Refractory myasthenia gravis: the more we learn, the less we know.

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ABSTRACT

Refractory myasthenia gravis (MG) identifies the group of patients who have inadequate symptom control and persistent muscle weakness and fatigability despite the use of multiple immune modulatory therapies. This manuscript highlights what is currently known about refractory MG and underlines major knowledge gaps, drawing attention to the unmet needs in our understanding of this disease subset. This review raises questions about our current understanding of refractory disease and how emerging data as well as therapies may alter our thinking and patients' disease course.

Key words: *refractory myasthenia gravis; quality of life; acetylcholine receptor; muscle specific kinase; thymectomy; eculizumab; rituximab; tacrolimus; cyclophosphamide*

Introduction

Myasthenia gravis (MG) is the prototype immune-mediated neuromuscular disorder with autoimmunity against components of the neuromuscular junction causing disruption of neuromuscular transmission and subsequent characteristic fatigable muscle weakness (1). As an autoimmune disorder, MG is categorized in several different ways including clinical phenotype (ocular versus generalized), early versus late onset (initial symptoms before or after age 50 years), association with thymoma, and serological subtypes (antibodies against acetylcholine receptor [AChR], muscle specific kinase [MuSK] or lipoprotein-related protein 4[LRP4])(2). MuSK+ MG, which accounts for <10% of all myasthenia, is unique from AChR+ antibody disease based on several differences including IgG subclass (IgG4 versus IgG1 and 3 subclass), target protein, clinical phenotype, association with thymoma, response to cholinesterase inhibitors, disease course, and immune modulatory treatment response. MuSK+ MG tends to have worse clinical nadir and faster progression than AChR+ disease. Given its propensity to affect bulbar muscles, there is greater risk of myasthenic crisis. A greater proportion of MuSK+ MG patients have refractory disease compared to AChR+ patients (3–5), though it is important to keep in mind that AChR+ disease is proportionally greater among most refractory MG cohorts. Thymoma-associated MG is similarly more difficult to treat than non-thymomatous MG. Across different populations, younger age of disease onset and women have been identified as patient-specific risk factors for poorer response to therapy.

Treatment response has been included in the conceptual framework of MG for as long as disease-modifying treatments have been a part of disease management strategy (6–8). Most studies estimate the prevalence of refractory MG to be between 10-20% of generalized MG (3,4,9). Refractory disease poses a significant challenge for clinicians and patients, as it is associated with impoverished quality of life, lifestyle challenges, health care resource utilization, and increased morbidity. There is a need to better understand the underlying mechanisms of refractory MG, identify biomarkers to guide therapy, and develop more effective treatments.

This review aims to provide an overview of refractory MG, including diagnostic criteria, disease burden and current treatment options. The manuscript will also discuss emerging therapies, including biologics and immunomodulatory agents, as well as the challenges and opportunities in managing refractory MG. By advancing understanding of refractory MG, the hope is to improve outcomes and quality of life for patients with this challenging condition.

Defining Refractory Myasthenia Gravis

Several publications (Table 1) have operationalized the term "refractory MG" for describing an MG cohort that in some way experiences suboptimal response to immune modulatory treatment, be it lack of response in terms of symptom relief, occurrence of disease exacerbations, clinician impression of treatment response, need for adjunct therapy, frequency of disease exacerbations, or undesired or intolerable side effects (3,5,10–12).

These definitions have variable degrees of subjectivity associated with them, both on the part of patients and providers. More importantly, while there may be considerable overlap between these definitions, the separation of refractory and non-refractory disease states differs significantly. The University of Toronto group applied these various criteria to a cohort of 237 patients within their group practice at two time points (at the time of the original cohort inception [2014-16] and at the last clinical visit [August 2019]) and found a high degree of

Table 1: Definitions of refractory myasthenia gravis arranged by date of publication, adapted from Tran C, *et al* (13).

PUBLICATION	DEFINITION
Drachman et al. 2008 (10)	1. Failure to respond to otherwise adequate doses and durations of conventional immunosuppressive treatments. 2. Have unacceptable adverse side effects of the treatments. 3. Require an excessive amount of potentially harmful agents. 4. Have comorbidities that preclude the use of conventional therapy. 5. Require repeated rescue with short-term intravenous immunoglobulin or plasma exchange treatments.
Suh et al. 2013 (3)	1. Unable to lower immunotherapy without clinical relapse. 2. Not clinically controlled on immunotherapy regimen. 3. Severe side effects from immunosuppressive therapy.
Sanders et al. International Consensus Guidance, 2016 (11)	Myasthenia Gravis Foundation of America (MGFA) Task Force post-intervention status (PIS) is unchanged or worse after corticosteroids and at least 2 other IS agents used in adequate doses for an adequate duration WITH (a) persistent symptoms OR (b) side effects that limit functioning, as defined by patient and physician.
Howard et al. REGAIN Study, 2017 (12)	1. Treatment with two or more immunosuppressive therapies for 12 months without symptom control, OR 2. At least one immunosuppressive therapy with intravenous immunoglobulin or plasma exchange given at least four times per year.
Mantegazza et al. 2018 (5)	1. Failure to respond adequately to conventional therapies: insufficient response to maximal safe doses of steroids and at least one immunosuppressive drug at an adequate dose and duration. 2. Inability to reduce immunosuppressive therapy without clinical relapse or a need for ongoing rescue therapy such as intravenous immunoglobulin (IVIg) or plasma exchange (PLEX). 3. Severe or intolerable adverse effects from immunosuppressive therapy ("treatment intolerant"). 4. Comorbid conditions that restrict the use of conventional therapies (also "treatment intolerant"). 5. Frequent myasthenic crises even while on therapy.

variability between the criteria (13). While the Drachman, Suh, and Mantegazza criteria identified about 40% of patients as refractory, this number significantly dropped to 10% and 3% when applying the Sanders/International Consensus Guidance and Howard/REGAIN Study criteria. Furthermore, there was significant difference in classification even between the Sanders and Howard criteria. Conversely, the Myasthenia Gravis Impairment Index (MGII), Neuro-QoL-Fatigue, and Myasthenia Gravis Quality of Life 15 (MG-QOL15) scores all showed worse patient-reported symptom states in patients classifiable as refractory using the Sanders and Howard criteria versus the other 3 criteria. Thus, comparing results from studies is challenging based on the differences amongst criteria.

These criteria may exclude certain disease subtypes within MG. For example, studies from a South Africa cohort of patients showed that Blacks were more likely than Whites to develop treatment-resistant oculoparesis and ptosis, termed the ophthalmoplegic variant of MG (14). Escalation of therapy may be considered an exercise in futility and higher risk than benefit for such patients by their providers. Based on this, patients would not fulfill

criteria for "refractory" yet would experience persistent and debilitating symptoms.

All the above criteria do not account for thymectomy as a potential therapy, for either thymoma-associated or non-thymomatous MG. Thymoma-associated MG is well known to pose greater therapeutic challenges than non-thymomatous disease. Conversely, the benefit of thymectomy in acetylcholine receptor antibody-positive, generalized, non-thymomatous MG now is indisputable on the basis of the MGTX study (15).

The term "refractory" also carries a sense of futility for a disease, and yet this is hardly the case. This point is emphasized by the pivotal phase 3 REGAIN study of eculizumab which required "refractory" status for inclusion into the trial. Despite this disease categorization, eculizumab therapy resulted in clear and rapid improvement in patient-reported and provider-assessed measures (12). Several retrospective studies have suggested efficacy of rituximab and cyclophosphamide in refractory MG (10,16–18). In their study, Tran *et al* found that some patients who fulfilled criteria for "refractory" status at the initial study period (2014-2016) subsequently moved to "non-refractory" status at the later study timepoint (2019), again supporting the notion that this designation is not exactly a "point of no return".

Burden Of Refractory Disease

That refractory disease associates with persistent MG symptoms is self-evident. Analyses of the MGFA Patient Registry showed that MG-QOL15, Myasthenia Gravis Activities of Daily Living (MG-ADL), and NeuroQoL Fatigue scores were higher in the refractory compared with the non-refractory cohort (19).

Another analysis of enrollment data from the MGFA Registry showed that, compared to patients with non-refractory disease, those with refractory disease were significantly more likely to have experienced at least one MG exacerbation, ER visit, hospitalization, ICU admission at any time for reasons associated with MG, or previously required a feeding tube (27). Data analysis from two administrative health plan databases showed that refractory patients had 4 times higher odds of experiencing a myasthenic crisis and 4.7 times higher odds of experiencing MG exacerbation compared with non-refractory patients (28). A Spanish MG Registry study showed that drug-refractory patients (defined per Sanders/ICT criteria) needed IVIg (86.9% vs 23.7%, $P<0.0001$) and PLEX (19% vs 4.4%, $P<0.0001$) more frequently compared with non-drug refractory patients (4). Whether or not patients with refractory MG are at higher risk of mortality compared to non-refractory patients is not certain though one Korean study reported higher hazard ratio (2.49) for the former group (29).

Danish and Japanese studies have shown that MG negatively impacts employment productivity among patients with MG (30,31). Patients with refractory disease fare worse: the MGFA Registry enrollment survey showed that non-refractory patients had higher odds of previous (2.643) and current (2.777) employment compared with refractory patients (32).

In recent years, there has been increasing interest in studying the impact of MG on symptoms and experiences other than those related to muscle weakness. There is increasing evidence that patients with MG have higher burdens of anxiety, depression, and poor sleep (20). While no studies have specifically compared the presence of these issues between refractory and non-refractory disease, findings of recent studies suggest a higher burden with more severe disease (21,22).

The generalized feeling of fatigue reported by many patients, distinct from muscle fatigability with continuous or repeated use, has been a particularly challenging issue in MG care. Providers often struggle with this symptom as it is difficult to understand from the pathophysiologic standpoint and difficult to correlate with disease activity. Thus, the tendency is to limit intervention on the basis of observable muscle weakness and muscle fatigability and not the perceived experience of patients. Yet, multiple studies point to fatigue being an important symptom of the disease even in patients with mild disease (23–25). At least one prospective study, the REGAIN phase 3 trial of eculizumab, reported improved fatigue that mirrored improvements in other MG scales (26). This is not to say that patient-reported fatigue should become a part of the conversation around refractory disease nor that it should lead to consideration of complement inhibitor therapy. Yet, there is increasing awareness of it as a contributor to disease burden, and its impact would presumably be greater in sub-optimally controlled disease.

Treatment Options

The initial International Consensus Guidance manuscript suggested the use of chronic IVIg or PLEX, cyclophosphamide, and rituximab in addition to other conventional immunosuppressive therapies (IST; azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus) for treatment of refractory MG (11). This work was completed prior to the publication of the pivotal phase 3 REGAIN study of eculizumab in refractory MG. A subsequent update included the use of eculizumab for severe refractory AChR+ generalized MG (33). Several studies have reported on the use of these agents

in mixed MG cohorts (AChR+, MuSK+, seronegative), whereas few studies have specifically studied refractory MG patients. To date, no clinical trials have assessed the efficacy of IVIg or PLEX in refractory MG.

The data on rituximab effectiveness in generalized MG were primarily based on observational studies and systematic reviews until recent years (34,35). These studies have shown improvement in both AChR+ and MuSK+ MG patients with both refractory and non-refractory disease, though response may occur more frequently in MuSK+ MG. Improvements were noted in clinical state (MGFA PIS, MG specific scores), clinical relapse, and need for immunosuppressive therapy. Rituximab was largely well-tolerated in all studies. Two recent randomized trials in AChR+ gMG are noteworthy. The phase 2 BEAT MG study randomized patients to two cycles of rituximab (four weekly infusions of 375 mg/m^2) six months apart versus placebo (36). The primary endpoint was a greater than 75% reduction of mean prednisone dose in the four weeks prior to week 52 compared to the four-week period prior to baseline with either clinical improvement or no worsening (≤2 point increase) in MGC scores and with rituximab treatment accounting for at least 30% of the observed difference between the two groups in a futility design; this primary outcome was not observed. Similarly, no significant differences were noted in several secondary outcomes. Patients treated with rituximab had a numerically lower relapse rate and need for rescue therapy compared to placebo. More recently, a multi-center, prospective, double-blind, placebo-controlled trial of low dose rituximab (single 500 mg infusion) in early gMG had more favorable results (37). The primary endpoint of achieving a QMG score ≤4 and prednisone dose ≤10 mg/day at week 16 with no rescue needed between weeks 9-16 was achieved by 71% of rituximab treated patients compared to 29% in the placebo group (p=0.007). Need for rescue therapy was also significantly lower in the rituximab group. Currently, rituximab treatment is well-recognized as being effective for, and is an early consideration in, MuSK+ MG. The Rinomax study suggests the same might be true in early management of AChR+ disease.

Several studies have shown potential therapeutic benefit of tacrolimus in MG, including a randomized, placebo-controlled study (38,39). One study looked at its use in "refractory" patients, though this was defined loosely as those patients who did not respond well to conventional treatment or were unable to withstand side effects (40). Wu *et al* treated 24 refractory MG patients with 3 mg/day oral tacrolimus. QMG, manual muscle testing (MMT), MG-ADL, and MG-QOL15 scores were significantly lower at 2, 6, and 12 months compared to baseline (40). Mean prednisone dose was reduced by about 60%, and therapy was generally well-tolerated with mild side effects. Tacrolimus use is recommended as next in line to prednisone in Japan (41).

A few small studies have shown benefit of cyclophosphamide in gMG. A small randomized trial showed statistically significant reduction in prednisone doses in both cyclophosphamide- and placebo-treated patients at 6 and 12 months and a significant difference between the two treatment groups at those time points (42). Drachman and colleagues treated 12 refractory MG patients with their "rebooting the immune system" protocol of high dose cyclophosphamide (50 mg/kg/day for 4 days) (10). Eleven patients had "clinically obvious beneficial effects", 6 had "very good to excellent responses" for at least a year, and 2 remained in complete remission for multiple years. Another retrospective study showed improvement by at least 1 point on the Osserman scale in six out of eight refractory MG patients treated with monthly cyclophosphamide at 30-50 mg/kg for at least 6 months (18). Response was maintained for a mean duration of nine months.

Eculizumab, a selective inhibitor of C5 activation, is the only agent exclusively tested in the refractory MG cohort in a large, randomized, double-blind phase 3 study (12). Based on worst-rank ANCOVA analysis, the study did not meet its primary efficacy endpoint of change in MG-ADL in treated versus placebo groups. However, QMG and MG-QOL15 scores did achieve significance on the worst-rank analyses, and all measures (MG-ADL, QMG, MG composite [MGC], and MG-QOL15) showed significant improvement compared with placebo on prespecified repeated-measures sensitivity analyses.

Several neonatal Fc receptor (FcRn) antagonists are currently in late stage development with efgartigimod being the first-in-class approved agent after the positive pivotal ADAPT study (12). Clinical trials with these agents have included, though not exclusively, some patients who would fulfill various criteria for refractory disease. It stands to reason that targeting this mechanism of action will be considered in patients with both refractory as well as non-refractory disease.

Discussion

"*When language is ambiguous, thought is imprecise and vice versa*" (43).

What exactly does "refractory MG" denote and how is this designation helpful with regard to management of MG? If this really identifies a group of patients who have difficult to treat disease with higher disease burden and worse outcomes, then ideally there should be ways to identify them beforehand. This in turn would better guide treatment approaches and create the ability to forecast their disease

course. However, we currently have no such ability, and we know precious little about what separates refractory from non-refractory disease. All current definitions determine refractory disease on a retrospective basis and in a somewhat arbitrary fashion.

Younger age, female gender, thymoma-associated MG, and MuSK+ disease confer greater risk of refractory MG. Yet, treatment choices are made moreso based on side effect profile rather than age and gender for the first two factors. For example, weight gain and teratogenic potential are important considerations, rather than potentially higher risk of refractory disease, when deciding on steroid and non-steroidal immunosuppressant use, respectively in young women. Similarly, the decision to perform thymectomy is based on the treatment of the thymoma itself, not to alter MG disease course. Treatment decisions are certainly influenced by the known worse disease course for MuSK+ disease; hence earlier consideration of rituximab in these patients, similar to other IgG4 mediated neurological and non-neurological disorders. However, a greater number of refractory MG patients are AChR+ rather than MuSK+ and, as discussed above, the data for rituximab in AChR+ are not as encouraging. Based on the seminal MGTX study, we know that early thymectomy in AChR+ non-thymomatous gMG confers significant advantages over prednisone alone in terms of clinical improvement, long-term steroid exposure, relative risk of exacerbations and crises, and need for adjunct non-steroidal immunotherapy (15,44). *Does this also confer relative risk reduction for refractory disease?*

All criteria for refractory MG require adequate dose and time on specific therapies. For steroids, the dose and duration are not specifically defined in any of the criteria. There is greater consensus among experts on the dose and duration for non-steroidal therapies like azathioprine, mycophenolate, methotrexate, and others. Even with the most lenient criteria, any individual patient would have to spend at least a year on steroids and non-steroidal immunotherapy while demonstrating a suboptimal response before being considered "refractory". Does a longer duration of sub-optimally treated disease adversely affect potential for improvement? This may hold true for at least a subset of patients, such as those with the "ophthalmoplegic" variant of MG (45). Conversely, though, the mean disease duration was nearly 10 years in the REGAIN study cohort, and yet these patients showed rapid and clinically meaningful improvements with eculizumab therapy (12). *Is the propensity for poor recovery uniform across the disease, or are there subsets within the disease that have better or poorer odds of recovery?*

Multiple other recent clinical trials of complement and FcRn inhibition have shown rapid, clinically meaningful, and statistically significant treatment responses compared to placebo, within days to weeks. *How will these newer therapies impact our current definitions of refractory MG? More importantly, would earlier use of these newer therapies "buy" more time and alter the odds of becoming refractory?*

The REGAIN trial and other studies also highlight the point that patients with "refractory" disease may still improve (4,12). So, defining a patient as having refractory MG does not signify a disease nadir from which there is no hope of improvement. It may simply mean that the correct treatments have not been tried. One study found that certain single nucleotide polymorphisms (SNPs) in the glucocorticoid gene influence steroid response in patients with MG (46). Similarly, another study identified polymorphisms in cytochrome P450 3A5 (CYP3A5) and heat shock protein 90AA1 (HSP90AA1) associated with refractory versus non-refractory MG (47). Rose *et al* demonstrated that AChR antibodies have varied specificity for epitopes on the acetylcholine receptor. While antibodies with a single specificity bind AChR, they alone do not activate complement. However, antibodies with different epitope specificities act synergistically, strongly activate complement, and damage the neuromuscular junction (48). Obaid *et al* showed that complement activation varied significantly between sera from different AChR+ MG patients, with only 60% sera activating complement and resulting in detectable membrane attack complex (MAC) formation (49). All of this points to the possibility that patient specific factors play a significant role in determining response to specific therapies and explain why one size does not fit all. Assays measuring levels of complement activation through patient sera are experimental and are not currently available for clinical use.

Conclusion

Refractory MG, in its current definition, describes a clinical response-based cohort of patients with suboptimal improvement and/or tolerability to current treatment options. While this group constitutes a smaller proportion of MG patients, they have a considerably higher burden of disease and impact on daily life, reduction in productivity, and increased health care resource utilization. At present, the designation of refractory MG does not provide any significant clinical utility and should certainly not imply therapeutic futility.

Current clinical tools do not afford the luxury of identifying these patients beforehand.

Determination of the underlying pathophysiology that modulates treatment response to specific therapies as well as factors unique to patients, such as genetic determinants, immune system function and interaction, and antibody

function and pathogenicity would form better substrates for classifying patients into treatment response therapies. Recent studies have provided important clues to potential mechanisms, but a lot of work remains before the field can transition from hind sight and reactive decision-making to proactive care and improved outcomes.

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