Clinical Outcomes in AchR Antibody-Positive Myasthenia Gravis: Where Does Rituximab Stand in the Current Times?

The current therapies in myasthenia gravis involve various immunosuppressive medications or symptomatic treatment with pyridostigmine. Pathogenetic mechanisms, the antibodies involved in pathogenesis, though well described, the current treatments do not target the specific antibody. There are autoantibodies against transmembrane/extracellular antigens (acetylcholine receptor antibody or AchR antibody, muscle-specific kinase or MUSK antibody, LRP4 antibody) which are pathogenetic and those against intracellular antigens (anti-titin, ryanodine receptor antibody) which are not proven to be pathogenetic. Thymus gland plays an important role in regulating the production and priming of autoantibody in myasthenia. In non-thymomatous AchR antibody-positive myasthenia gravis, thymectomy has shown to reduce the number of hospitalizations, relapses, and the dose of prednisolone required for remission.[1] Immunosuppression with oral prednisolone alone or with a steroid-sparing agent (azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, tacrolimus) is the standard treatment in myasthenia gravis.[2,3] Approximately, 80–85% of patients respond to this conventional treatment. The remaining 15–20% are refractory requiring higher doses of prednisolone (≥10 mg/day) and may have frequent relapses and/or hospitalizations or fail to tolerate conventional immunosuppression due to adverse reactions. Also, conventional drugs have a long latency period to be effective. Optimizing treatment is therefore a challenge, particularly in an Indian setting as the risk of infection is high with the use of higher doses of immune suppression. Plasmapheresis or intravenous immunoglobulin can be used as periodic treatments in refractory disease but again high treatment cost, maintaining the plasmapheresis catheter, risk of thrombosis and infection, and availability of expertise with well-equipped centers are the limiting factors.

Monoclonal or targeted therapies are being explored as an option in these patients to improve morbidity and mortality.[3] B cell depleting therapy is described in the treatment of autoimmune diseases.[4] Rituximab (RTX) has good evidence in the treatment of anti-MUSK myasthenia gravis.[5,6] A long-term prospective open-label study in refractory myasthenia gravis added more evidence to the safety and efficacy of rituximab, resulting in lowering of immunosuppressant drug dosage and IVIG and plasmapheresis frequency.[6] The phase II clinical trial of rituximab vs placebo in AchR antibody-positive myasthenia gravis (BEAT-MG), however, failed to show a significant difference in lowering the dose of steroid; however, there was a reduction in the number of relapses in the study group. That may have been due to the fact that the study selected patients with mild–moderate severity in whom RTX may not have a clinically steroid-sparing effect as steroids will help in this group.[7] Several retrospective studies and case series of RTX in refractory myasthenia gravis reported improvement in outcome measures with remission.[8-11]

The current study was designed as a retrospective observational single-center study of patients with AchR antibody-positive myasthenia gravis from December 2019 to February 2022.[12] The objectives were to evaluate the factors contributing to remission and study the subgroup that received rituximab in refractory myasthenia gravis. They also evaluated the effects of thymectomy in non-thymomatous and thymomatous myasthenia gravis. They studied 108 patients, and 67 were male with age groups from 18 to 50 years. Myasthenia classically presents with a bimodal distribution with two peaks, young females and elderly males.[13,14] 59.3% of patients progressed to generalized myasthenia within a year. The majority had a higher MGFA class (class III, IV A and B) at the time of the presentation. Nearly one-third had thymoma. About a third of patients went into a crisis requiring a ventilator. In this study, late-onset myasthenia gravis (LOMG) had higher remission rates.[12]

In the current study, 9/35 patients with refractory myasthenia were treated with rituximab. Five achieved remission, and three had minimal manifestation at 23.71 ± 2.42 months. Outcomes such as any type of remission, minimal manifestation status, and exacerbations requiring hospitalizations were statistically significant in the rituximab group as compared to those who were on other immunosuppressants. None had a myasthenia crisis requiring a ventilator in those who received rituximab.[12] The limitation was the small number treated with rituximab and retrospective design to draw strong evidence favoring the same.

Currently, oral corticosteroids remain the mainstay of treatment of myasthenia. There is a paucity of high-quality evidence to guide treatment decisions.[2] Recently, eculizumab, ravulizumab, and efgartigimod are approved in refractory severe myasthenia gravis.[15-17] These are expensive therapies, and the risk of opportunistic infections needs us to carefully select their use in Indian patients. Comparatively, rituximab is a cheaper alternative in AchR-Ab myasthenia in refractory cases in India. The indication of rituximab in AchR Ab myasthenia, its dose, and the dosing interval remain uncertain. A recent randomized double-blind study by Piehl *et al.*[18] in new-onset myasthenia used 500 mg rituximab or placebo as a single dose was associated with a greater probability of minimal manifestation and reduced need for rescue medications. Larger multicenter studies are needed in India. A single small dose is worth considering as a cost-effective strategy in treating refractory myasthenia and also in the early phase of the disease to achieve remission.

The thymectomy group in the current study showed favorable results.[12] Thymectomy should be considered early in refractory AchR-Ab-positive generalized myasthenia gravis to improve clinical outcomes, reduce the requirements of immunosuppressive medications, and minimize hospitalizations.[1] Data in the Indian scenario are lacking. It is the need of the hour to join hands for a multicenter trial to study the clinical features of myasthenia gravis and the outcomes of various treatments.

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Conflicts of interest

There are no conflicts of interest.

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