Myasthenic Crisis – Comorbidities, Complications, Long-Term Outcomes: The Challenges

Myasthenia gravis (MG) is a disorder of neuromuscular transmission resulting from binding of immunoglobulin G (IgG) autoantibodies against the nicotinic acetylcholine receptor (AChR) or other components of neuromuscular junction and is characterized by skeletal muscle weakness.[1,2] MG is divided into several subgroups according to the presence of autoantibodies.

Myasthenic crisis (MC) is a serious complication of MG and is associated with mortality and morbidity. Approximately 15%–20% of patients with MG experience crisis in their lifetime, typically within the first 2 years of the diagnosis.[3,4] Advances in mechanical ventilation and critical care have improved mortality associated with MC. Currently, the reported mortality is 4.47% and is primarily the result of comorbid medical conditions.[5] Comorbidities and complications associated with MC might alter the natural history and long-term outcomes. In this issue of *Annals of Indian Academy Neurology*, Sivadasan *et al.*[6] studied some of these aspects in a cohort of 62 patients (89 episodes) with first-episode MC. This study identified several comorbid medical conditions in association with MC, some of which can be either corrected or modified. Many of these medical comorbidities might influence the length of neurological intensive care unit stay adding to the costs of care.

In this cohort, one of the predictors of mortality in patients with MC was cardiac complications. However, in a largest US cohort, cardiac involvement was high in MC but not an independent predictor of death.[5] Heart muscle is a target for autoimmune inflammation in MG. Advanced age, thymoma, and ant-Kv1 antibodies are the risk factors. Manifestations of cardiac involvement include heart failure, arrhythmias, and sudden death.[7] There is no specific treatment for cardiac involvement in MG. Close cardiac monitoring and early institution of appropriate therapeutic strategies is likely to reduce mortality associated with cardiac involvement in patients with MC.

In a largest US cohort, age >50 years, the diagnosis of MC, and respiratory failure needing endotracheal intubation are the independent predictors of in-hospital mortality.[5] Despite advances in mechanical ventilation and respiratory care, there has been no significant change in the time on mechanical ventilation in patients with MC. In this cohort, the median time of mechanical ventilation was 14.5 days (range 5–43 days). Similar was the mean duration of mechanical ventilation in the older studies. A 1997 review found that patients with MC required mechanical ventilation for a mean duration of 2 weeks similar to the duration of mechanical ventilation reported in 1960s at the same institute.[8] Patients with a prolonged intubation were hospitalized three times longer and were less likely to be functionally independent on discharge.[8] Extubation failure is most commonly associated with a weak cough and inadequate airway clearance.[9] These observations show the limitation of the current nonspecific immunotherapies.

MC requires rapidly acting immunomodulatory therapies. Both immunoglobulin (IVIg) and plasma exchange (PLEX) have comparable efficacy in MC. PLEX is preferred as it has more rapid onset of action than IVIg.[10] However, there are no randomized studies to test the efficacy of these agents in MC.[10] Of the patients with moderate to severe MG receiving IVIg or PLEX, 20% required additional treatment, probably other than IVIg or PLEX.[11] Targeted immunotherapy seems to be the most promising therapeutic approach in MG and probably in MC because it can effectively overcome the limitations of current nonspecific immunotherapies and has potential to induce remission. Several biologics have potential as therapies for MG because they target molecules within the MG immune network. Biologics that are relevant to treating MG include rituximab, eculizumab, and efgartigimod.[12]

Rituximab is a chimeric monoclonal antibody against CD20, and its binding leads to depletion of circulating B cells. MuSK-MC responds well to PLEX, while IVIg seems to be less effective.[10] In patients with MuSK-MC who have an unsatisfactory response to the initial immunotherapy, rituximab should be considered as an early therapeutic option.[2]

The neonatal Fc receptor (FcRn) plays a central role in IgG homeostasis by rescuing IgGs from lysosomal degradation, resulting in long half-lives of IgGs compared with other Ig isotypes. By binding to the FcRn, efgartigimod interrupts this recycling process and lowers the levels of IgG antibodies in the blood stream.[13] Phase 2 exploratory study showed that efgartigimod is safe and lowers antibodies. The strong correlation between reduction in the levels of pathogenic IgG autoantibodies and disease improvement validates the hypothesis that reducing pathogenic autoantibodies with an FcRn antagonist may offer an innovative approach to treat MG. When compared with the short efgartigimod terminal half-life (4.89 days), the clinical effects are long-lasting (8 weeks). This drug may be a rescue therapy for patients in MC, as an alternative to plasmapheresis with easier vascular access than PLEX.[14] In this cohort, 18 (29%) patient had ≥1 recurrence of crisis. Probably efgartigimod by its long-lasting effect may reduce the risk of recurrence of MC.

In this study, during the follow-up 17 (27%) patients developed refractory MG. Eculizumab is an option in these patients. Eculizumab is a monoclonal antibody against complement

C5 that intercepts the formation of membranolytic attack complex that is fixed at the end-plate by anti-AChR antibodies. Eculizumab is the first drug to be approved for refractory MG. This approval was based on the results of a phase II study[15] and the subsequent phase III REGAIN trial.[16] Eculizumab significantly improved the MG activities of living, muscle strength, and health-related quality of life relative to placebo in secondary analyses of the pivotal REGAIN study in patients with refractory disease, but did not achieve statistical significance in the prespecified primary endpoint analysis. Treatment benefits maintained for up to at least 52 weeks in an ongoing extension study.[17]

Treatment of MC should be comprehensive and should include management of associated comorbidities and complications to reduce short- and long-term morbidity and mortality. Targeted immunotherapy seems to be the most promising therapeutic approach in MG and probably in MC because it can effectively overcome the limitations of current nonspecific immunotherapies and has potential to induce remission.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Gilhus NE, Verschuuren JJ. Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023-36.
2. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, *et al*. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016;87:419-25.
3. Bedlack RS, Sanders DB. On the concept of myasthenic crisis. J Clin Neuromuscul Dis 2002;4:40-2.
4. Murthy JMK, Meena AK, Chowdary GVS, Naraynan JT. Myasthenic crisis: Clinical features. Complications and mortality. Neurol India 2005;53:36-40.
5. Alshekhlee A, Miles JD, Katirij B, Preston DC. Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospital. Neurology 2009;72:1548-54.
6. Sivadasan A, Alexander M, Aaron S, Mathew V, Nair S, Muthuswamy K, *et al*. Comorbidities and long-term outcomes in a cohort with myasthenic crisis: Experiences from a tertiary care center. Ann Indian Acad Neurol 2019;22:464-71.
7. Shivamurthy P, Parker MW. Cardiac manifestations of myasthenia gravis: A systemic review. IJC Metab Endocr 2014;5:3-5.
8. Thomas CE, Mayer SA, Gungor Y, Swarup R, Webster FA, Chang I, *et al*. Myasthenic crisis: Clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology 1997;48:1253-60.
9. Wu JY, Kuo PH, Fan PC, Wu HD, Shih FY, Yang PC. The role of non-invasive ventilation and factors predicting extubation outcome in myasthenic crisis. Neurocrit Care 2009;10:35-42.
10. Dhawan PC, Goodman BP, Harper CM, Bosch PE, Hoffman-Snyder CR, Wellik KE, *et al*. IVIG versus PLEX in the treatment of worsening myasthenia gravis: What is the evidence? Neurologist 2015;19:145-8.
11. Barth D, Nabavi Nouri M, Ng E, New P, Bril V. Comparison of IVIG and PLEX in patients in with myasthenia gravis. Neurology 2011;26:2017-23.
12. Dalkas MC. Immunotherapy in myasthenia gravies in the era of biologics. Nat Rev Neurol 2019;15:113-24.
13. Roopenian DC, Akilesh S. FcRn: The neonatal Fc receptor comes of age. Nat Rev Immunol 2007;7:715-5.
14. Howard Jr J, Bril V, Burns TM, Mangegazza R, Bilinska M, Szczud; ik A, *et al*. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e2661-673.
15. Howard JF Jr, Barohan RJ, Culter GR, Freimer M, Juel VC, Mozaffer T, *et al*. A randomized, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Muscle Nerve 2013;48:76-84.
16. Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, *et al.* REGAIN Study Group. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): A phase 3, randomised, double blind, placebo controlled, multicentre study. Lancet Neurol 2017;16:976-86.
17. Dhillon S. Eculizumab: A review in generalized myasthenia gravis. Drug 2018;78:367-76.

Submission: 12.09.2019 **Acceptance:** 12.09.2019 **Published:** 25.10.2019

DOI: 10.4103/aian.AIAN_472_19