patients were MGFA Class IVb at enrollment, with a median time since initial MG diagnosis of 5.4 years. Overall, 59% of enrolled patients had a history of a positive AChR antibody test; amongst the efficacy-evaluable population, 32 (74%) were AChR antibody-positive at baseline and 11 (26%) were AChR antibody-negative. Patients had significant weakness, with mean baseline scores of 22.0 ± 4.60 points for QMG, 28.9 ± 6.80 points for MG Composite, and 13.8 ± 3.96 points for MG-ADL.

At day 14, there was a significant decrease from baseline in mean QMG score (primary endpoint) of – 6.4 ± 5.2 points (95% confidence interval – 7.96 to – 4.79, $p < 0.001$); Figure 2 [22], indicative of clinically meaningful improvement (decrease of ≥3 points). Improvement was evident by day 7, and was even more pronounced at days 21 and 28. Subjects with positive or negative baseline AChR levels responded similarly to IVIg-C

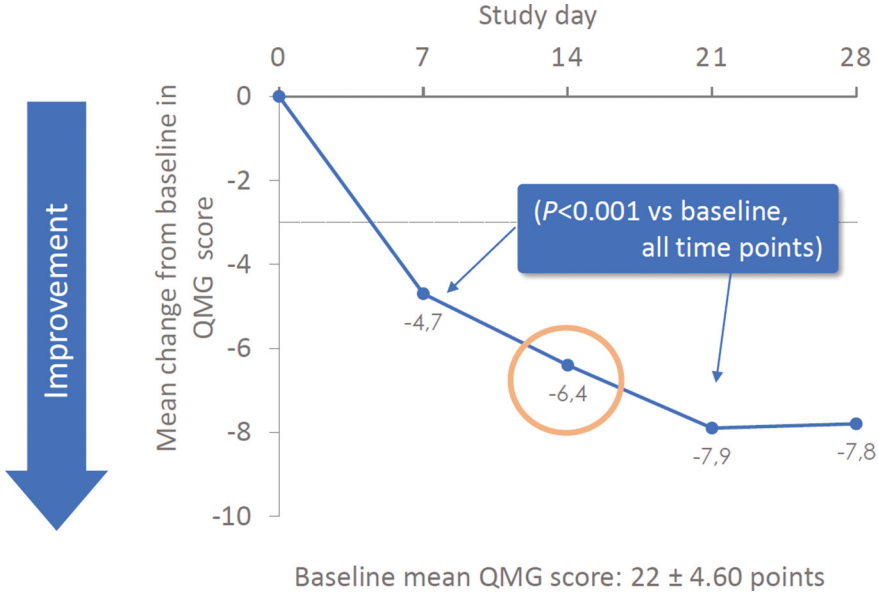

Figure 2. Efficacy of IVIg-C in patients with exacerbation of myasthenia gravis: change in Quantitative Myasthenia Gravis (QMG) score from baseline to day 14. Data from [22]. IVIg-C = immune globulin caprylate/chromatography purified.

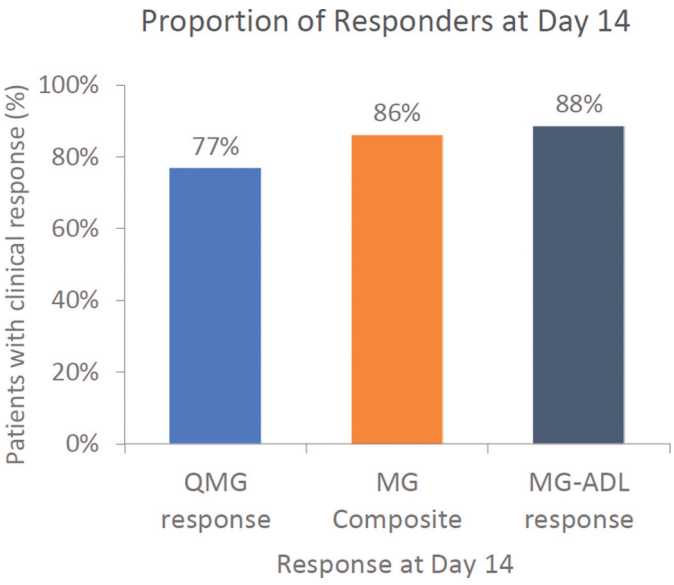

Figure 3. Efficacy of IVIg-C in patients with exacerbation of myasthenia gravis: percentage of participants with a clinical improvement from baseline to day 14 (QMG decrease ≥3 points; MG Composite decrease ≥3 points; MG ADL decrease ≥2 points). Data from [22]. IVIg-C = immune globulin caprylate/chromatography purified; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MG Composite = Myasthenia Gravis composite; QMG = Quantitative Myasthenia Gravis score.

treatment, and both achieved statistically significant improvements in the QMG score at Day 14. Improvements over time were observed for MG Composite and MG-ADL scores, with mean decreases of − 12.1 ± 7.7 and − 6.2 ± 3.9 points, respectively, recorded at day 14. The majority of patients experienced a clinically meaningful improvement in QMG, MG Composite and MG-ADL scores at day 14 (secondary endpoints; Figure 3) [22].

Overall, 80% of patients experienced a treatment-emergent adverse event (TEAE). Most TEAEs were mild or moderate in severity. There were no serious adverse events and no thromboembolic events. The most frequent TEAEs were headache (38.8%) and pyrexia (16.3%), followed by urticaria (8.2%) and influenza-like illness, rash and vomiting (each 6.1%). Three participants discontinued treatment after receiving IVIg-C because of mild or moderate adverse events; these events resolved within 1 day [22].

4. Conclusion

IVIg works by multiple mechanisms that restore immune balance, many of which are relevant for its effects in patients with MG. IVIg affects antibodies by providing idiotypic antibodies and potential neutralization of pathogenic autoantibodies, by accelerating the catabolism of pathogenic IgG through saturation of the FcRn transport receptors, and by suppressing B-cell trophic factors such as BAFF. Other effects include: inhibition of complement binding and prevention of MAC formation; suppression of pathogenic cytokines; upregulation of FcγRIIb inhibitory receptors, which intercepts antibody-dependent cell-mediated cytotoxicity; effects on APCs, T-cell modulatory functions and antigen recognition. Recent evidence suggests that polymorphisms in the *VNTR3* gene that encodes the FcRn receptor can affect IVIg kinetics and patient outcomes, which may explain at least in part the lower responsiveness of some patients to IVIg.

Fatigability is the central clinical feature of MG. Standard initial treatment is pyridostigmine, often with the addition of corticosteroids. As disease severity progresses, treatment is escalated to include IVIg, plasmapheresis or immunoadsorption therapies. A multicentre, prospective, open-label, non-controlled clinical trial of IVIg-C showed that it reversed the symptoms of severe acute exacerbation in patients with MG. Clinically meaningful improvements were observed for efficacy outcome measures as early as day 7, and continued to study end (day 28). There was a significant decrease in QMG at day 14 (primary endpoint) and high response rates were recorded for other outcome measures at this timepoint. Safety outcomes supported the well-established safety profile of IVIg-C in patients with severe acute exacerbations of MG.

5. Expert opinion

The pathogenesis of MG is mediated by various immunoregulatory events. IVIg has a range of immunomodulatory effects on relevant therapeutic targets for MG, such as suppression of circulating antibodies or antibody production, suppression of complement activation, and immunomodulation of cytokines or T cells. An emerging area of research is the pharmacogenomics of IVIg in MG. Recent data indicating that *VNTR3* genotype can affect the efficacy of IVIg in patients with MG are interesting. The potential for *VNTR2/3* genotype to act as a predictive marker for a poor response to IVIg in patients with MG, and the best approach to dose modification in these patients, require further study. Additional data on the role of pharmacogenomics in MG is likely to emerge in the coming years.

Plasmapheresis and IVIg are fast-acting therapies that are used to treat exacerbations and myasthenic crisis. Results of a phase 3 study provide evidence of the efficacy and safety of IVIg-C for treatment of severe acute exacerbations of MG. The magnitude of the treatment effect was impactful and clinically significant and consistent with improvements reported in randomized controlled clinical trials of IVIg in worsening MG/MG exacerbations.

Patients who experience exacerbations or myasthenic crisis despite ongoing immunosuppressive treatment may require escalation of therapy. Rituximab, a monoclonal antibody targeting B cells, is one option. However, most data on its use in MG come from uncontrolled studies, and a placebo-controlled study did not meet the primary endpoint mostly related to study design [23]. Considering the impressive clinical benefit reported with rituximab in uncontrolled series, additional studies to clarify how many cycles of rituximab are required to achieve treatment success and determination of biomarkers to help identify patients who would benefit from such treatment are needed. Eculizumab, a monoclonal antibody directed against complement has been approved for the treatment of generalized AChR+ MG [21] and other anti-complement agents are in the offing. Several other biologic agents, including agents directed against B cells and the FcRn receptor are currently being evaluated [2]. Efgartigimod, an FcRn inhibitor,

was recently approved by the FDA for the treatment of generalized MG [24] and other FcRn inhibitors are in Phase II–III clinical trials. It is hoped that in the near future additional targeted immunotherapies will be available for the treatment of patients with MG, including those with refractory disease, and this will likely change the therapeutic algorithm.

IVIg is effective for treating acute exacerbations by providing immediate relief. However, it is often used as maintenance therapy, although its long-term efficacy has not been established [2]. Clinical trials to formally evaluate the efficacy of IVIg in the long-term management of MG and as a steroid-sparing therapy have now been completed, but have not yet been reported (ClinicalTrials.gov: NCT 02473952; NCT 02473965). Considering that MG is a chronic autoimmune disease the results of these studies will add to the knowledge about the role of IVIg in the long-term management of MG.

Acknowledgments

Medical writing support in line with Good Publishing Practice-3 guidelines was provided by Drs Kathy Croom and Steve Clissold on behalf of Content Ed Net, Spain.

Declaration of interests

MC Dalakas has received consultancy fees from Baxter (data and safety monitoring board and lecture fees); Grifols/Talecris, Novartis, Octapharma (lecture fees and serving on DSMB); Alexion, Argenx, and Dysimmune Diseases Foundation (consulting fees). A Meisel has received speaker honoraria from Alexion, Argenx, BMS, Grifols, Hormosan, Novartis, Nutricia, and Pfizer; consultation fees from Alexion, Argenx, Bayer, and UCB; and research grants from Alexion and Octapharma; and is Chairman of the Medical Advisory Board of the German Myasthenia Society e.V, and Chairman of the Board of the Berlin Stroke Alliance e.V. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Funding

This project was funded by Grifols, during the 16th International Congress of Neuromuscular Diseases (ICNMD 2021).

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Dalakas MC. Immunotherapy in myasthenia gravis in the era of biologics. Nat Rev Neurol. 2019;15(2):113–124.
2. Dalakas MC. Progress in the therapy of myasthenia gravis: getting closer to effective targeted immunotherapies. Curr Opin Neurol. 2020;33(5):545–552.
3. Zhu KY, Feferman T, Maiti PK, et al. Intravenous immunoglobulin suppresses experimental myasthenia gravis: immunological mechanisms. J Neuroimmunol. 2006;176(1–2):187–197.
4. Ragheb S, Lisak R, Lewis R, et al. A potential role for B-cell activating factor in the pathogenesis of autoimmune myasthenia gravis. Arch Neurol. 2008;65(10):1358–1362.
5. Dalakas MC, Spaeth PJ. The importance of FcRn in neuro-immunotherapies: from IgG catabolism, *FCGRT* gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. Ther Adv Neurol Disord. 2021;14:17562864211997381.
•• **Recent review that discusses the role of FcRn in IgG catabolism and the effects of *VNTR2/3* genotypes in IVIg efficacy**
6. Basta M, Illa I, Dalakas MC. Increased in vitro uptake of the complement C3b in the serum of patients with Guillain-Barré syndrome, myasthenia gravis and dermatomyositis. J Neuroimmunol. 1996;71(1–2):227–229.
7. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest. 1994;94(5):1729–1735.
8. Tackenberg B, Jelcic I, Baerenwaldt A, et al. Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci U S A. 2009;106(12):4788–4792.
9. Xu W, Ren M, Ghosh S, et al. Defects of CTLA-4 are associated with regulatory T cells in myasthenia gravis implicated by intravenous immunoglobulin therapy. Mediators Inflamm. 2020;2020:3645157.
10. Su S, Liu Q, Zhang X, et al. VNTR2/VNTR3 genotype in the *FCGRT* gene is associated with reduced effectiveness of intravenous immunoglobulin in patients with myasthenia gravis. Ther Adv Neurol Disord. 2021;14:17562864209867 47.
• **Recent study showing that *VNTR3* genotype matters with respect to the efficacy of IVIg in MG**
11. Monsul NT, Patwa HS, Knorr AM, et al. The effect of prednisone on the progression from ocular to generalized myasthenia gravis. J Neurol Sci. 2004;217(2):131–133.
12. Jayam Trouth A, Dabi A, Solieman N, et al. Myasthenia gravis: a review. Autoimmune Dis. 2012;2012:874680.
13. Hehir MK, Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. Neurol Clin. 2018;36(2):253–260.
14. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task force of the medical scientific advisory board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. 2000;70(1):327–334.
15. Oger J, Frykman H. An update on laboratory diagnosis in myasthenia gravis. Clin Chim Acta. 2015;449:43–48.
16. Schroeter M, Thayssen G, Kaise J. Myasthenia gravis – exacerbation and crisis. Neurology International Open. 2018;2(1):E10–E15.
17. Hoffmann S, Kohler S, Ziegler A, et al. Glucocorticoids in myasthenia gravis - if, when, how, and how much? Acta Neurol Scand. 2014;130 (4):211–221.
18. Gilhus NE, Tzartos S, Evoli A, et al. Myasthenia gravis. Nat Rev Dis Primers. 2019;5(1):30.
19. Wolfe GI, Kaminski HJ, Aban IB, et al. MGTX Study Group. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375(6):511–522.
20. Rückert JC, Swierzy M, Kohler S, et al. Thymectomy in myasthenia gravis. Neurol Int Open. 2018;2(2):E124–E130.
21. Howard JF Jr, Utsugisawa K, Benatar M, et al. REGAIN Study Group. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976–986.
22. Karelis G, Balasa R, De Bleecker JL, et al., A phase 3 multicenter, prospective, open-label efficacy and safety study of immune globulin (human) 10% caprylate/chromatography purified in patients with myasthenia gravis exacerbations. Eur Neurol. 2019; 81(5–6): 223–230.
• **Phase 3 trial showing efficacy and safety of IVIg-C for the treatment of MG exacerbations.**
23. Nowak RJ, Coffey CS, Goldstein JM, et al. NeuroNEXT NN103 BeatMG Study Team. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized Myasthenia Gravis: the BeatMG Study. Neurology. 2021 Dec 2. Doi:10.1212/WNL.0000000000013121.
24. FDA News Release. FDA approves new treatment for Myasthenia Gravis. [cited Dec 2021] Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-myasthenia-gravis