Original Article

Outcome Predictors of Generalized Myasthenia Gravis: A Prospective Observational Study

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Abstract

Background and Objectives: There is paucity of studies on long-term remission of autoimmune generalized myasthenia gravis (MG) from Southeast Asia. We report the outcome predictors of generalized MG and also evaluate the influence of high- versus low-dose prednisolone and prednisolone with or without azathioprine (AZA). **Methods:** Fifty-seven patients with generalized MG were included, who completed 2 years of follow-up. Demographic information, comorbidities, Myasthenia Gravis Foundation of America (MGFA) class at baseline and follow-up, acetylcholine receptor (AChR) and muscle-specific kinase antibodies, decremental response, thymectomy, and treatments were recorded. Maximum doses of prednisolone, AZA, and acetylcholinesterase inhibitors were noted. The predictors of MGFA 0 at 3 and 6 months and minimal manifestation (MM) status at 2 years were evaluated. **Results:** MGFA 0 was achieved by 27 (47.4%) patients at 3 months, 35 (61.4%) patients at 6 months, and 46 (80.7%) patients at 12 months. At 2 years, 48 (84.2%) patients achieved the MM status and none achieved complete stable or pharmacologic remission. On multivariate analysis, AChR antibody titer (adjusted odds ratio [AOR] 1.08, 95% confidence interval [CI] 1.006–1.167; $P = 0.03$) and MG activity of daily living (MGADL) at 6 months (AOR 1.28, 95% CI 1.066–1.558; $P = 0.01$) predicted the MM status. Maximum dose of prednisolone and adjunctive AZA did not predict the MM status. **Conclusions:** About 84.2% of patients with generalized MG, especially those with a low AChR antibody titer and MGADL < 4 at 6 months, achieved the MM status at 2 years.

Keywords: Acetyl choline receptor antibody, azathioprine, myasthenia crisis, myasthenia gravis, outcome, prednisolone, prognosis

Introduction

Myasthenia gravis (MG) is an antibody-complement-mediated, T-cell–dependent autoimmune disorder, and manifests with fatigable muscle weakness of varying severity. About 80% of autoimmune MG is due to antibodies against acetylcholine receptor (AChR), 1%–10% is due to antibodies against muscle-specific kinase (MuSK), and 1%–3% is due to antibodies against lipoprotein receptor-related protein-4.[1] The first-line treatment of autoimmune myasthenia is oral corticosteroid with acetylcholinesterase inhibitors (AChEIs).[2,3] Pyridostigmine and neostigmine are reversible AChEIs, and block degradation of acetylcholine at cholinergic synapses including neuromuscular junction. These drugs are used as a symptomatic treatment of MG. Corticosteroid produces immune suppression of T cells, and thereby reduces antibody production. About 20%–40% of MG patients may deteriorate within 2 weeks of treatment with prednisolone, especially the elderly patients, and those with higher dose of prednisolone and thymoma.[4,5] Therefore, a starting dose of 25 mg or lower may reduce paradoxical worsening.[6] The other immunosuppressants such as azathioprine (AZA), methotrexate, mycophenolate mofetil, tacrolimus, cyclosporine, and rituximab are used as second-line drugs or steroid-sparing agents.[7] Out of these drugs, AZA is more commonly chosen because of its efficacy and safety profile.[8-10]

Immunosuppressants help in improvement of the myasthenic symptoms; however, complete remission occurs in a few patients only.[11-13] In a study on 24 MG patients, 18 tolerated AZA, and improvement was solely due to AZA in eight (44%) only.[8] Studies have reported higher response rate with early administration of AZA with corticosteroid.[14-16] In another study, the prednisolone dose could be reduced to 5 mg/day in only 29.7% patients at 1 year and 71% at 2 years. The clinical severity at baseline, age, thymoma, and thymectomy were not determinants of prednisolone dose at 2 years.[17-19] In tropical countries, the prevalence of infections is high.[20] The diabetes and prediabetic states are also high in India, China, Pakistan, and USA. The number of prediabetics is far higher, which might be unmasked by the use of corticosteroid.[21] These epidemiological data raise concern about the high dose and prolonged use of corticosteroid.

There is paucity of studies from developing countries about the long-term remission of MG in patients on prednisolone

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alone or in combination with AZA. We report the outcome predictors of generalized MG and also evaluate the influence of high versus low dose of prednisolone and prednisolone with or without AZA.

Methods

Study design and participants

This is a descriptive study with one of the outcomes being exploration of remission based on the prospective registry of MG from January 2019 to December 2023. We have followed up the patients in RESTOREX trial,[22] as well as newly diagnosed patients with MG who completed at least 2 years of follow-up. Patients with generalized MG were admitted for initial workup. The study protocol was approved by the Institute Ethics Committee (PGI/BE/199/2022, IEC code: 2018–138-IP-106). An informed consent was obtained from all the participants.

Inclusion criteria: Patients fulfilling three out of four following criteria were included[22]:

a) fatigable muscle weakness (mandatory criterion),
b) improvement following neostigmine test,
c) >10% decrement at 3 Hz repetitive nerve stimulation in more than or equal to two muscles, and
d) elevated serum anti-AChR/anti-MuSK antibody

Exclusion criteria: Patients < 15 and > 80 years, with congenital or Lambert–Eaton MG, ocular MG, renal, liver, or heart failure, or malignancy (except thymoma) were excluded. Patients receiving immunomodulation for other diseases were also excluded.

Clinical evaluation and investigations

A detailed history including duration of illness, topography of muscle weakness, and comorbidities was noted. General and systemic examinations were done. Ophthalmoplegia, dysphagia, dysarthria, muscle power, and tendon reflexes were noted.

The severity of MG was classified using MG Foundation of America (MGFA) into five classes [Supplementary Table 1].[23]

MG Activity of Daily Living (MGADL) is a self-reported assessment of eight functions including chewing, swallowing, breathing, talking, brushing teeth or combing hair, rising from chair, eyelid droop, and double vision. Each function is given a score from 0 (no problem) to 3 (severe problems) due to weakness.[22]

MG Quality of Life-15 (MGQoL-15) is a 15-point self-administered disease-specific questionnaire that has been designed to assess the quality of life in MG. The patient gives a score of 0–4 (0 = no problem, 4 = very much affected). Total score ranges from 0 to 60.

Investigations: The investigations done were complete hemogram, serum chemistry, anti-AChR and or anti-MuSK antibody determined using enzyme-linked immunosorbent assay, and thyroid stimulating hormone. Patients underwent an electrocardiogram and a contrast-enhanced computed tomographic (CT) scan of the thorax. Three-Hertz repetitive nerve stimulation test was done recording from abductor digiti minimi, nasalis, and trapezius using standard technique.[25] A decrement of >10% in more than or equal to two muscles was considered significant.

Treatment: The patients were prescribed 10–20 mg of prednisolone, which was gradually increased depending on their response and complications. Maximum prednisolone dose of ≤ 20 mg/day was defined as low dose and > 20 mg/day as high dose. The dose of AChEIs was adjusted time to time. The starting dose of pyridostigmine in MGFA class II patients was 30 mg thrice daily and in others was 60 mg three or four times daily. Additional neostigmine 15 mg, 30 min before lunch and dinner, was advised if needed. Patients not improving on prednisolone at 3 months or those having steroid-related side effects or associated comorbidities (heart disease, diabetes, and hypertension) received AZA. The maximum and minimum doses of prednisolone, AChEIs, and AZA during the treatment course were recorded. Patients with thymic enlargement and thymoma were advised thymectomy. Patients with myasthenic crisis received plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) along with other life support. The patients were followed up at 3 months interval in a dedicated MG clinic. We also monitored their problems through a dedicated MG WhatsApp group.

Outcome: Assessment with MGFA, MGADL, and MGQoL-15 was done at 3, 6, 12, and 24 months. At 2 years, the MGFA post intervention status was defined as complete stable remission (CSR), pharmacologic remission (PR), minimal manifestation (MM), improved, unchanged, worse, exacerbation, and died [Supplementary Table 2].[23]

The known side effects of prednisolone and AZA, such as hypertension, diabetes, fracture, anemia, thrombocytopenia, liver dysfunctions, and infections, were noted.

Statistical analysis

The normalcy of data was verified using the Shapiro–Wilk test The predictors of achieving MGFA 0 and MM status at 2 years were evaluated by univariate followed by multivariate analysis. Chi-square/Fisher's exact test was used for categorical data, independent *t*-test for continuous normally distributed data, and Mann–Whitney *U* test for skewed continuous/scaled data. The statistical analysis was done using Statistical Package for the Social Sciences software and GraphPad prism 7. A variable with a two-tailed *P* value of < 0.05 in the statistical analysis was considered significant.

Results

Fifty-seven patients with generalized MG were included. Their median age was 51 (19–80) years, and of them, 26 (45.6%) were females. The median duration of illness at the time of presentation was 4 months. Fifty (87.7%) patients had anti-AchR antibody and three (5.3%) had anti-MuSK antibody. Thirty-one (54.4%) patients had comorbidities. CT of the

thorax revealed thymoma in 16 (28.1%) and thymic hyperplasia in eight (14.0%) patients. Twenty-one (36.8%) patients underwent thymectomy. At presentation, 23 (40.4%) patients had MGFA II, 23 (40.4%) had MGFA III, seven (12.3%) had MGFA IV, and four (7.0%) had MGFA V. All received prednisolone and AChEIs. Twenty-nine (50.9%) patients received AZA: three (10.3%) within 3 months and 26 (89.7%) after 3 months [Supplementary Table 3].

Outcome

Majority of the patients achieved MGFA 0 status in the long run: 27 (47.4%) at 3 months, 35 (61.4%%) at 6 months, 46 (80.7%) at 12 months, and 46 (80.7%) at 24 months [Figure 1]. The proportion of achieving MGFA 0 (with treatment) increased till 12 months; thereafter, it was negligible. Forty-three (75.4%) patients achieved MM2/MM3 status, and five patients became asymptomatic on pyridostigmine only, by 24 months. During 24 months of follow-up, 15 patients had myasthenic crisis (24 episodes); one third had repeated crisis (two to three episodes). Myasthenic crisis occurred within the first year of diagnosis, except in one patient who had it in the second year.

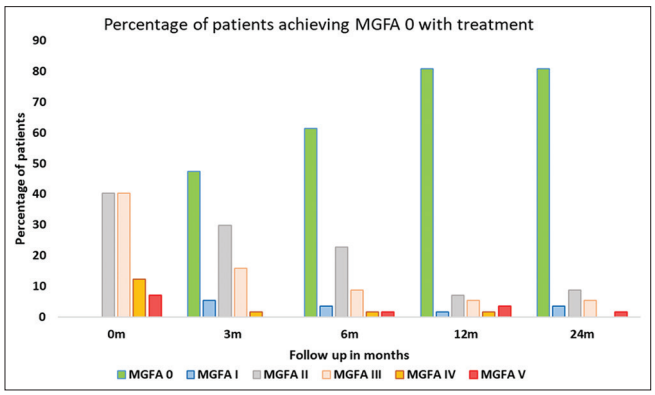

Figure 1: Proportion of patients in different MGFA classes following treatment. The maximum improvement occurred by 12 months. Improvement is seen from all the baseline MGFA classes. MGFA: Myasthenia Gravis Foundation of America

Transition of MGFA class

Improvement or exacerbation occurred from all MGFA classes. At 3 months, the transition to MGFA 0 was the highest from MGFA III (12/23, 52.2%) followed by class II (11/23, 47.8%) and class IV (3/7, 42.8%), and was the lowest in class V (1/4, 25%) [Figure 2]. Occurrence of crisis was more frequent with higher baseline severity of MG: 21.7% with class II, 26.1% in class III, 42.9% with class IV, and 25% with class V ($P = 0.02$).

Predictors of MGFA 0 at 3 and 6 months

At 3 months, 27 (47.4%) patients achieved MGFA 0 and were able to join back their work without difficulty. Significant proportion of male patients achieved MGFA 0, compared to females ($P = 0.03$). The other variables were not related to 3 months' outcome [Table 1].

At 6 months, 35 (61.4%) patients achieved MGFA 0. Higher proportion of patients with normal CT of the thorax achieved MGFA 0, compared to those with CT abnormality (77.1% vs. 22.9%, $P < 0.001$). The details are presented in Table 2.

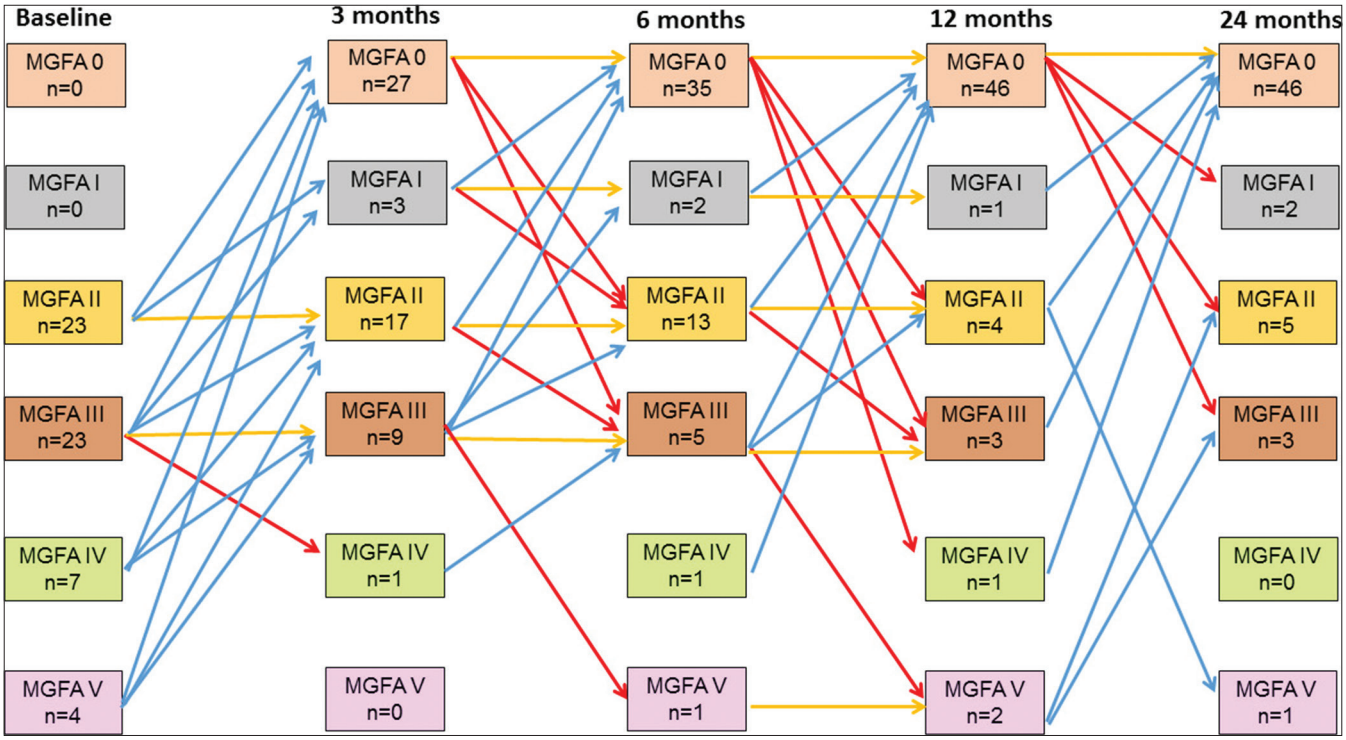

Figure 2: Transitions of MGFA class during follow-up. Improvement and exacerbation occurred from all the classes despite treatment. MGFA: Myasthenia Gravis Foundation of America

Table 1: Predictors of achieving MGFA 0 at 3 months

Baseline variables	MGFA 0 (n=27)	MGFA ≥1 (n=30)	*P*
Age* (years)	49.22±14.29	49.23±14.81	0.99
Females†	8 (29.6%)	18 (60.0%)	0.03
Pretreatment duration (months)‡	4 (Q1, 2; Q3, 14)	5 (Q1, 1.75; Q3, 10.50)	0.89
MGFA at presentation†			
MGFA II	11 (40.7%)	12 (40.0%)	0.88
MGFA III	12 (44.4%)	11 (36.7%)	
MGFA IV	3 (11.1%)	4 (13.3%)	
MGFA V	1 (3.7%)	3 (10.0%)	
Baseline MGADL score‡	10 (Q1, 9.0; Q3, 12.0)	11 (Q1, 10.0; Q3, 14.0)	0.18
Baseline MGQoL-15‡	9 (Q1, 6.0; Q3, 13.0)	11 (Q1, 9.0; Q3, 15.0)	0.08
Comorbidities†			
Hypertension†	3 (11.1%)	5 (16.7%)	0.85
Diabetes mellitus†	3 (11.1%)	4 (13.3%)	1.00
Hypothyroidism†	3 (11.1%)	5 (16.7%)	0.71
Immunologic biomarkers†	9 (33.3%)	9 (30.0%)	0.94
Thymoma/thymic hyperplasia†	8 (29.6%)	16 (53.3%)	0.11
Thymectomy†	7 (25.9%)	14 (46.7%)	0.17
AChR antibody*	13.71±10.48	11.59±11.12	0.46
Maximum decrement* %	20.25±7.65	20.81±7.42	0.78
Prednisolone†	12 (44.4%)	16 (53.3%)	0.60
Prednisolone + AZA†	15 (55.6%)	14 (46.7%)	
Maximum dose of prednisolone* (mg)	21.30±8.16	22.17±9.10	0.70
Maximum dose of AZA* (mg)	107.14±51.35	97.92±31.00	0.58
Maximum dose of AChEIs* (mg)	285.56±124.35	318.00±94.74	0.28
Prednisolone†			
High dose (>20 mg/day)	11 (40.7%)	10 (33.3%)	0.59
Low dose (≤20 mg/day)	16 (59.3%)	20 (66.7%)	

AChEIs: acetylcholinesterase inhibitors, AChR: acetylcholine receptor, AZA: azathioprine, MGADL: Myasthenia Gravis Activity of Daily Living, MGFA: Myasthenia Gravis Foundation of America, MGQoL-15: Myasthenia Gravis Quality of Life-15, *denotes mean ± SD; †denotes n (%); ‡denotes median (IQR)

Predictors of MM status

None of our patients achieved complete remission, complete PR, MM0, or MM1 at 24 months. One patient achieved MM2 category and 42 achieved MM3 category, whereas five patients required prednisolone for a short duration and thereafter remained asymptomatic with pyridostigmine alone. Nine (15.8%) patients complained some amount of weakness. Univariate analysis revealed significant association of MM status with AChR antibody titer, number of admissions, MGADL at 6 months, and prednisolone dose at 3 months. The outcome was independent of single versus dual immunosuppressants, high versus low dose of prednisolone, and maximum dose of prednisolone, AZA, and AChEIs. Patients who achieved MGFA 0 at 6 months were likely to achieve MM status at 24 months (70.8% vs. 33.3%) [Table 3]. All the patients in MGFA V at baseline achieved the MM status, whereas 91.3% patients from MGFA II achieved the MM status (P = 0.39) [Figure 3]. On multivariate analysis, the independent predictors of MM status included AChR antibody titer (adjusted odds ratio [AOR] 1.08, 95% confidence interval [CI] 1.006–1.167; P = 0.03) and MGADL at 6 months (AOR 1.28, 95% CI 1.066–1.558; P = 0.01).

Treatment modalities and MGFA status at baseline: There was no difference in choosing the treatment such as single versus double immunosuppressant, high versus low dose of prednisolone, thymectomy, and rescue treatment with IVIg/PLEX in the patients with different MGFA classes. The proportion of thymoma patients was also similar in all the classes [Table 4].

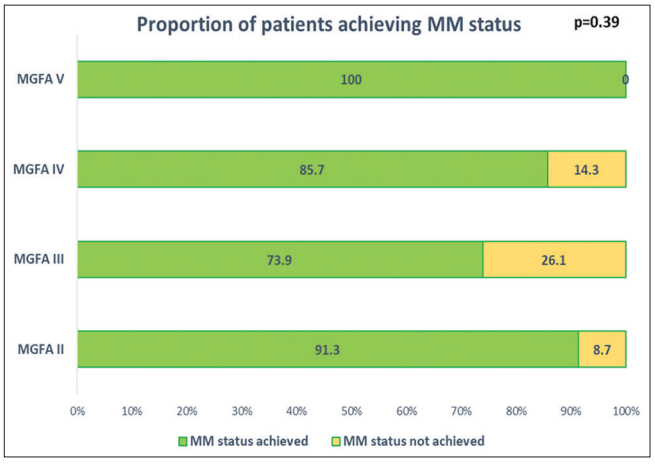

Figure 3: Number of patients achieving MM status at 24 months. The baseline MGFA class was not associated with achievement of MM status. MGFA: Myasthenia Gravis Foundation of America, MM: minimal manifestation

Table 2: Predictors of achieving MGFA 0 at 6 months

Baseline variables	Achieved MGFA 0 (n=35)	Not achieved MGFA 0 (n=22)	*P*
Age* (years)	48.40±15.48	50.55±12.85	0.57
Females†	18 (51.4%)	8 (36.4%)	0.29
Pretreatment duration of illness (months)‡	3 (Q1, 2.0; Q3, 16)	5 (Q1, 2.0; Q3, 8.5)	0.57
MGFA at admission†			
MGFA II	18 (51.4%)	5 (22.7%)	0.06
MGFA III	11 (31.4%)	12 (54.5%)	
MGFA IV	5 (14.3%)	2 (9.1%)	
MGFA V	1 (2.9%)	3 (13.6%)	
MGADL‡	11 (Q1, 9.0; Q3, 13)	11 (Q1, 9.0; Q3, 14.5)	0.54
MGQoL-15‡	10 (Q1, 7.0; Q3, 14)	11 (Q1, 7.75; Q3, 15.25)	0.58
Comorbidities†	18 (51.4%)	13 (59.1%)	0.60
Hypertension†	5 (14.3%)	3 (13.6%)	0.53
Diabetes†	3 (8.6%)	4 (18.2%)	0.07
Hypothyroid†	5 (14.3%)	3 (13.6%)	1.00
Immunologic biomarkers†	11 (31.4%)	7 (31.8%)	0.94
CT of the thorax†			
Thymic hyperplasia	1 (2.9%)	7 (31.8%)	<0.001
Thymoma	7 (20.0%)	9 (40.9%)	
Normal	27 (77.1%)	6 (27.3%)	
AChR-Ab titer* (nmol/L)	12.02±11.20	13.49±10.26	0.62
Maximum decrement* %	20.49±7.24	20.63±7.98	0.95
Prednisolone†	20 (57.1%)	8 (36.4%)	0.18
Prednisolone + AZA†	15 (42.9%)	14 (63.6%)	
Maximum dose of prednisolone* (mg)	21.43±7.53	22.27±10.20	0.74
Maximum dose of AZA* (mg)	91.07±33.41	116.67±49.24	0.14
Maximum dose of AChEIs* (mg)	282.00±111.82	335.00±100.84	0.07
Prednisolone dose†			
High (>20 mg/day)	13 (37.1%)	8 (36.4%)	1.00
Low (≤20 mg/day)	22 (62.9%)	14 (63.6%)	

AChEIs: acetylcholinesterase inhibitors, AChR: acetylcholine receptor, AZA: azathioprine, CT: computerized tomography, MGADL: Myasthenia Gravis Activity of Daily Living, MGFA: Myasthenia Gravis Foundation of America, MGQoL-15: Myasthenia Gravis Quality of Life-15. *denotes mean±SD; †denotes n (%); ‡denotes median (IQR)

Novel outcome group: In our cohort, five patients received prednisolone for a median of 4 months (range 2–5). Thereafter, these patients received pyridostigmine only in a dose of 120–180 mg/day. None of them had exacerbation or crisis. All the patients achieved MGFA 0 by 4 months [Table 5].

Complications: Twenty-four patients had steroid-induced complications: hypertension in five, diabetes in five, infection in seven, cataract in two, and Cushingoid features in one. Only one patient had AZA-related hepatic complication characterized by epigastric pain and raised serum bilirubin and liver enzymes, which normalized after stopping AZA.

Discussion

In this study, 35 (61.4%) patients achieved MGFA 0 class at 6 months and 46 (80.7%) achieved it at 12 months; thereafter, the improvement was negligible. At 24 months, none of our patients achieved CSR, PR, MM0, and MM1. Forty-three (75.4%) patients achieved MM2/3 status and five (8.8%) patients remained asymptomatic with AChEIs alone. The predictors of MM status included anti-AChR antibody titer, number of admissions, prednisolone dose at 3 months, and MGADL at 6 months. In multivariate analysis, anti-AChR antibody titer and MGADL at 6 months remained as independent predictors. During the course of treatment, improvement or exacerbation occurred from all the stages, especially within the first year. There are studies evaluating the long-term prognosis of MG; however, the definition of outcome and duration of follow-up are heterogeneous in them. CSR and PR are rare even after 10 years. In a large cohort from Italy, MG patients were followed up for a mean duration of 5.3 years. Cumulative probability of CSR was 1% by 1 year, 8% by 3 years, 13% by 5 years, and 21% by 10 years. Similarly, PR was achieved in 5%, 24%, 33%, and 41%, respectively. Younger age predicted CSR.[26] A later study from Italy in 2003 reported remission in 58.3% patients. The patients were followed up for 55.1 ± 48.1 months. On univariate analysis, female gender, age < 40 years, thymectomy, and thymic hyperplasia were the predictors of remission. On multivariate analysis, age and thymectomy remained as independent predictors.[27] However, the outcome was not defined as per MGFA outcome measure. Cosi et al.[28] reported CSR in 9.5% of patients and overall remission in 77.6% of patients. CSR was associated with pretreatment duration of illness and

Table 3: Predictors of MM status at 24 months

Variables	Total (n=57)	MM status achieved (n=48)	MM status not achieved (n=9)	*P*
Age* (years)	49.23±4.44	48.15±4.55	55.0±13.08	0.19
Female†	26 (45.6%)	23 (57.9%)	3 (33.3%)	0.41
Pretreatment duration of illness (months)‡	4 (Q1, 2.0; Q3, 11.0)	4 (Q1, 2.0; Q3, 15.5)	5 (Q1, 2.0; Q3, 6.5)	0.84
MGFA at presentation†				
MGFA II	23 (40.4%)	21 (43.8%)	2 (22.2%)	0.40
MGFA III	23 (40.4%)	17 (35.4%)	6 (66.7%)	
MGFA IV	7 (12.3%)	6 (12.5%)	1 (11.1%)	
MGFA V	4 (7%)	4 (8.3%)	0 (0%)	
Mean AChR antibody titer*	12.59±10.78	11.34±10.28	19.26±11.53	0.042
Comorbidities†				
Hypertension	8 (14.0%)	7 (14.6%)	1 (11.1%)	0.27
Diabetes	7 (12.3%)	6 (12.5%)	1 (11.1%)	1.00
Hypothyroidism	8 (14.0%)	8 (16.7%)	0	0.33
Immunologic biomarkers	18 (31.6%)	15 (31.2%)	3 (33.3%)	0.14
CT of the thorax findings†				
Thymoma	16 (28.1%)	14 (29.2%)	2 (22.2%)	0.22
Thymic hyperplasia	8 (14.0%)	5 (10.4%)	3 (33.3%)	
Normal	33 (57.9%)	29 (60.4%)	4 (44.4%)	
Thymectomy†	21 (36.8%)	16 (33.3%)	5 (55.5%)	0.41
Immunosuppression†				
Steroid	28 (49.1%)	25 (52.1%)	3 (33.3%)	0.47
Steroid + AZA	29 (50.9%)	23 (47.9%)	6 (66.7%)	
MGFA 0 at 3 months†				
Achieved	30 (52.6%)	24 (50%)	6 (66.7%)	0.47
Not achieved	27 (47.4%)	24 (50%)	3 (33.3%)	
MGFA 0 at 6 months†				
Achieved	37 (64.9%)	34 (70.8%)	3 (33.3%)	0.05
Not achieved	20 (35.1%)	14 (29.2%)	6 (66.7%)	
MGFA 0 at 12 months†				
Achieved	47 (82.5%)	41 (85.4%)	6 (66.7%)	0.34
Not achieved	10 (17.5%)	7 (14.6%)	3 (33.3%)	
No. of admissions in the first year*	1.49±0.91	1.35±0.78	2.22±1.20	0.007
No. of crisis in the first year*	0.39±0.67	0.29±0.50	0.89±1.17	0.013
No. of admissions in the second year*	0.33±0.58	0.31±0.55	0.44±0.73	0.53
No. of crisis in the second year*	0.11±0.31	0.8±0.28	0.22±0.44	0.22
MGADL at baseline‡	11 (Q1, 9.0; Q3, 13.0)	11 (Q1, 9.0; Q3, 12.75)	11 (Q1, 9.0; Q3, 13.5)	0.87
MGADL at 3 months‡	4 (Q1, 3.0 Q3, 7.0)	4 (Q1, 3.0 Q3, 7.0)	4 (Q1, 2.5 Q3, 9.5)	0.72
MGADL at 6 months‡	3 (Q1, 2.0; Q3, 6.0)	3 (Q1, 2.0; Q3, 4.75)	7 (Q1, 3.0; Q3, 11.5)	0.03
MGADL at 12 months‡	2 (Q1, 1.0; Q3, 4.0)	2 (Q1, 1.0; Q3, 4.0)	4 (Q1, 2.5; Q3, 12.0)	0.04
MGQoL at presentation‡	10 (Q1, 7.5; Q3, 14.0)	10.5 (Q1, 8; Q3, 14.75)	9 (Q1, 6.5; Q3, 11.0)	0.27
MGQoL at 3 months‡	7 (Q1, 5.0; Q3, 10.0)	7 (Q1, 5.0; Q3, 10.0)	9 (Q1, 4.0; Q3, 12.5)	0.71
MGQoL at 6 months‡	7 (Q1, 5.5; Q3, 9.0)	7 (Q1, 5.0; Q3, 8.0)	9 (Q1, 2.0; Q3, 13.0)	0.13
MGQoL at 12 months‡	5 (Q1, 4.0; Q3, 7.5)	5 (Q1, 4.0; Q3, 7.0)	6 (Q1, 3.5; Q3, 17.0)	0.42
Prednisolone dose†				
Low (≤20 mg/day)	36 (63.2%)	31 (64.6%)	5 (55.6%)	0.71
High (>20 mg/day)	21 (36.8%)	17 (35.4%)	4 (44.4%)	
Maximum dose of prednisolone* (mg)	21.75±5.58	21.35±6.90	23.89±15.16	0.63
Maximum dose of AZA* (mg)	102.88±42.62	101.25±41.73	108.33±49.16	0.73
Maximum dose of AChEIs* (mg)	302.63±109.98	299.38±107.63	320.00±127.28	0.66
Prednisolone at initiation* (mg)	17.89±10.39	16.67±8.71	24.44±15.89	0.18
Prednisolone at 3 months* (mg)	14.56±7.62	13.65±7.33	19.44±7.68	0.03
Prednisolone at 6 months* (mg)	12.10±6.98	11.15±6.76	17.22±6.18	0.01
Prednisolone at 12 months* (mg)	10.72±6.48	9.87±6.23	15.28±6.18	0.02
Maximum decremental response*	-20.54±7.47	-19.90±6.51	-24.01±11.19	0.31

AChEIs: acetylcholinesterase inhibitors, AChR: acetylcholine receptor, AZA: azathioprine, CT: computerized tomography, MGADL: Myasthenia Gravis Activity of Daily Living, MGFA: Myasthenia Gravis Foundation of America, MGQoL: Myasthenia Gravis Quality of Life, MM: minimal manifestation. *denotes mean±SD; †denotes n (%); ‡denotes median (IQR)

Table 4: Baseline MGFA status in patients and their treatment modalities

MGFA	II	III	IV	V	*P*
Prednisolone alone†	14 (60.9%)	11 (47.8%)	3 (42.9%)	0 (0%)	0.18
Prednisolone + AZA†	9 (39.1%)	12 (52.2%)	4 (57.1%)	4 (100%)	
Prednisolone dose†					
High (>20 mg/day)	8 (34.8%)	8 (34.8%)	3 (42.9%)	2 (50%)	0.92
Low (≤20 mg/day)	15 (65.2%)	15 (65.2%)	4 (57.1%)	2 (50%)	
Thymectomy†	8 (34.8%)	10 (43.5%)	2 (28.6%)	1 (25%)	0.72
Thymoma†	8 (34.8%)	6 (26.1%)	1 (14.3%)	1 (25%)	0.56
IVIg/PLEX†	7 (30.4%)	5 (21.7%)	4 (57.1%)	2 (50.0%)	0.30

AZA: azathioprine, IVIg: intravenous immunoglobulin, MGFA: Myasthenia Gravis Foundation of America, PLEX: plasmapheresis. †denote n (%)

Table 5: Novel group of generalized myasthenia gravis patients treated with pyridostigmine

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	37	47	53	56	42
Gender	F	M	M	M	M
MGFA at presentation	2a	2b	3a	2b	3a
Thymoma	+	+	-	+	-
Thymectomy	Done	Done	-	Done	-
Timing of thymectomy	2 m	3 m	-	3 m	-
Initial pyridostigmine (mg)	120	120	180	180	180
Pyridostigmine (mg) at 2 years	180	180	150	180	120
Number of admission	1	0	1	1	0
Number of crisis	0	0	0	0	0
Time for achieving MGFA 0	3m	2m	3m	1m	4m

MGFA: Myasthenia Gravis Foundation of America

thymectomy. A systematic review of MG outcome revealed better remission in those who were treated within 1 year of illness and more frequent stable remission in younger patients (<40 years).[18] In our study, age of patients was not related to outcome. We found association of two novel variables with MM status, that is, MGADL at 6 months of treatment and dose of prednisolone at 3 months. Patients who achieved MGADL < 4 at 6 months more frequently achieved the MM status at 2 years. Those who required lower dose of prednisolone at 3 months achieved the MM status at 2 years. The predictive value of these parameters suggests that stable course may be predicted at 6 months of treatment in generalized MG, rather than at baseline. The response to treatment is more important, rather than the severity at baseline. All four patients who presented with myasthenic crisis achieved the MM status at 2 years. Anti-AChR antibody titer was associated with MM status, and this may suggest underlying immunologic status. Association of AChR antibody titer with 1-year outcome has also been reported in an earlier study.[29]

Although newer immunomodulators improve the outcome, it is difficult to achieve a long-term CSR.[3,11-13,17] In a study from Japan, 29.5% patients achieved prednisolone 5 mg/day at 1 year and 71% achieved it at 2 years. About 60% patients achieved the MM status at 2 years. Patients requiring higher dose of prednisolone and more frequent PLEX within 3 months achieved the MM status less frequently at 2 years. The baseline severity and thymectomy were not associated with MM status.[17] In our study, lower dose of prednisolone at 3 months was associated with MM. Additional doses of AZA and IVIg/PLEX were not significantly different between the patients with and without MM status.

In our study, five patients did not require long-term immunomodulating drugs. The outcome of this group may suggest that the patients who are asymptomatic on lower dose of AChEIs (< 180 mg/day) may be followed up without immunomodulators till their response wears off.

Patients in our cohort did not have severe adverse effect to prednisolone or AZA, compared to that reported in literature.[7,16] This may be due to the use of lower dose of prednisolone and AZA in our cohort.

Limitation: This is an observational study, and the treatment was heterogonous. However, the patients were followed up regularly, and one of the investigators examined and verified their treatment records.

Conclusion

CSR and PR at 2 years is rare in generalized MG. MM status was achieved in 84.2% of our patients, which could be predicted by anti-AChR antibody titer and MGADL at 6 months.

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Authors' contribution

JK contributed to the conception, design of the study and writing of the manuscript. NBG and FA were involved with the data collection. All were involved with the data analysis. NBG done the literature review. JK and FA contributed to the discussion of the study findings.

Data statement

Data will be available on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Myasthenia Gravis Foundation of America – Clinical severity classification

MGFA Class	Description
Class I	Any ocular muscle weakness
Class IIa Class IIb	Mild weakness predominantly affecting Limb and truncal muscles with or without oropharyngeal weakness Predominant weakness of oropharyngeal, respiratory muscles or both, with or without weakens of limb or truncal muscles
Class IIIa and IIIb	Moderate weakness, the distribution is similar to class II a & b
Class IVa and IVb	Severe weakness, distribution similar to II a & b
Class V	Intubation with or without mechanical ventilation except postoperative

Supplementary Table 2: MGFA Post-intervention status (MGFA-PIS)

Complete stable remission (CSR)	No symptoms and signs of MG for 1 year without treatment. Isolated weakness of eyelid closure may present.
Pharmacological remission (PR)	Same as CSR but may continue some form of therapy except AChEIs.
Minimal manifestations (MM)	Similar to PR, but minimal weakness is detectable on examination. MM0: No treatment for MG in past l year. MM1: Receive some form of immunosuppression, but no AChEIs. MM2:Similar to MM1 but requires AchEI (<120mg pyridostigmine/day) for at least past 1 year MM3: Similar to MM but received AchEIs or other symptomatic treatment.
Change in status	Improved (I): Substantial improvement in QMG after treatment. Unchanged (U): Response to MG medication is not substantial. Worse (W): Determination or increase need of medication than the pre-treatment level. Exacerbation (E): After achieving CSR, PR or MM developed clinical findings, which are non-permissible for that criterion. Died (D): MG patients died of MG, treatment complication or within 30 days of thymectomy.

MG: Myasthenia gravis, AChEIs: acetylcholinesterase inhibitors, QMG: Quantitative Myasthenia Gravis

Supplementary Table 3: Baseline characteristics of generalized myasthenia gravis patients

Baseline characteristic	Number=57
Age -years[§] (Median - range)	51 (19-80)
Gender (female)[†]	26 (45.6%)
Median duration of illness § presentation[§] (range)	4 (1-144)
MGFA at presentation[†]	
IIa or IIb	23 (40.4%)
IIIa or IIIb	23 (40.4%)
IVa or IVb	7 (12.3%)
V	4 (7%)
Anti-AChR antibodies[†]	50 (87.7%)
Anti-MuSK antibodies[†]	3 (5.3%)
Comorbidities (total)[†]	31 (54.4%)
Hypertension[v]	8 (14.0%)
Diabetes[†]	7 (12.3%)
Hypothyroidism[v]	8 (14.0%)
Immunological diseases[v]	18 (31.6%)
CT Thorax findings[†]	
Thymoma	16 (28.1%)
Thymic hyperplasia	8 (14.0%)
Thymectomy[†]	21 (36.8%)
Treatment[†]	
AChEI	57 (100%)
Prednisolone alone	28 (49.1%)
Prednisolone + Azathioprine	29 (50.9%)

AChEIs: acetyl cholinesterase inhibitors, CT: computerized tomography, MGFA: Myasthenia Gravis Foundation of America. [†]denotes n (%); [§]denotes (Median - range)