ACHR-Positive Generalized Myasthenia Gravis: The Old is Gold and the New Is for us to Explore

The majority of patients with myasthenia gravis (MG) are primarily treated with anticholinesterase inhibitors, corticosteroids, and immunotherapy with conventional immunosuppressants. About 10–20% of them have treatment-refractory disease.[1] In this issue, the study by Ojha PT, *et al*.[2] analyzed the clinical outcome of 108 patients with AChR-positive generalized MG (gMG) treated in their center. The focus was on the use of rituximab for subgroup of patients with refractory disease and the outcome of patients underwent thymectomy.

Before the availability of new evidence on the use of rituximab for new onset gMG from the recently published RINOMAX randomized clinical trial, rituximab was frequently the third-line treatment for MG and reserved for patients with refractory disease.[3-5] This is partly due to factors including cost and safety concerns. On another hand, surgical treatment with thymectomy, although it has been performed since 1939 and with improved techniques, has not been a mainstay treatment for MG both due to patient's fear of surgery and the existence of important unanswered questions on whom and how it should fit into the management of MG.[6,7]

Rituximab is a chimeric mouse/human monoclonal immunoglobulin directed against short-lived plasma cells with CD20 expression and rapidly depletes the mature and memory B cells in the peripheral blood, therefore resulting in suppression of antibody production.[8] Whilst the efficacy of rituximab in muscle-specific tyroxine kinase (MuSK) has been well established due to the more selective depletion of short-living plasma blast cells, the treatment effect on a patient with generalized MG with positive AChR is less well proven.[9,10] In a recently published randomized controlled trial (RCT) for rituximab for mild to moderate generalized MG with positive AChR (BeatMG) on a minimum of 15 mg prednisolone per day, rituximab treatment for 52 weeks failed to show significant steroid-sparing effect compared to placebo although the requirement for rescue therapy for exacerbations was lower in the rituximab group.[11] In contrast, a recently published systematic review and meta-analysis reported positive treatment efficacy in up to 77% of patients with AChR-positive MG.[12,13] Therefore, being a more commonly available monoclonal antibody compared to other B cell depleting therapies and other novel therapies such as complement inhibitors and neonatal Fc receptor (FcRn) blockers, many clinicians will consider the use of rituximab in refractory MG despite lacking in RCT evidence. In addition, as rituximab has been approved for clinical use since 1997, clinicians are familiar with its use and safety profile. Therefore, the finding and data from ___ *et al*. have important clinical implications and where it represented a real-world clinical practice. Although the number of patients treated with rituximab was only nine, eight of them achieved at least minimal manifestation status after failed trials with oral immunosuppressant after 1–4 years. This further affirmed that in selected patients with refractory MG, rituximab has its potential role and may be superior to conventional immunosuppressants. Looking forward, earlier administration of rituximab in their cohort of patients may further improve outcomes. Unfortunately, there are no specific biomarkers available to date in identifying patients who may potentially fail to respond to conventional immunosuppressants.[14]

Thymectomy has been historically performed for AChR-positive gMG with thymoma with most evidence to date demonstrated a favorable response.[15] The randomized thymectomy trial in nonthymomatous MG patients receiving prednisone therapy (MGTX) compared the outcome of extended transsternal thymectomy plus prednisone (surgical arm) versus prednisone alone (nonsurgical arm) in 126 nonthymomatous gMG diagnosed within the past 5 years.[16] The dual primary outcome study using average quantitative myasthenia gravis scores and time-weighted average required prednisone doses showed that thymectomy not only produced a better clinical outcome but also did so with lower prednisone requirements. The thymectomy arm also demonstrated a significant reduction in hospital admissions for disease exacerbations. Although the MGTX included nonthymomatous gMG patients, we expect similar clinical outcomes among thymomatous MG patients. There are two important factors from MGTX. First, MGTX included young patients below 50 years old with a disease duration of no more than 5 years. The consensus recommendation is to perform thymectomy as early as possible in the disease course. In the current study by ___ *et al*., a good clinical outcome of their patients who underwent thymectomy is expected as all were 55 years old and below with a disease duration of less than 5 years. Second, various surgical approaches are used. The aim is to remove as much thymic tissue as possible. The successful outcome described by ___*et al*. with video-assisted thoracoscopic thymectomy showed promising development of minimally invasive thymectomy techniques, which rivaled the outcome of a more invasive approach. Therefore, thymectomy will remain an important surgical treatment option for gMG.

In summary, the majority of AChR gMG respond to conventional immunotherapy with a subgroup of refractory cases that show positive improvement with rituximab. Selected AChR gMG patients with thymoma should be considered for thymectomy for better long-term outcomes.

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