Long-Term Patient Outcomes: The Role of Sustained Treatment Efficacy in Myasthenia Gravis

Interviewees:



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Interview Summary

There have been great advances in the field of generalised myasthenia gravis (gMG) in recent years, but many patients remain dissatisfied with their disease state despite being on treatment. There is a growing consensus among specialists that minimising symptom burden, with sustained treatment efficacy, is the best way to improve outcomes.

gMG is a chronic autoimmune disorder, characterised by fluctuating muscle weakness. Traditional treatments focus on immunosuppression, but patients often face challenges with efficacy and side effects, including corticosteroid complications. Up to 20% of patients do not respond to standard treatments and still experience symptoms.

In this key opinion leader article, Carlos Casasnovas, Bellvitge University Hospital, Barcelona, Spain; Kristl Claeys, Department of Neurology, University Hospitals Leuven, Belgium; and John Vissing, Copenhagen Neuromuscular Centre, Rigshospitalet, Denmark, share their expert knowledge on the past, present, and future of gMG management. Speaking to EMJ in October and November 2024, they discussed how ongoing symptoms can have an important impact on the daily activities and quality of life of affected patients, the challenges of achieving sustained treatment efficacy with traditional approaches, and how emerging novel therapies may help address this critical unmet medical need.

INTRODUCTION

Myasthenia gravis (MG) is a rare IgG autoantibody-mediated disease caused by the pathogenic IgG-mediated disruption of cholinergic transmission at the neuromuscular junction.[1,2] It results in fluctuating weakness of the skeletal/voluntary muscles, which worsens with activity as the day progresses,[1] and has a prevalence of around 15–20 cases per 100,000 people.[3] Around 85% of people living with the condition have antibodies against the muscle acetylcholine receptor (AChR), while between 5–10% are muscle-specific kinase positive.[2] Up to 10% of patients are classed as seronegative, while receptor-related protein 4-positive gMG is a rarer form of the disease.[4]

There are two types of autoimmune MG: ocular and generalised. Ocular MG causes weakness of the extraocular muscles and manifests with diplopia and/or ptosis of the eyelid, while generalised MG (gMG) can also affect a range of other muscles.[1] "The clinical hallmark of MG is fluctuating muscle weakness," explained Claeys. "It can affect the eyes, causing ptosis or hanging eyelids, or the movement of the eyes, causing diplopia or double vision. Weakness can also be located in the bulbar muscles, meaning patients have difficulties swallowing, talking, and, in some cases, breathing. When the arms and legs are involved, people may, for example, have difficulties climbing the stairs or brushing their hair."

As an autoimmune disease, gMG follows a relapsing/remitting course, and patients can experience symptom fluctuations in the short term, as well as exacerbations in the long term.[5] "When you are with a patient you can see the ptosis, for example, fluctuating in the half hour of the consultation. When there is weakness in the arms, they can brush their hair to start with, but then become progressively fatigued. This is typical in gMG," explained Claeys. People can also experience extreme symptom exacerbations, presenting as progressive muscle weakness, dysphagia, diplopia, and respiratory deterioration, which can lead to life-threatening myasthenia crises requiring hospitalisation, respiratory support, and rescue medication.[5] "Exacerbations can be

caused by infections, for instance, influenza or a common cold, or triggered by certain medications, such as antibiotics," she added.[5]

MG can have a profound impact on quality of life (QoL). Low income, partnership status, lower activities of daily life, symptoms of depression, anxiety and fatigue, and self-perceived low social support have all been associated with a lower QoL in those with MG.[3] It can even impact major life decisions. More than half (58.4%) of women and 29.7% of men taking part in a German study of 1,660 patients with MG said the disease had influenced their decisions regarding family planning.[6] "This is a chronic disease: something people will have to live with the rest of their lives. It impacts on family life, on the person's job or education," said Vissing, with Claeys adding that the QoL impact "cannot be minimalised". "MG is really an important burden. Many patients are young people, and working can be difficult. Daily activities and taking care of their families can become very difficult. Psychologically, it's a heavy burden. At the beginning of the day, they have to think about what they can and can't do, they have to pace their efforts, because their muscles will not carry on for the whole day without resting," she explained. While the psychological burden appears to be more pronounced for younger patients, older people are not immune from the impact, Vissing added. "While it doesn't impact so heavily on your life, it is still demanding because, in many cases, people simply cannot do the things they used to," he explained.

CHALLENGES OF THE TRADITIONAL TREATMENT LANDSCAPE

Currently, gMG management guidelines vary from country to country, and the treatment framework is based primarily on expert consensus and clinical experience. In 2016, an international guidelines consensus paper from the Myasthenia Gravis Foundation of America-appointed Task Force set two goals of treatment: minimal manifestation status (i.e., no symptoms or functional limitations, with some muscle weakness on examination), and no or mild treatment side effects.[7] German guidelines, published in 2023, recommend aiming for the rapid achievement of complete disease control while restoring the patient's quality of life.[8]

Carlos Casasnovas said that, in general, the goal of treatment was to give people "as normal a life as possible". "In day-to-day clinic, the best way to define positive patient evolution is minimal symptom expression (MSE), or pharmacological/clinically stable remission for more than 1 year," he said. "MG is a relapsing–remitting disease, and you will always find exacerbations, improvements, and episodes of worsening, but 1 year with no special clinical findings is a very good objective." Claeys agreed, adding that the optimal objective should be sustained treatment efficacy, eliminating symptoms while avoiding any treatment side effects. MSE, defined as an MG Activities of Daily Living (MG-ADL) score of between 0–1, is "the ultimate goal", said Vissing.[9] While this is "usually achievable with conventional treatments", around 20% of patients still experience symptoms and QoL impact.[10]

As per the 2016 consensus paper, first-line therapy is usually cholinesterase inhibitors, such as pyridostigmine: a recommendation that remained unchanged in the document's 2020 update.[7,11] In mild MG, these agents can produce rapid relief of symptoms, but most people will need some form of immunosuppression to suppress autoantibody production.[12] Available agents include azathioprine, mycophenolate mofetil, cyclosporin, cyclophosphamide, tacrolimus, and rituximab.[12] Such medications, however, can take months to elicit a response, so patients are also usually prescribed corticosteroids.[12] "Steroids work quickly, are cheap, and can be tapered down once you have the effect of the other agents," explained Vissing. This approach, however, does not work for everyone, and some patients will still require small doses of corticosteroids to maintain control, said Claeys, adding: "The problem here is that there are so many side effects." Steroid treatment is associated with insomnia, mood changes, high blood pressure, significant weight gain,

and impaired glucose tolerance in the short term, and osteoporosis, skin atrophy, and glaucoma, as well as an increased risk of infection and cardiovascular events, in the long term.[12] Other patients will require more acute treatments, such as intravenous Ig or plasmapheresis, to manage MG crises, explained Vissing.[5]

SUSTAINED TREATMENT EFFICACY

Despite all these options, the experts highlighted that there is still a subset of patients, up to 20%, who experience symptoms and relapses, despite using conventional treatments.[10] "There are still patients who are not well controlled, even though they have been treated for years and may have tried three, four, or five treatments. There is an unmet need here," said Vissing.

Furthermore, achieving MSE can be challenging. In a study of 85 patients with AChR+ refractory gMG treated with immunotherapy, for example, only a little more than half (55.8%) had reached MSE by Year 1, and 60.3% at Year 2.[13] Another analysis showed patients with a high disease burden (MG-ADL score ≥6) "rarely achieved" MSE after 1 year of treatment.[14]

"Only very few patients will be completely symptom-free," said Claeys. In her clinical experience, she sees patients who still experience ongoing issues, including fatigue and myasthenic crisis, despite receiving conventional therapies. "They can be doing well, then they suddenly have an infection, a stressful period with less sleep, or they receive antibiotics or other medications that interact with their immunosuppressive treatment, and have a myasthenic crisis," she said.

In addition, many patients remain dissatisfied with their level of symptoms and the impact on their QoL. This has been demonstrated by studies utilising the Patient Acceptable Symptom State (PASS). PASS consists of asking the patient a single yes or no question: 'Considering all the ways you are affected by myasthenia gravis, if you had to stay in your current state for the next months, would you say that your current disease status is satisfactory?'[15] In one study of 100 patients in Denmark, a third said they were dissatisfied with their current symptom state, with increasing MG symptoms, fatigue, depression, and low MG-related QoL all playing a role.[16]

All three experts said asking the PASS question was a useful way to understand the impact of gMG on a patient's daily life. However, its subjective nature means it has limitations when attempting to assess the sustained efficacy of treatment. As such, it should be combined with other scales, such as the MG-ADL, they highlighted.[17] "Some patients will say they are satisfied, despite not being very well controlled, because they have come from a much worse place and can now do more things," said Vissing. "This is something we should be attentive to, because even though they tell us they're happy, there may be things we can do to make it better." Furthermore, some patients will have a relatively light symptom burden and perceive it as high; whereas, others may experience a wide range of troublesome symptoms, but "not want to complain", added Claeys. Casasnovas agreed, explaining that it was important to consider the patient's individual circumstances when assessing symptom burden.

EMERGING THERAPIES

Recent years have seen the emergence of novel therapies that could help improve treatment efficacy, potentially with an improved tolerability profile. C5 complement inhibitors, which have been developed in the AChR+ population, prevent C5a-induced chemotaxis of the proinflammatory cells, which in turn may prevent complement-mediated membrane damage at the post-synaptic membrane of the neuromuscular junction.[18] Neonatal fragment crystallizable receptor (FcRn) blockers selectively target FcRn IgG recycling. This lowers levels of circulating IgG, including the gMG pathogenetic autoantibodies.[19] "Some of these novel treatments have already been approved

and are being used, and I am sure others will be arriving on the market soon," said Claeys. These subcutaneous and intravenous biologic agents have a rapid effect,[19,20] and, according to Claeys, appear to have fewer side effects and drug–drug interactions than traditional approaches. "This is important because these are the problems we have with conventional therapies. Of course, we still need to gather the long-term data, but, for now, it looks very promising."

The novel FcRn blockers are based on two different dosing schedules: cyclic (symptom-based), where patients undergo an initial course of treatment with any additional treatment cycle being based on clinical evaluation, or predictable (fixed dosing), where treatment cycles are administered on a regular, ongoing basis.[21-24] There are pros and cons with each, said Claeys. "In cyclic dosing, the benefit could be that the treatment cycles are administered based on the patient's needs. For the predictable or fixed dosing, the benefits could be that this may provide more sustained disease control. Potential drawbacks in cyclic dosing could be that you have to wait for a clinical deterioration before you can start a new cycle of treatment, and the treatment-free periods could be short. The potential drawback for predictable dosing could be logistical challenges, such as patients having to come into the clinic every 2 weeks."

These new treatments, however, are not universally available. At present, they are not reimbursed in some countries,[25,26] and others, including Spain (Servei Catala, personal communication) and Belgium, have restricted their use to patients with MG-ADL scores of $^{3}5$ or $^{3}6$, depending on the agent, in line with clinical trial inclusion criteria. "Many patients who have remaining symptoms and are not satisfied with their treatment will not have a sufficiently high MG-ADL score to be considered eligible," said Claeys. Casasnovas said the cut-off point raised concerns for "people in the middle". "For the very severe patients with an MG-ADL of >6, we have these new treatments, and we will try to do our best for them. But for me, the main unmet need is the patients who are doing better than at the onset of the disease, and for whom the classical treatment is working, but they have not achieved MSE and have an MG-ADL score of 3, 4, or 5." The impact of this "gap" is different for different patients, he went on, using examples from his own clinic. "I have one patient who is a pilot with a flight company, another who is a neurosurgeon, and many who are retired, all of whom experience double vision and have low MG-ADL scores." How the symptom impacts each of their everyday lives, however, is vastly different. "It's an extreme example, but it shows that while MG-ADL is a good score, it is not definitive." It's important to remember that a score of 3 or 4 means a patient will experience symptoms that impact fundamental parts of their everyday lives, from washing their hair and brushing their teeth, to chewing and swallowing food, he added. Claeys said she was "convinced" that these less affected patients could benefit from novel therapies. "Some patients become refractory to treatment because they are not treated early and intensively enough. At a certain stage, none of the medications will help them anymore, so I think we could be missing a chance by not treating people who have a lower MG-ADL with these new treatments." Cost is, of course, the main barrier to reimbursement, but the wider benefits should also be considered, she went on. "I'm sure if you calculated all the missing workdays and all the other socioeconomic results of not being treated completely, or treated well, it would come to a very high figure. Perhaps if we had that data, it could help convince the authorities that it might be interesting to start the novel therapies at a lower MG-ADL score," she said.

FUTURE DIRECTIONS

The MG treatment field has come a long way in the last decade or so, but the healthcare community "can never be satisfied when there is still a sizable fraction of the patient population that is not well controlled," said Vissing. "There is not a single centre that has 100% well-controlled patients. It just doesn't exist," he went on.

"So, although we have come a long way, I don't think we should be pleased or satisfied with the current situation."

Casasnovas said the new therapies had "raised the bar" on what can be achieved in gMG management. Twenty years ago, there was "no hope" for the very refractory patients, he said, and 10 years ago, he was satisfied with achieving sustained treatment efficacy in 70% of patients. However, things have changed. "With the new treatments, I have definitely become more ambitious; I want more. With more options to treat these patients, why can't we achieve remission in 99% or even 100% of them? With the new treatments, we are looking forward and thinking about the possibility of achieving MSE in all patients," he said.

CONCLUSION

Clinical experience suggests that enhancing symptom management and QoL is what matters to patients with gMG. Sustained treatment efficacy, experts are convinced, is key. Despite a range of available treatments, however, many patients fail to achieve MSE with conventional therapy, and few live symptom-free lives. In addition, many are exposed to the potential side effects of corticosteroids and other conventional immune suppressants.

In the future, new therapies could allow for more sustained disease management. As research progresses, these therapies could provide improved management options that enhance the daily lives of people affected by this chronic condition.

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