Original Article

The Clinical Outcome in AChR-Positive Generalized Myasthenia Gravis: A Retrospective Observational Study

Pawan T. Ojha, Abhijeet M. Gaikwad, Rakesh Singh, Kamlesh Jagiasi, Shashank Nagendra

Department of Neurology, Grant Government Medical College and Sir J. J. Hospital, Mumbai, Maharashtra, India

Abstract

Background: Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction, and in over 80% of cases, antibodies are identified against the nicotinic type of acetylcholine receptor (AChR) on the muscle endplate. Despite the availability of various treatment options, patients with MG experience relapses and remission during the course of the disease. Aims and Objective: To understand the clinical profile, predictors of outcomes in acetyl choline receptor (AChR) antibody positive generalized MG. **Methods:** This is a retrospective, single-centre, observational study of 108 patients with AChR positive generalized MG. We collected data on clinical and demographical profiles, treatments received, and treatment responses from those who fulfilled inclusion criteria over a mean follow up period of 33.75 ±7.30 months. Clinical outcomes were studied in terms of the type of remission and crisis or disease exacerbations patients had, considering different variables and treatment received. **Results:** We found the commonest initial symptoms were ocular or oculo-bulbar, which progressed to generalized MG in the first year of disease onset. 36 (33.3%) patients experienced a crisis requiring mechanical ventilation within a mean period of 9.4 ±4.77 months from the disease onset. Multivariate regression analysis showed late-onset MG (age of onset between 50-70 years) and treatment with rituximab were better correlated with remission, (odd ratio of 4.7; 95 % CI ,1.12 -12.6; *P* value < 0.05 and odd ratio of 4.56; 95 % CI ,1.2 -10.04; *P* value < 0.05) respectively. While treatment with Mycofenolate Mofetile (MMF) was associated with a higher number of relapses (odd ratio of 1.8; 95 % CI ,0.08 -0.96; *P* value < 0.05). Treatment with Rituximab showed a higher rate of remission as compared to treatment refractory (TR) on conventional immunosuppressant therapy (IST). Out of 35(32 %) thymoma patients, 21 patients underwent thymectomy and these patients showed significantly greater rate of remission as compared both thymoma patients who denied thymectomy as a treatment option (*N* = 10 ;55.60 % vs *N* = 4; 23.50%). **Conclusion:** In this study of AChR antibody positive generalized MG patients, we found that nearly one-third of them experienced myasthenic crisis despite receiving the best medical care. Rituximab appeared to be effective in the treatment of refractory MG and those who failed thymectomy. Thymectomy was associated with better outcomes in patients, both with or without a thymoma.

Keywords: AChR positive, myasthenia gravis (MG), rituximab, treatment refractory

Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting neuromuscular junction, and in over 80% of cases, antibodies against the nicotinic type of acetylcholine receptor (AChR) on muscle endplate are identified.[1] It has an annual incidence of 1.7–21.3 cases per million person-years and a prevalence of 15–179 per million.[2] Patients typically present with fatigability and fluctuating or persistent weakness of extraocular, limb, truncal, and/or respiratory muscles.[3-5] In nearly 15% of patients, the presenting complaints are bulbar weakness, leading to slurred or nasal speech, voice alterations, or difficulty in chewing or swallowing.[5-8]

Treatment options include acetylcholinesterase inhibitors, short-term rescue immune therapies (plasmapheresis or intravenous immunoglobulin), and long-term treatment with conventional immunosuppressive therapy (IST) like corticosteroids, azathioprine, mycophenolate mofetil (MMF), and cyclosporine.[9] About 10% of patients require more aggressive therapy to halt the progression to life-threatening myasthenia, including respiratory crisis. Thymectomy is recommended not only for thymomatous MG but also in some carefully selected nonthymomatous generalized MG.[10]

Rituximab (RTX) is a chimeric mouse/human monoclonal antibody that targets CD20 B lymphocytes, and several authors have described its role and efficacy in the treatment of drug-resistant MG.[11-14]

Most previous studies have highlighted the diverse clinical manifestations and variable course of MG, but there is a paucity of data on treatment outcomes. This study was planned to understand the clinical profile, outcome, and factors

Address for correspondence: Dr. Abhijeet M. Gaikwad, Department of Neurology, Grant Government Medical College and Sir J. J. Hospital, Mumbai, Maharashtra, India.
E-mail: abhijitgaikwad10491@gmail.com

Submitted: 27-Feb-2023 **Revised:** 23-Mar-2023 **Accepted:** 13-Jun-2023
Published: 25-Aug-2023

DOI: 10.4103/aian.aian_186_23

affecting remission in AChR antibody-positive generalized MG, with a special focus on the benefits of thymectomy and rituximab.

Materials and Methods

We conducted a retrospective, observational study of patients who had AChR antibody-positive generalized MG between December 2019 and February 2022. It is a pilot study of a larger multicentric trial. We included patients who were >18 years of age and were diagnosed with generalized MG based on the presence of suggestive clinical features of MG, and either elevated antibodies (AChR antibodies) with abnormal electrodiagnostic studies (≥10% decrement on repetitive nerve stimulation) and patients who had made a minimum of two visits to our institute, with the last visit being not more than 6 months prior to the time of data collection. Those with AChR antibody-positive ocular MG and Musk antibody-associated (MUSK) MG were excluded. The study was approved by the institutional ethics committee. All demographic data, details of investigations done, treatment administered, and response to treatment were retrieved from computerized case records with proper consent. The mean duration of follow-up at our institute was 33.75 ± 7.30 months.

Early-onset MG (EOMG) was defined as symptom onset before the age of 50 years, late-onset MG (LOMG) between the ages of 51 and 70 years, and very late-onset MG (VLOMG) for symptom onset after the age of 70 years.

Based on CT HRCT, patients were grouped on thymomatous and nonthymomatous groups. AChR antibody-positive generalized MG patients with thymoma with ages between 18 and 55 and generalized nonthymomatous MG with a disease duration of less than 5 years, refractory to treatment, and willing for surgery underwent video-assisted thoracoscopic thymectomy.[10]

A measure of relapse was considered as myasthenic crisis requiring ventilation and disease exacerbation requiring hospitalization. A measure of remission included all types of remissions achieved at the last follow-up visit, including complete stable remission or pharmacological remission or status of MM (minimal manifestation). These outcome parameters were defined as per the postintervention status criteria of MGFA (PSC–MGFA).[15]

Statistical analysis was performed using SPSS 26 software. An independent sample *t*-test was done for continuous variables and a Chi-square test for categorical variables; the level of significance used was $P < 0.05$. Multivariate analysis was done to measure clinical outcome parameters.

Results

Data of 108 patients meeting the eligibility criteria were collected in the study. The majority of patients were male ($N = 67$; 62%) and belonged to the age group of up to 50 years ($N = 62$; 57.4%). Clinicodemographic characteristics of the study population are mentioned in Table 1. Among them, 95% patients had symptoms up to 60 days before the diagnosis. Ocular symptoms were the most commonly reported clinical feature ($N = 76$; 70.4%) at time of presentation, followed by oculo-bulbar symptoms ($N = 21$; 19.4%) with the majority (about 95%) of patients were MGFA Class IIIa, IV a, b at presentation. Maximum patients ($N = 64$; 59.3%) progressed from ocular or oculobulbar symptoms to generalized weakness during 9–12 months of disease duration from onset. Diabetes mellitus was the commonest comorbidity seen in 34 patients (31.5%). Thirty-five (32%) patients had evidence of thymoma on the HRCT chest.

All patients received oral steroids as the initial immunosuppressant and nearly two-thirds received azathioprine, and 15 patients also received MMF in addition.

Table 1: Clinicodemographic characteristics

Variables	Frequency	Percentage
Age group (years)		
Up to 50	62	57.4
51–70	38	35.2
More than 70	8	7.4
Gender		
Female	41	38
Male	67	62
Duration (days) symptom onset to diagnosis		
Up to 15	4	3.7
16–30	48	44.4
31–60	50	46.3
61–90	4	3.7
>90	2	1.8
Initial symptoms		
Ocular	76	70.4
Oculobulbar	21	19.4
Bulbar	6	5.6
Limb weakness	5	4.6
Dysgeusia	2	3.7
Initial MGFA class		
Class Ia	1	0.9
Class IIa	4	3.7
Class IIIa	49	45.4
Class IIIb	15	13.9
Class IVa	31	28.7
Class IVb	6	5.6
Class V	2	1.9
Ocular to generalized MG		
9–12 months	64	59.3
6–9 months	32	29.6
3–6 months	5	4.6
Up to 3 months	7	6.5
Past medical history		
Diabetes mellitus	34	31.5
Hypertension	29	26.9
Others	17	15.7
None	46	42.6

Among treatment refractory (TR) group, on the last follow-up mean dose of oral prednisolone, azathioprine, and MMF were 24.48 mg/day (minimum 10; maximum 60 mg), 2.76 mg/kg/day (minimum 1; maximum 3 mg/kg/day), and 1.56 g bid (minimum 1; maximum 2 g bid), respectively.

Rituximab was prescribed after 1–4 years of the trial period with oral immunosuppressant therapy in nine (8.3%) patients. It was prescribed for a mean duration of 21.11 ± 5.25 months. Indication of starting rituximab in seven patients was refractoriness to oral immunosuppressants, all of them had previously received azathioprine at mean dose of 1.76 mg/kg/day and two patients; additional MMF at average dose of 2 g bid. In two patients, it was prescribed as they had disease relapse even after thymectomy.

Thirty-six (33.3%) patients had experienced a respiratory crisis at a mean of 9.4 ± 4.77 months from the onset of symptoms. Twenty-three (63.9%) patients had received IVIG and 13 (36.1%) patients received plasmapheresis as rescue therapy.

Clinical outcomes

The study population on IST could be divided into two groups based on response to best medical treatment: (1) remission group (R): those who achieved at least MM with no dose adjustment required on the last follow-up. (2) Treatment refractor (TR) group: those whose postinterventional status (MGFA-PIS) was unchanged or worse after corticosteroids and two or more other immunosuppressive agents or do not respond adequately to IST or experience intolerable adverse events, and those could be an ideal candidate for either rituximab or thymectomy.

We found that out of 87 patients who received only medical management, 38 patients (44%) achieved remission at a mean follow-up duration of 33.75 ± 7.30 months, while 40 patients (46%) were TR. Out of nine patients who received rituximab and had a mean treatment duration of 21.11 ± 5.25 months, five patients achieved PR status and three achieved MM status at a mean treatment duration of 23.71 ± 2.42 months.

Table 2 compares the clinical outcomes of TR on conventional IST, and patients who received rituximab (RTX), which showed significantly higher remission rates (N = 5; 55. 60%) compared to TR group (N = 1; 2.50%) (P < 0.01). TR on conventional IST group showed a very high rate of exacerbations requiring hospitalization (N = 39; 97.50%) as compared to RTX group (N = 2; 22%) (P < 0.01). Ten patients (25%) of the TR group had respiratory crisis requiring mechanical ventilation (N = 10; 25%) as against none of those who received rituximab (RTX).

Ninety-five patients underwent HRCT scans, and 35 patients (32%) were detected to have thymoma, but not all of them underwent thymectomy surgeries. Eighteen patients with thymoma and two patients with normal thymus underwent thymectomy.

Table 2: Clinical outcome in patient treatment refractory (TR) on conventional IST versus rituximab (RTX) group

Clinical outcome		Group		*P**
		TR	RTX	
Total	*n*	40	9	
Any type of remission	*n*	1	5	**0.00001**
	%	2.50%	55.60%	
Minimal manifestation (MM)	*n*	32	3	**0.005**
	%	80.00%	33.30%	
Myasthenia crisis requiring ventilation	*n*	10	0	NA
	%	25.00%	0%	
Exacerbations requiring hospitalizations	*n*	39	2	**0.00001**
	%	97.50%	22.22%	

*Analyzed using Chi-square test; bold values indicate P<0.05

We compared the clinical outcomes of patients with thymoma to those of who did not have thymoma on the HRCT chest.

Ventilatory support during a crisis was required in a significantly higher number of thymoma patients (N = 13; 37%) as compared to those without a thymoma (N = 10; 16.80%), P value <0.05. Patients with thymoma also had more acute exacerbations requiring hospitalization (N = 31; 85%) as compared to those without a thymoma (N = 49; 81%), but statistical significance criteria were not met, P value = 0.3 [Table S1].

We also compared clinical outcomes in patients who underwent thymectomy for thymoma with those who did not undergo the surgery. Table 3 shows that patients who underwent thymectomy for a thymoma had a significantly greater rate of remission (N = 10; 55.60%) as compared to those who chose to remain on medical treatment (P value <0.05) and four patients (22.22%) achieved complete stable remission. The thymectomy group had a lower incidence of crises requiring ventilation (N = 2; 11.11%) and exacerbations requiring hospitalization (N = 4; 22.22%) than the others, P values <0.01.

Outcomes in patients who had undergone thymectomy for nonthymoma MG (N = 3) were also compared with those who received the best medical treatment (N = 57) in Table 4. Higher rates of remission were achieved in thymectomy patients (2 out of 3; 66.66%) as compared to those on medical treatment (11 out of 57; 19.0%). None of the thymectomy patients had a crisis as compared to the medical treatment group (N = 10; 17.5%).

Another interesting observation was that out of the 14 patients who were infected with COVID-19 during the pandemic, only 1 developed a disease exacerbation requiring admission and recovered uneventfully.

Predictors of remission using univariate and multivariate regression analysis consider age at onset, gender, symptom at onset, initial MGFA classification, time required to develop generalized weakness, and treatment received. Treatment with rituximab was associated with a higher rate of remission (odd ratio of 4.56; 95% CI, 1.2–10.04; P value <0.05) in both univariate and multivariate analysis. On multivariate analysis,

Table 3: Clinical outcome in patients with thymoma undergoing thymectomy versus those who denied thymectomy

Clinical outcome		Thymoma patients		*P**
		With thymectomy	Without thymectomy	
Total	*n*	18	17	
Any type of remission	*n*	10	4	**0.04**
	%	55.60%	23.50%	
Minimal manifestation (MM)	*n*	10	12	0.35
	%	55.60%	70.60%	
Myasthenia crisis requiring ventilation	*n*	2	9	**0.007**
	%	11.11%	52.90%	
Worsening requiring hospitalizations	*n*	4	15	**0.00008**
	%	22.22%	88.20%	

*Analyzed using Chi-square test; bold values indicate $P<0.05$

Table 4: Clinical outcome in patients with normal thymus comparing those who underwent thymectomy versus those on medical treatment

Clinical outcome		With thymectomy	On medical treatment	*P**
Total	*n*	3	57	
Any type of remission	*n*	2	11	0.052
	%	66.66%	19.00%	
Minimal manifestation (MM)	*n*	1	39	0.20
	%	33.33%	68.00%	
Myasthenia crisis requiring ventilation	*n*	0	10	NA
	%	00.00%	17.5%	
Worsening requiring hospitalizations	*n*	2	46	0.55
	%	66.66%	80.7%	

*Analyzed using Chi-square test

late-onset MG had higher remission (odd ratio of 4.7; 95% CI, 1.12–12.6; *P* value <0.05), while treatment with MMF was associated with a higher number of relapses (odd ratio of 1.8; 95% CI, 0.08–0.96; *P* value <0.05). No relation was established with other variables like gender, symptom at onset, initial MGFA classification, or time required to develop generalized weakness [Table S2].

Discussion

In our analysis of 108 patients with AChR antibody-positive generalized MG, the commonest initial symptoms were ocular or oculobulbar, becoming generalized MG in the first year of disease onset in all patients. Nearly one-third had thymomas, and a similar proportion had relapses on immunosuppressive treatment. This compares well with some previous Indian studies.[16,17] Saha *et al*.[16] studied the clinical characteristics of 73 patients with MG. Khadilkar *et al*.[17] studied the natural course of 100 MG patients and analyzed factors affecting remission and relapse. Our study is one of the largest studies that has included only AChR antibody-positive generalized MG. We have also tried to examine the benefit of rituximab and thymectomy in refractory MG and thymoma-related MG.

In the overall study population, 36 (33.3%) patients experienced a crisis requiring mechanical ventilation during their course of illness, at a mean of 9.4 ± 4.77 months from the symptom onset. It parallels the findings of a few previous studies.[18,19] Grob *et al*.[18] found that most severity of weakness and crisis occurred during the first 1–2 years of the disease.

Interestingly, we found two (1.8%) patients who had dysgeusia (lack of sweet taste sensation) as a presenting symptom. This has been mentioned in a few case reports[20] and could be due to an autoimmune mechanism altering selective taste receptors in taste cells. These patients did not regain the sweet taste sensation even after treatment.

We tried to identify predictors of remission using multivariate regression analysis and found that late-onset MG had higher remission (odd ratio of 4.7; 95% CI, 1.12–12.6; *P* value <0.05). A similar finding was mentioned by Pasqualin *et al*.,[21] while analyzing 208 MG patients, retrospectively, found better outcomes in LOMG.

Treatment with rituximab was associated with a higher rate of remission (odd ratio of 4.56; 95% CI, 1.2–10.04; *P* value <0.05). The role of B-cell depletory agent such as rituximab is justifiable in MG as it is an autoimmune disease with B cells having an important role in pathogenesis.[22] In our study population, the rituximab group (RTX) showed better outcomes and fewer exacerbations or respiratory crises as compared to the TR on conventional IST. It echoes the findings of a few previous studies.[11-14] Zebardast *et al*. and Lindberg *et al*.[11,12] found a reduced need for immunosuppressant and/or

improvement in clinical function in terms of quantitative MG score, and forced vital capacity in rituximab-treated TR MG patients. Although Díaz-Manera *et al*.[23] showed better efficacy of rituximab in MuSK MG as compared to AChR-positive MG as anti-MuSK Abs are mostly IgG4, sustained response to RTX is considered to be related to decreasing MuSK Ab production by short-lived Ab-secreting cells derived from specific $CD20^+$ B cells,[24] while B-cell depletion justifies the role of rituximab in AChR positive MG also.[22] We offered rituximab as a treatment option to all TR group patients, but affordability and willingness deprived them of better management.

On the other hand, treatment with MMF was associated with a higher number of relapses (odd ratio of 1.8; 95% CI, 0.08–0.96; *P* value <0.05). Though MMF has been frequently used as a steroid-sparing agent, its therapeutic benefit has been previously challenged in a meta-analysis by Heatwole and Ciafaloni.[25]

In a comparison of outcomes in patients with thymoma against those without a thymoma, we found that the thymoma group had a significantly higher incidence of myasthenia crisis requiring a mechanical ventilator (*N* = 13; 37% vs. *N* =10; 16.80%) with *P* value <0.05 and much more exacerbations requiring hospitalization (*N* = 31; 85% vs. *N* =49; 81%). This was also seen in a multicenter trial by Rodrigo Álvarez-Velasco *et al*.[26] in which the author concluded that thymoma-associated MG patients had more severe myasthenic symptoms and a worse prognosis.

Only 18 patients with thymoma (51%) underwent thymectomy. We compared the clinical outcome between these two groups and found patients who underwent thymectomy for a thymoma had a significantly greater rate of remission than those on medical management (*P* value <0.05). Also, we found thymectomy cohort had a lower rate of crisis and exacerbations. The most common reason for not undergoing thymectomy was the patient's fear of surgery.

While comparing the outcome in patients with normal thymus who underwent thymectomy with those on medical management, patients who underwent thymectomy showed a higher rate of remission comparatively with better outcomes in terms of relapses. Role of thymectomy in nonthymomatous MG is well established by Baram *et al*. and Cataneo *et al*.[27,28]

As data collection was done during the era of the COVID-19 pandemic, we collected information on whether COVID-19 infection altered the disease course; we found those out of 14 patients who were infected, only 1 patient had a disease exacerbation. While exploring published articles regarding the impact of COVID-19 on disease course, we found mixed findings. Digala *et al*.[29] showed that mean length of hospital stay was prolonged in myasthenia patients in a retrospective study of 27 MG with COVID-19 patients. Abbas *et al*.[30] quoted that although COVID-19 may exaggerate the neurological symptoms and worsen the outcome in MG patients, there is not enough evidence to support this notion.

Limitations of the study: Our study has the obvious limitations of retrospective studies and possible institutional bias. Being a pilot study, we had a small RTX-treated group; further larger study may establish its actual role in the treatment. Despite this, being a large study with carefully documented clinical outcomes, it offers a clearer perspective on the clinical course of this serious disease and effective therapies.

Conclusion

In this study of AChR antibody-positive generalized MG, we found that nearly one-third of patients had myasthenic crisis despite the best medical treatment and required rescue therapy with IVIG or plasmapheresis. Late-onset MG (age of onset between 50 and 70 years), rituximab, and thymectomy were positively correlated with remission, whereas MMF was negatively correlated with it. Thymectomy was associated with better outcomes in patients, both with or without thymoma. Rituximab appeared to be highly effective in the treatment of refractory MG, even in those with failed thymectomy. The benefit of rituximab and thymectomy in refractory generalized MG needs further investigation in larger studies.

Acknowledgment

The authors would like to thank Dr. S. V. Khadilkar (Dean and Professor and Head of the Neurology Department, Bombay Hospital, Mumbai) and Dr. Sudhir Kothari (Head, Department of Neurology, Poona Hospital and Research Centre, Pune, Maharashtra, India) for their insightful suggestions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Glossary

AChR = acetylcholine receptor; CI = confidence interval; CSR = complete stable remission; EOMG = early-onset MG; IST = immunosuppressive therapy; LOMG = late-onset MG; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MM = minimal manifestation; MuSK = muscle-specific tyrosine kinase; OR = odds ratio; PR = pharmacologic remission; RTX = rituximab; TR = treatment refractory; VLOMG = very late onset MG.

References

1. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis, prevalence, clinical correlates, and diagnostic value. Neurology 1976;26:1054-9.
2. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol 2010;10:46.
3. Trouth AJ, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: A review. Autoimmune Dis 2012;2012:874680. doi: 10.1155/2012/874680.
4. Clarke C, Howard R, Rossor M, Shorvon S, editors. Neurology: A Queen Square Textbook. Oxford: Blackwell Publishing Ltd.; 2009. ISBN: 978-1-405-13443-9.

5. Engel AG, editor. Myasthenia Gravis and Myasthenic Disorders. Oxford: Oxford University Press; 2012. ISBN-13: 9780199738670.
6. Angelini C, Martignago S, Biscigli M, Albertini E. Myasthenia gravis with anti-MuSK antibodies: Clinical features and histopathological changes. In: Pruitt JA, editor. A Look into Myasthenia Gravis. Rijeka: InTech; 2011. ISBN 978-953-307-821-2.
7. Scherer K, Bedlack RS, Simel DL. Does this patient have myasthenia gravis? JAMA 2005;293:1906-14.
8. Myasthenia Gravis Foundation of America. Myasthenia Gravis: A Manual for the Health Care Provider. 2008. Available from: http://www.myasthenia.org/docs/MGFA_ProfessionalManual.pdf.
9. Sathasivam S. Steroids and immunosuppressant drugs in myasthenia gravis. Nat Clin Pract Neurol 2008;4:317-27.
10. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, *et al*. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375:511-22.
11. Zebardast N, Patwa HS, Novella SP, Goldstein JM. Rituximab in the management of refractory myasthenia gravis. Muscle Nerve 2010;41:375-8.
12. Lindberg C, Bokarewa M. Rituximab for severe myasthenia gravis – experience from five patients. Acta Neurol Scand 2010;122:225-8.
13. Collongues N, Casez O, Lacour A, Tranchant C, Vermersch P, de Seze J, *et al*. Rituximab in refractory and non-refractory myasthenia: A retrospective multicenter study. Muscle Nerve 2012;46:687-91.
14. Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: A retrospective study. Ther Adv Neurol Disord 2011;4:259-66.
15. Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, *et al*. Myasthenia gravis: Recommendation for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000;55:16-23.
16. Saha SP, Mukherjee S, Das SK, Ganguly PK, Roy TN, Maiti B, *et al*. Clinical profile of myasthenia gravis. J Assoc Physicians India 1998;46:933-6.
17. Khadilkar SV, Chaudhari CR, Patil TR, Desai ND, Jagiasi KA, Bhutada AG, *et al*. Once myasthenic, always myasthenic? Observations on the behavior and prognosis of myasthenia gravis in a cohort of 100 patients. Neurol India 2014;62:492-7.
18. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37:141-9.
19. Oosterhuis HJ. The natural course of myasthenia gravis: A long term follow up study. J Neurol Neurosurg Psychiatry 1989;52:1121-7.
20. Nakazato Y, Ito Y, Naito S, Tamura N, Shimazu K. Dysgeusia limited to sweet taste in myasthenia gravis. Intern Med 2008;47:877-8.
21. Pasqualin F, Guidoni SV, Ermani M, Pegoraro E, Bonifati DM. Outcome measures and treatment effectiveness in late onset myasthenia gravis. Neurol Res Pract 2020;2:45. doi: 10.1186/s42466-020-00091-z.
22. Peres J, Martins R, Alves JD, Valverde A. Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost–utility analysis. Porto Biomed J 2017;2:81-5.
23. Díaz-Manera J, Martínez-Hernández E, Querol L, Klooster R, Rojas-García R, Suárez-Calvet X, *et al*. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 2012;78:189-93.
24. Marino M, Basile U, Spagni G, Napodano C, Iorio R, Gulli F, *et al*. Long-lasting Rituximab-induced reduction of specific-but not total-IgG4 in MuSK-positive myasthenia gravis. Front Immunol 2020;11:613. doi: 10.3389/fimmu.2020.00613.
25. Heatwole C, Ciafaloni E. Mycophenolate mofetil for myasthenia gravis: A clear and present controversy. Neuropsychiatr Dis Treat 2008;4:1203-9.
26. Álvarez-Velasco R, Gutiérrez-Gutiérrez G, Trujillo JC, Martínez E, Segovia S, Arribas-Velasco M, *et al*. Clinical characteristics and outcomes of thymoma-associated myasthenia gravis. Eur J Neurol 2021;28:2083-91.
27. Baram A, Salih KA, Saqat BH. Thymectomy for non-thymomatous myasthenia gravis: Short and long term outcomes, a single-center 10 years' experience. Int J Surg Open 2021;35:10081. doi: 10.1016/j.ijso.2021.100381.
28. Cataneo AJM, Felisberto G Jr, Cataneo DC. Thymectomy in nonthymomatous myasthenia gravis-systematic review and meta-analysis. Orphanet J Rare Dis 2018;13:99.
29. Digala LP, Prasanna S, Rao P, Qureshi AI, Govindarajan R. Impact of COVID-19 infection among myasthenia gravis patients-A cerner real-world data™ study. BMC Neurol 2022;22:38. doi: 10.1186/s12883-022-02564-x.
30. Abbas AS, Hardy N, Ghozy S. Characteristics, treatment, and outcomes of Myasthenia Gravis in COVID-19 patients: A systematic review. Clin Neurol Neurosurg 2022;213:107140. doi: 10.1016/j.clineuro.2022.107140.

Supplementary Table 1: Clinical outcome in patients with thymoma vs normal thymus

Clinical outcome		Thymoma		*P**
		No	Yes	
Total	*n*	60	35	
Any type of remission	*n*	11	12	0.07
	%	18.00%	34.00%	
Minimal manifestation (MM)	*n*	43	22	0.37
	%	71.00%	62.00%	
Myasthenia Crisis requiring ventilation	*n*	10	13	**0.02**
	%	16.80%	37.00%	
Worsening requiring hospitalizations	*n*	49	31	0.3
	%	81.00%	85.00%	

*Analysed using Chi-square test; Bold values indicate $P<0.05$

Supplementary Table 2: Predictors of any type of remission

Variables	Univariate analysis				Variables	Multivariate model			
	Odds ratios	95% C.I.for OR		*P**		Adjusted OR	95% C.I.for OR		*P***
		Lower	Upper				Lower	Upper	
Age					Age				
Up to 50		constant			Up to 50		constant		
51 to 70	2.64	0.59	11.79	**0.05**	51 to 70	4.7	1.12	12.6	**<0.05**
More than 70	0.31	0.09	1.01	**0.21**	More than 70	0.33	0.09	1.16	0.08
Female	1.11	0.44	2.79	0.81	Female		NA		
Symptoms					Symptoms		NA		
Ocular symptoms	2.4	0.88	2.91	0.91	Ocular symptoms				
Oculo-bulbar symptoms	1.2	0.78	1.65	0.91	Oculo-bulbar symptoms				
Bulbar symptoms	1.4	0.88	1.98	0.91	Bulbar symptoms				
Limb weakness	1.1	0.91	1.4	0.66	Limb weakness				
Dysgeusia	2.3	0.17	12.9	0.52	Dysgeusia				
Initial MGFA class					Initial MGFA class		NA		
class Ia		constant			class Ia				
ClassIIa	0.17	0.01	1.67	0.91	ClassIIa				
Class IIIa	0.19	0.08	1.54	0.91	Class IIIa				
Class IIIb	0.44	0.01	1.33	0.94	Class IIIb				
Class IV a	0.23	0.12	2.34	0.91	Class IV a				
Class IVb	0.43	0.12	1.98	0.91	Class IVb				
Class V	0.21	0.11	1.99	0.91	Class V				
Ocular to gen MG					Ocular to gen MG				
Up to 1 month		constant			Up to 1 month		constant		
1 to 2 months	1.19	0.44	3.22	0.73	1 to 2 months	1.41	0.47	4.22	0.53
2 to 3 months	2.38	0.36	15.67	**0.16**	2 to 3 months	2.38	0.33	11.07	0.38
More than 3 months	0.59	0.066	5.36	0.64	More than 3 months	0.7	0.07	6.54	0.75
Treatment given					Treatment given				
Azathioprine	0.68	0.27	1.72	0.42	Azathioprine		NA		
Mycophenolate mofetil	0.21	0.02	1.64	**0.13**	Mycophenolate mofetil	0.18	0.02	1.67	0.13
Rituximab	4.93	1.21	14.08	**<0.05**	Rituximab	4.56	1.2	10.4	**<0.05**

Variables with *$P<0.25$ was included in the multivariate model, ***significant value in bold

Supplementary Material

Outcome Parameters Defined as per the Post-Intervention Status Criteria of MGFA (PSC –MGFA):

(a) Complete Stable Remission (CSR) is defined as the patient having no symptoms or signs of MG for at least 1 year and receiving no therapy for MG during that time. There is no weakness of any muscle on careful examination. (b) Pharmacologic Remission (PR) - The same criteria as for CSR, except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness. (c) Minimal Manifestations (MM) - The patient has no symptoms of functional limitations from MG but shows some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have a weakness that is only detectable by careful examination. (d) Exacerbation (e) - Patients who have fulfilled the criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria. (f) Treatment -Refractory defined as post-interventional status (MGFA-PIS) was unchanged or worse after corticosteroids and two or more other immunosuppressive agents, or do not respond adequately to immunosuppressive therapy (IST), or experience intolerable adverse events.