


# Impact of Ravulizumab on Patient Outcomes and Quality of Life in Generalized Myasthenia Gravis

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**Abstract:** Myasthenia gravis (MG) is an autoimmune ion channel disorder in which antibodies to different end-plate antigens impair neuromuscular transmission, ultimately leading to muscle weakness and fatigability. In about 85% of patients with MG, autoantibodies against the acetylcholine receptor (AChR) activate the complement cascade, causing damage to the neuromuscular junction. MG is a chronic disorder for which standard therapies with corticosteroids, immunosuppressive drugs, and immunomodulation with plasma exchange or intravenous immunoglobulins modify the course of the disease, but the residual burden of physical, psychological, and social disability highlights several unmet needs, among these the need for specific, targeted, and well tolerated therapies able to improve the patients' quality of life. Complement inhibition paved the way to precision medicine in MG since, for the first time, a specific therapy targeting a crucial pathogenetic step has been designed, tested, and proven to be effective in a controlled fashion. Ravulizumab represents the first long-acting complement inhibitor approved for treatment of patients with generalized MG, able to provide rapid, complete, and sustained complement inhibition. Ravulizumab improved the MG Activity of Daily Living scale and other clinical parameters up to 26 weeks as shown by the CHAMPION MG trial, and by its open label extension, with the added value of being administered every 8 weeks. The schedule of administration is likely to improve patients' adherence and hence their quality of life. The introduction of complement inhibition will considerably change the traditional therapeutic strategy for MG.

**Keywords:** Myasthenia Gravis, complement, eculizumab, ravulizumab, quality of life

## Introduction

Myasthenia gravis (MG) is an autoimmune ion channel disorder affecting the neuromuscular junction characterized clinically by fluctuating muscle weakness and fatigability, worsened by exercise and improved by rest. Most patients present with impairment of extraocular muscles at onset, but usually within two to three years develop muscle weakness involving the limbs and bulbar and respiratory muscles in various combinations and degrees of disability.<sup>1</sup> MG is a chronic disorder for which current therapies are able to improve the natural history of the disease, but the residual burden of physical, psychological, and social disability highlights several unmet needs.

## The Immunopathogenesis of MG

The molecular immunopathology of MG has evolved considerably since the initial identification of the acetylcholine receptor (AChR) as the main target of autoimmunity in about 85% of MG patients.<sup>2,3</sup> Anti-AChR antibodies (Abs), belonging to the IgG1 and IgG3 subclasses, have several functions contributing to impairing neuromuscular transmission: they activate complement ultimately leading to tissue damage, increase internalization of the AChR by antigenic modulation, and interfere with ACh binding. The role of complement remains a crucial step in the pathogenesis of MG mediated by anti-AChR antibodies, a step suitable for specific immunointervention. Other autoantibodies have been later identified such as antibodies against the muscle-specific tyrosine kinase (MuSK), the low-density lipoprotein receptor-related protein 4 (LRP4), and agrin.<sup>4</sup>

The sequential identification of different autoantibodies has led to the immunological classification of the disease as anti-AChR-, anti-MuSK-, and anti-LRP4-associated MG. Despite the advances in the immunological techniques available

for the accurate detection of autoantibodies with the recent introduction of cell-based assays engineered to display the AChR to improve the diagnostic yield,<sup>5</sup> a small subgroup of patients is defined as seronegative MG (ie, patients without anti-AChR, MuSK, and LRP4 antibodies detected with conventional techniques) in which the pathogenetic mechanisms are still not understood. The possibility that antibodies against the AChR may be present but below the detection threshold may still be viable.<sup>4</sup>

The immunological classification of MG on the basis of the antibody specificity detected in each patient is now mandatory, not only for the sake of diagnosis but mainly as a guide to therapeutic decisions, even more so after the introduction of new targeted therapies. Indeed, the identification of anti-AChR antibodies represents the rational basis for considering complement inhibition in the therapeutic approach in the candidate patient.

## MG and Disability

Several factors, including symptoms of MG, the low chance of complete remission, the uncertainty regarding the clinical outcome, residual disability, and side effects of medications, have a great impact on the quality of life (QoL) of MG patients. It is not only the severity of the individual symptom that counts but also the context in which it occurs, and even symptoms mistakenly considered as minor such as ptosis and diplopia can be particularly disabling, especially in some social and work contexts. The scenario is even easier to understand considering deficits such as those affecting the limbs and the bulbar and respiratory districts which can compromise the patient's autonomy and require admission to the intensive care. The response to standard treatments is highly variable in terms of degree of improvement and time to achieve it. Consequently, the patient may be left with considerable physical limitations for a variable period of time. Moreover, about 10% of MG patients are considered refractory to standard treatments,<sup>6</sup> making the above considerations even more obvious since refractoriness can be long-lasting, is associated with increased frequency of clinical exacerbations or myasthenic crises, and with prolonged use of glucocorticosteroids, the main source of poorly tolerated side effects.<sup>7</sup> Finally, the proportion of employed people with MG is lower compared with the healthy population as emerged from a recent meta-analysis.<sup>8</sup> Moreover, the interference of MG on physical performance often leads to a reduction in work activity or a change in the type of work.

## How Do We Measure Disability and QoL in MG?

The International Classification of Functioning (ICF), Disability and Health identified three main areas in which a disease affects an individual: a) impairment of body functions (ie, signs and symptoms), b) activity limitations (ie, the effects of the disease on daily life activities), and 3) participation limitations (ie, the effects of the disease on social interactions).<sup>9</sup> Disability is therefore defined as the interaction between symptoms, activities and participation limitations, and the environment. In this context, the health-related quality of life represents a multidimensional concept that goes beyond disability itself and explains the need and complexity of its measurement. MG, due to its clinical features, is a challenge since typical signs and symptoms fluctuate within the same day and from day to day. Therefore, the assessment of a single time point cannot cover and represent correctly the wide range of manifestations of MG as well as its subjective implications over time. Several outcome measures have been developed to measure signs and symptoms of MG, most of which are used in clinical trials, and provide information on impairment of body functions: the most widely used are the QMG (Quantitative MG score), the MG-ADL (MG Activity of Daily Living), and the MGC (MG Composite).<sup>10</sup> These scores have been validated and the minimal important difference identified; their description is beyond the scope of this review (for details see ref).<sup>11–15</sup>

However, the importance of measuring the QoL, that is directly linked to and influenced by disability, is increasingly recognized, and some effort has been made to give space to the voice and experience of patients in the complex array of assessment tools. Besides the MG-ADL, available instruments are the MG-DIS (MG Disability scale),<sup>16</sup> the MGQoL15r (MG Quality of Life 15r),<sup>17</sup> and the recently described MG Symptoms PRO (Patient Reported Outcome), designed to capture symptoms as they are perceived by MG patients over a period of 7 days.<sup>18</sup>

The MGQoL15r, derived from the MGQoL60 and its shorter version MGQoL15, was found to have a good internal consistency and construct validity with correlation with QMG and MG-ADL scores.<sup>17</sup> The MGQoL15r is now widely used in clinical trials, but the information available from patients enrolled in clinical studies cannot be considered as a comprehensive picture of the whole population of MG patients, since they are strictly related to the RCT setting and the compound under investigation.

## The Impact of MG on QoL

The physical limitations imposed by the disease itself represent only one of the factors involved in reducing the QoL in myasthenic patients.<sup>19</sup> They are easily measured by rating scales at specific times, but the continuum of fluctuating impairment and disability is much more difficult to be reported and quantified. The humanistic burden including anxiety, depression, and sleep disorders adds to the physical limitations, particularly in patients with more severe symptoms. Comorbidities and side effects from standard treatments, particularly from corticosteroids, should not be underestimated, even though patients acknowledge that treatment is necessary to obtain improvement.<sup>7,20–24</sup> The burden of MG from the patient perspective has been recently reported by the observational survey-based study MyRealWorld MG, providing preliminary information on QoL and disease management of MG in patients from different countries.<sup>25</sup> Indeed, the use of corticosteroids was reported by 65.4% and immunosuppressive drugs by 48.1% of patients; 64.6% reported at least one additional medical condition. The mean total MG-ADL score was 5.7, and 19% of patients had a score equal to or greater than 10. The mean total MG-QoL15r score was 11.9. Anxiety and depression were reported in a considerable proportion of subjects, as well as a considerable impact on work or study.

The extent of the disease burden has emerged from a case-control study recently reported in 1660 German patients compared to the general population.<sup>19</sup> As far as QoL is concerned, the domains of physical functioning, vitality, social functioning, and emotional well-being were significantly impaired in MG patients. The burden was higher in female patients, particularly in those with high disease severity, low income, middle-aged or older. MG was also a limitation from the working point of view, such as incapacity of work or recurrent occupational disability.

## Standard Treatments and Unmet Needs in MG

Given the role of the thymus in the pathogenesis of the disease, thymectomy has been proposed with the aim to remove the site of possible initiation or perpetuation of the autoimmune attack in AChR-associated MG to promote improvement or remission. Conflicting results from observational studies have been reported by the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) study and its extension.<sup>26,27</sup> The main result was that thymectomy reduced the severity of MG and corticosteroid dosage, with the best results observed in patients younger than 40 years of age and with thymic hyperplasia. Therefore, the International Consensus recommends thymectomy in non-thymoma AChR+ MG patients, aged 18 to 50 years.<sup>28</sup>

MG is a chronic disorder requiring long-term immunosuppression in the majority of patients. Most of them, after initial symptomatic treatment with anticholinesterase inhibitors, are treated with corticosteroids (oral prednisone or prednisolone) at high doses which provide a rapid effect, usually within one month. Corticosteroids are progressively tapered up to the minimal effective dose, and are frequently associated with steroid-sparing immunosuppressive drugs such as azathioprine and mycophenolate mofetil (less frequently methotrexate, cyclosporin, or tacrolimus). The effect of immunosuppressive drugs is very slow, up to 6–9 months to exert their effect. Immunomodulatory treatments (plasma exchange and intravenous immunoglobulins) are used as rescue therapies in patients with clinical deterioration or MG crisis. IVIG are also used as maintenance therapy in selected patients, even though their long-term efficacy has not been demonstrated in a controlled fashion.<sup>28</sup>

Considerable progress has been made with standard treatment regarding survival rate, management of respiratory insufficiency and MG crisis, and global reduction of disability. Nevertheless, improvement can be achieved but at the price of potentially serious side effects that further reduce the QoL of MG patients. Despite the results obtained, the rate of complete stable remission of MG is still low, and refractory patients remain a therapeutic challenge.<sup>6,29,30</sup> Moreover, the diagnosis of MG in the elderly has increased in recent years, making the treatment of the disease even more difficult due to the frequency of comorbidities.<sup>31,32</sup>

## From Immunopathogenesis of MG to Innovative Treatments

The clinical experience over several decades has highlighted the urgent need for effective, targeted, and well tolerated therapies for MG. In this regard, the pathogenesis of MG, a prototypic IgG antibody-mediated disease, offers the extraordinary opportunity to investigate new therapies. Targeted immunotherapies in MG have focused on three main areas of intervention: a) B cells, as the source of autoantibodies; b) the neonatal Fc receptor for IgG, the inhibition of which increases IgG catabolism; and c) the complement system.<sup>33</sup>

The complement pathway represents the final step by which the anti-AChR Abs cause the junctional damage underlying the symptoms presented by patients, the first specific target involved in the pathogenesis of the disease to be exploited for therapeutic purposes. The complement system includes an enzymatic cascade leading to the production of factors that start the lytic pathway, and a lytic pathway itself leading to formation of the C5b-9 membrane attack complex (MAC). The enzymatic cascade includes three pathways, ie the classical, the lectin, and the alternative pathway. The classical pathway is activated when IgG1-3 (not IgG4) bind to C1q and alter its conformation with subsequent activation of C1r that leads, after several steps, to the formation of the C5 convertase complex that produces C5a and C5b. C5b promotes the lytic pathway and formation of the MAC, responsible for the formation of pores in the target membrane.<sup>34</sup>

Anti-AChR Abs, belonging to the IgG1 subtype, are able to activate the complement cascade, ultimately leading to damage of the postsynaptic membrane after MAC formation. Several lines of evidence supported the role of complement in MG. Deposition of complement has been demonstrated in damaged post-junctional folds in the animal model of MG as well as in humans.<sup>35,36</sup>

Complement-deficient animals develop a less severe disease, and the experimental disease is improved by complement-inhibition. In contrast, MuSK antibodies, belonging to the Ig4 subclass, do not bind complement and do not cause damage to the post-synaptic membrane, and therefore MuSK-associated MG is not a candidate for complement inhibition.<sup>34</sup>

## New Targeted Therapies: Complement Inhibition

Targeting C5, and hence inhibiting the formation and deposition of MAC, is a specific therapeutic strategy. C5 represents an optimal target since its blockade stops the complement cascade regardless of the activation pathway, and does not alter the upstream C3b-mediated opsonization function.

The first compound with this activity to be investigated is eculizumab, approved for generalized MG in the USA and for refractory MG in Europe after the phase III randomized trial REGAIN (NCT01997229).<sup>37</sup> A total of 125 AChR-positive MG patients were randomized to receive eculizumab (900 mg on day 1 and at weeks 1, 2, and 3; 1200 mg at week 4; and then 1200 mg every 2 weeks as maintenance treatment). MG-ADL, QMG, and MGQoL15 scores improved from baseline to week 26 in patients assigned to eculizumab compared to controls; MG exacerbations were less frequent as well as the use of rescue therapy in treated patients. Interestingly, the benefit from eculizumab administration was evident since the first weeks of treatment. Results from the REGAIN trial were further confirmed by its open label extension study with sustained improvement, and reduced rate of exacerbations and hospitalization (NCT02301624).<sup>38</sup> By week 130 of the open label extension, 51% of patients in the eculizumab/eculizumab group and 63% of the placebo/eculizumab group reached the minimal manifestations post-intervention status. Improvement of MGQoL15 total score observed during the REGAIN study was also maintained along the open label extension.

Post-hoc analyses of patients enrolled in the REGAIN study and its extension provided further information on the impact of complement inhibition on other parameters contributing to impaired quality of life in MG. Indeed, a significant proportion of patients achieved the minimal manifestation post-intervention status<sup>39</sup> and “minimal symptoms expression” defined as MG-ADL of 0–1 and MG-QoL15 of 0–3.<sup>40</sup> Eculizumab was associated with a better clinical outcome compared to rituximab in a subset of patients (however, the risk of myasthenic crisis was not modified); fatigue assessed by means of the NeuroQoL Fatigue score was improved, and 49% of patients were able to reduce the dose and 11% to discontinue corticosteroids.<sup>41,42</sup> It is worth noting that the REGAIN study (and its extension) was designed to investigate the efficacy of eculizumab in patients with refractory AChR-associated MG, making the results thus obtained even more encouraging considering the real-life management of MG patients. Eculizumab therefore represents the benchmark for complement inhibition in MG.

## From Eculizumab to Ravulizumab

Ravulizumab is a humanized long-acting monoclonal antibody inhibiting C5 developed from eculizumab to increase the half-life of the molecule and reduce the frequency of infusion of eculizumab that must be chronically administered every two weeks. The aminoacid substitution made to the eculizumab molecule resulted in improved dissociation of ravulizumab from C5 and increased recycling by FcRn with considerable extension of the molecule half-life and duration of action.<sup>43</sup>

The efficacy of ravulizumab has been investigated in the phase III CHAMPION MG study (NCT03920293).<sup>44</sup> Weight-based dosing of ravulizumab was found to achieve target serum concentrations within 30 minutes from the end of the first infusion, and concentrations were sustained independently from body weight up to 26 weeks of the maintenance treatment with ravulizumab administered every 8 weeks. Ravulizumab half-life was 56.6 days (8.1 weeks), considerably longer than that of eculizumab (18.2 days) in patients with AChR-associated MG. The pharmacokinetics and pharmacodynamics of ravulizumab are the basis for the results obtained by the CHAMPION MG study in which 175 patients were randomized to receive ravulizumab IV or placebo for 26 weeks. Ravulizumab dose was based on the patients's body weight, starting with a loading dose (2400, 2700, or 3000 mg) at baseline followed by maintenance doses (3000, 3300, or 3600 mg) given every 8 weeks. The primary efficacy endpoint was the change of the MG-ADL score from baseline to week 26. Ravulizumab was more effective than placebo in improving MG-ADL ( $-3.1$  vs  $1.4$ ) and QMG ( $-2.8$  vs  $0.8$ ) scores. Improvement occurred as early as week 1 from initiation and was sustained through week 26. A total of 35.5% of patients treated with ravulizumab reached 5 points improvement of the QMG score compared to 12.8% in the placebo group. Similarly, 9% of patients in the ravulizumab group and 17% in the placebo group met the criteria for clinical deterioration; 9% treated with ravulizumab compared to 16% in the placebo group needed rescue therapy. Improvement of MG-ADL was correlated with the time from diagnosis, since the reduction of the score was greater in patients diagnosed less than 2 years ( $-4.6$  compared to  $-2.9$  in patients diagnosed since  $>2$  years).

The CHAMPION MG study was followed by the open label extension (OLE) to assess long-term effects of treatment.<sup>45</sup> A total of 162 MG patients completed the CHAMPION MG study, 161 of whom entered the OLE, 78 from the ravulizumab/ravulizumab group and 83 from the placebo/ravulizumab group. The primary end-point was the change of the MG-ADL recorded at week 60; further outcome measures were the QMG, MGQoL15r, and the NeuroQoL Fatigue scales. Improvement provided by ravulizumab was sustained up to week 60 in all efficacy endpoints; moreover, MG-ADL improved  $>3$  points in 76% of patients, and QMG  $>5$  points in 49% of patients. Improvement was observed within 2 to 4 weeks in the placebo/ravulizumab group. The clinical deterioration event rate per 100 patient-years was reduced by 59.8% for ravulizumab compared to pre-study values and by 71% for ravulizumab versus placebo. The safety profile of ravulizumab during the OLE was similar to that of the CHAMPION study; upper respiratory tract infections and diarrhea were more frequently recorded in patients treated with ravulizumab. Four deaths occurred (three related to Covid, and one due cerebral hemorrhage in a patient with several comorbidities). Meningococcal infections were not reported in CHAMPION MG and its extension.

The overall results from REGAIN and CHAMPION MG studies definitively demonstrate that complement inhibition is an effective therapy able to modify the course of the disease and improve the QoL of MG patients. The positive clinical results obtained allowed the FDA approval of ravulizumab for the treatment of generalized MG on April 2022, followed by approval in Japan in August 2022 for the treatment of patients with MG poorly responsive to intravenous immunoglobulins or plasma exchange. Finally, ravulizumab has been approved in Europe as add-on treatment on September 2022.

## Perspectives

The experience with ravulizumab leads to several considerations on the treatment of myasthenia gravis and on how the traditional therapeutic approach is going to change progressively.

Thanks to the molecular modifications of eculizumab, ravulizumab provides complete and prolonged inhibition of complement, the biological basis of the sustained clinical improvement, with the added benefit of considerably reducing the infusion frequency (8 weeks versus 14 days), a feature that can further improve the patient's quality of life and adherence to treatment. The reduced frequency of administration also leads to lower disease management costs per patient.

From a clinical standpoint, patients enrolled in the REGAIN study had to fulfill the criteria for refractory MG, a feature not required by the CHAMPION MG study for which the MG-ADL total score of 6 or more was required for enrollment. This aspect is particularly important since the condition of refractory MG, still debated, requires a very long follow-up before being declared as such. Therefore, the clinical improvement obtained by the CHAMPION protocol and its OLE was recorded in a population of patients with a range of disease severity more close to real life without the limitations of refractory issues, a condition that is thought to occur in about 10% of MG patients. In practice, ravulizumab offers the added value of rapid improvement, while standard immunosuppressive drugs require several months to exert their effect, and biomarkers of



response to these treatments are not yet available. Therefore, it will no longer be necessary to try sequentially slow-acting immunosuppressive drugs over several months to obtain improvement.

Moreover, the rapid improvement provided by ravulizumab, together with the ease of administration, suggests the possibility of starting to treat patients directly, avoiding (or limiting as much as possible) the use of corticosteroids, a major source of poorly tolerated side effects for MG patients. No less important can be the role of ravulizumab for MG in the elderly, burdened by multiple comorbidities, a condition diagnosed more and more frequently in recent years thanks to greater attention and improved diagnostic techniques.

The impact of eculizumab and ravulizumab has been investigated in the context of clinical trials and their open label extension in patients with mild to moderately severe MG; given the fast action of these complement inhibitors, the question arises about the need to investigate their administration as rescue therapy, an issue to be addressed with a dedicated protocol. Clinical evaluation tools have shown that clinical efficacy is already evident in the first weeks of therapy with complement inhibitors in the great majority of MG patients; nevertheless, the chance of late clinical response or lack of improvement still exists. Because of the specific and selective mechanism of action of these compounds, the investigation of biomarker of response to complement inhibitors will be very important in the future to better address treatment prescription.

## Concluding Remarks

Complement inhibition has opened the long-awaited path to “precision medicine” in MG, since for the first time a specific therapy directed against a crucial pathogenetic step (ie, the complement-mediated damage of the neuromuscular junction) has been designed, tested, and proven to be effective in a controlled fashion, with a further support from open label extension studies. The success of complement inhibition in MG associated with anti-AChR antibodies is a dramatic achievement for a rare disease for which treatment protocols had remained unchanged for many years.

Indeed, the availability of new specific molecules has stimulated the design of clinical studies and the use of evaluation tools, making clinicians more aware of the importance not only of the objective assessments but also of the patients’ reported outcomes, in evaluating the effect of new therapies. In this regard, since MG and its standard therapies are a source of considerable disability for the patient, much more attention should be paid in the future to addressing the humanistic burdens of the disease as well as the impact of innovative therapies on them. The way to improvement has just begun since complement inhibitors, as well as other innovative therapies under investigation, are likely to change the therapeutic algorithm of MG in the years to come.

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## References

1. Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular disorders. *Lancet Neurol.* 2022;21(2):176–188. doi:10.1016/S1474-4422(21)00297-0
2. Huijbers MG, Marx A, Plomp JJ, LePanse R, Phillips WD. Advances in understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol.* 2022;21(2):163–175. doi:10.1016/S1474-4422(21)00357-4
3. Verschuuren JJGN, Palace J, Murai H, Tannemaat MR, Kaminski HJ, Bril V. Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders. *Lancet Neurol.* 2022;21(2):189–202. doi:10.1016/S1474-4422(21)00463-4
4. Masi G, O’Connor K. Novel pathophysiological insights in autoimmune myasthenia gravis. *Curr Opin Neurol.* 2022;35(5):586–596. doi:10.1097/WCO.0000000000001088

5. Damato V, Spagni G, Monte G, et al. Clinical value of cell-based assays in the characterisation of seronegative myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 2022;93(9):995–1000. doi:10.1136/jnnp-2022-329284
6. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord*. 2018;11:1756285617749134. doi:10.1177/1756285617749134
7. Bacci ED, Coyne KS, Poon JL, Harris L, Boscoe A. Understanding side effects of therapy for myasthenia gravis and their impact on daily life. *BMC Neurol*. 2019;19(1):335–347. doi:10.1186/s12883-019-1573-2
8. Guastafierro E, Tramacere I, Toppo C, et al. Employment in myasthenia gravis: a systematic literature review and meta-analysis. *Neuroepidemiology*. 2020;54(4):304–312. doi:10.1159/000506310
9. World Health Organization. How to use the ICF: a practical manual for using the International Classification of Functioning, Disability and Health (ICF). In: *Exposure Draft for Comment*. Geneva, Switzerland: World Health Organization; 2013.
10. Burns TM. History of outcome measures for myasthenia gravis. *Muscle Nerve*. 2010;42(1):5–13. doi:10.1002/mus.21713
11. Muppidi S, Silvestri NJ, Tan R, Riggs K, Leighton T, Phillips GA. Utilization of MG-ADL in myasthenia gravis clinical research and care. *Muscle Nerve*. 2022;65(6):630–639. doi:10.1002/mus.27476
12. Burns TM, Conaway M, Sanders DB. The MG Composite. A valid and reliable measure for myasthenia gravis. *Neurology*. 2010;74(18):1434–1440. doi:10.1212/WNL.0b013e3181dc1b1e
13. Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis: assessment of responsiveness and longitudinal validity. *Neurology*. 2005;64(11):196. doi:10.1212/01.WNL.0000163988.28892.79
14. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology*. 1999;52(7):1487–1489. doi:10.1212/WNL.52.7.1487
15. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score a. *Ann N Y Acad Sci*. 1998;841(1):769–772. doi:10.1111/j.1749-6632.1998.tb11015.x
16. Raggi A, Leonardi M, Schiavolin S, et al. Validation of the MG-DIS: a disability assessment for myasthenia gravis. *J Neurol*. 2016;263(5):871–882. doi:10.1007/s00415-016-8072-9
17. Burns TM, Sadjadi R, Utsugisawa K, et al. International clinimetric evaluation of the MG-QoL15, resulting in slight revision and subsequent validation of the MG-QoL15r. *Muscle Nerve*. 2016;54(6):1015–1022. doi:10.1002/mus.25198
18. Regnault A, Morel T, de La Loge C, Mazerolle F, Kaminski HJ, Habib AA. Measuring overall severity of myasthenia gravis (MG): evidence for the added value of the MG symptoms PRO. *Neurol Ther*. 2023. doi:10.1007/s40120-023-00464-x
19. Lehnerer S, Jacobi J, Schilling R, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. *J Neurol*. 2022;269(6):3050–3063. doi:10.1007/s00415-021-10891-1
20. Garzon-Orjuela N, van der Werf L, Prieto-Pinto LC, Lasalvia P, Castaneda-Cardona C, Rosselli D. Quality of life in refractory generalized myasthenia gravis: a rapid review of the literature. *Intractable Rare Dis Res*. 2019;8(4):231–238. doi:10.5582/irdr.2019.01121
21. Gelinas D, Parvin-Nejad S, Phillips G, et al. The humanistic burden of myasthenia gravis: a systematic literature review. *J Neurol Sci*. 2022;437:120268. doi:10.1016/j.jns.2022.120268
22. Andersen JB, Owe JF, Engeland A, Gilhus NE. Total drug treatment and comorbidity in myasthenia gravis: a population-based cohort study. *Eur J Neurol*. 2014;21(7):948–955. doi:10.1111/ene.12439
23. Gilhus N, Nacu A, Andersen JB, Owe JF. Myasthenia gravis and the risk of comorbidity. *Eur J Neurol*. 2015;22(1):17–23. doi:10.1111/ene.12599
24. Kliemec-Moskal E, Quirke M, Leite MI. Comorbidities in older patients with myasthenia gravis - Comparison between early- and late-onset disease. *Acta Neurol Scand*. 2022;145(3):371–374. doi:10.1111/ane.13549
25. Berrih-Aknin S, Palace J, Meisel A, et al. Patient-reported impact of myasthenia gravis in the real world: findings from a digital observational survey-based study (MyRealWorld MG). *BMJ Open*. 2023;13(5):e068104. doi:10.1136/bmjopen-2022-068104
26. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375(6):511–522. doi:10.1056/NEJMoal602489
27. Wolfe GI, Kaminski HJ, Aban IB. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. *Lancet Neurol*. 2019;18(3):259–268. doi:10.1016/S1474-4422(18)30392-2
28. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for management of myasthenia gravis: 2020 update. *Neurology*. 2021;93(3):114–122. doi:10.1212/WNL.0000000000011124
29. Baggi F, Andreetta F, Maggi L, et al. Complete stable remission and autoantibody specificity in myasthenia gravis. *Neurology*. 2013;80(2):188–195. doi:10.1212/WNL.0b013e31827b907b
30. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve*. 2008;37(2):141–149. doi:10.1002/mus.20950
31. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12:1–16. doi:10.1177/1756286419832242
32. Bubuic AM, Kudebayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. *J Med Life*. 2021;14(1):7–16. doi:10.25122/jml-2020-0145
33. Dalakas MC. Role of complement, anti-complement therapeutics, and other targeted immunotherapies in myasthenia gravis. *Expert Rev Clin Immunol*. 2022;18(7):691–701. doi:10.1080/1744666X.2022.2082946
34. Sanderson NSR. Complement and myasthenia gravis. *Mol Immunol*. 2022;151:11–18. doi:10.1016/j.molimm.2022.08.018
35. Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. *Mayo Clin Proc*. 1997;72:267–280.
36. Morgan BP, Chamberlain-Banoub J, Neal JW, et al. The membrane attack pathway of complement drives pathology in passively induced experimental autoimmune myasthenia gravis in mice. *Clin Exp Immunol*. 2006;146(1):146–302. doi:10.1111/j.1365-2249.2006.03181.x
37. Howard JF, Utsugisawa K, Benatar M, et al. 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):976–998. doi:10.1016/S1474-4422(17)30369-1
38. Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. 2019;60(1):14–24. doi:10.1002/mus.26447

39. Mantegazza R, Wolfe GI, Muppidi S, et al. Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and its open-label extension. *Neurology*. 2021;96(4):e610–e618. doi:10.1212/WNL.0000000000011207
40. Vissing J, Jacob S, Fujita KP, et al. “Minimal symptom expression” in patients with acetylcholine receptor antibody-positive refractory generalized myasthenia gravis treated with eculizumab. *J Neurol*. 2020;267(7):1991–2001. doi:10.1007/s00415-020-09770-y
41. Siddiqi ZA, Nowak RJ, Mozaffar T, et al. Eculizumab in refractory generalized myasthenia gravis previously treated with rituximab: subgroup analysis of REGAIN and its extension study. *Muscle Nerve*. 2021;64(6):662–669. doi:10.1002/mus.27422
42. Andersen H, Mantegazza R, Wang JJ, et al. Eculizumab improves fatigue in refractory generalized myasthenia gravis. *Qual Life Res*. 2019;28(8):2247–2254. doi:10.1007/s11136-019-02148-2
43. Sheridan D, Z-X Y, Zhang Y, et al. Design and preclinical characterization of ALXN1210: a novel anti-C5 antibody with extended duration of action. *PLoS One*. 2018;13(4):e0195909. doi:10.1371/journal.pone.0195909
44. Vu T, Meisel A, Mantegazza R, et al. Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. *NEJM Evid*. 2022;1(5):1–12. doi:10.1056/EVIDoa2100066
45. Meisel A, Annane D, Vu T, et al. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open label extension. *J Neurol*. 2023;270(8):3862–3875. doi:10.1007/s00415-023-11699-x

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