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Satisfactory Response with Achieving Maintenance Low-dose Prednisone in Generalized Myasthenia Gravis

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Abstract

Objectives—To estimate, the satisfactory response rate (SR%) with achieving maintenance low-dose prednisone in acetylcholine receptor antibody-positive generalized myasthenia gravis (MG).

Methods—In this retrospective study we estimate the SR% as defined by [remission/minimal manifestations status for at least 6months using 7.5mg or less of prednisone daily, for maintenance treatment at 2, 4 and 6 years following symptoms onset] for patients who were not taking steroid-

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sparing immunosuppressant (SSI) as a primary outcome and for patients taking an SSI as a secondary outcome.

Results—Forty-five patients were not taking an SSI at 2 years, 34 patients at 4 years and 17 patients at 6 years; SR% was 44.4%, 64.7% and 58.8%, respectively. Thirty-six patients were taking an SSI at 2years, 22 patients at 4years and 15 patients at 6years; the SR% was 50.0%, 45.4% and 66.7%, respectively.

Conclusion—Nearly half of the generalized MG patients who were not taking an SSI achieved an SR.

Search terms

myasthenia gravis; steroid; immunosuppressant; prognosis

Introduction

Steroid immunosuppression is the mainstay therapy for generalized myasthenia gravis (MG). However, the large number of side effects contribute to problematic long-term steroid use, especially at high doses. Steroid-sparing immunosuppressants (SSIs) are often added to steroids at the initiation of therapy to achieve a satisfactory response (SR), that is, a remission/minimal manifestation status while on low-dose prednisone (LDP) without receiving plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) during maintenance treatment.(1–5) The proportion of generalized MG patients who can achieve an SR without the addition of SSIs is unknown. The need for such information is important for planning clinical trials and for making decisions in daily clinical practice. Determining the SR rate (SR%) of low dose prednisone without an SSI is important for clinical trial planning, as the negative results of several trials of SSIs in MG were attributed in part to the likelihood of a strong response to a low-dose steroid in the placebo group which was mostly less than 10 mg after steroid tapering down.(2, 6, 7) This suspected strong response rate to low dose prednisone was never determined. From a clinical practice perspective, the response to low-dose prednisone needs to be investigated, as several recent studies that were used to inform clinical practice regarding the effect of SSIs on generalized MG patient outcomes did not include a control group (i.e., an SSI-free group).(5, 8, 9) This omission was attributed in part to the lack of such a control group in some MG centers.(10) Lack of knowledge about generalized MG outcomes in patients who were not taking an SSI makes the clinical decision regarding the efficacy of SSIs less accurate, as it would not be clear how the SR% could be improved with an SSI compared to the SR% achieved with low dose prednisone only.

Specific data on the SR% with and without an SSI in generalized MG treatment is needed to complement the current literature because the available retrospective studies that inform long-term generalized MG prognosis lack important information, which limits the use of these studies.(11–13) First, prior prognostic studies did not distinguish whether the outcome was achieved with a low versus high dose of prednisone. Rather, most studies have described the long-term prognosis in terms of complete remission rate (no signs or symptoms with no prednisone and no pyridostigmine) or pharmacological remission rate (no signs or symptoms

with no limits on steroids or other immunosuppressant agents' dosages). In addition, many generalized MG patients may have subtle orbicularis oculi or hip flexion weakness that is noticeable only upon examination. These patients are in a minimal manifestation status and are considered a treatment success.(14) The second limitation is that prior studies have either excluded patients receiving PLEX or IVIG or the studies did not distinguish between the response to PLEX or IVIG and that to prednisone alone.(12, 13, 15–17) The third limitation is that long-term MG prognostic studies (longer than 1 year) have not stratified patients based on taking SSIs or not.

Our primary objective is to estimate the percentage of patients with acetylcholine receptor antibody (AChR)-positive generalized MG who achieved an SR without an SSI at 2, 4 and 6 years. Our secondary aims include determining the SR% for patients taking SSIs and for the overall cohort while investigating independent SR predictors. Identifying the SR% with and without SSI administration among generalized MG patients will be important not only for treatment decisions, such as the benefit of adding SSIs, but also for clinical trial design.

Methods

Study design

We performed a retrospective review of electronic medical records at the University of Kansas Medical Center between January 1999 and July 2015. This protocol was approved and determined to be exempt by our center Human Subjects Committee. Patients meeting criteria for generalized MG were identified from 1) the neuromuscular research data base at our center and 2) a search of our center electronic medical records using the following computable phenotype (ICD9 code 358, at least one visit to outpatient neurology clinic). The inclusion criteria were 1) AChR antibody-positive generalized MG, 2) generalized weakness, which included patients with Myasthenia Gravis Foundation of America (MGFA) class II and higher, and 3) first assessment by our neuromuscular service within 3 years from symptom onset. Patients were excluded if they had another disorder causing weakness such as mitochondrial myopathy, neuromyelitis optica, multiple sclerosis or chronic inflammatory demyelination polyneuropathy. Patients were assigned to the “not taking an SSI” group if they received no SSI or less than 12 months of any SSI, since the SSI onset of action is likely delayed by more than 1 year.(3, 5) Patients were assigned to the “taking an SSI” group if they fulfilled two conditions a) If they received 12 months or more, of azathioprine, mycophenolate mofetil or methotrexate and b) if they were on these SSIs for the last three months prior to group assignments. For example, at 4 years, if the patient received an SSI for 12 months or more over the last 2 years, including the last 3 months before the 4-year mark, then the patient was assigned to the SSI group. Otherwise, the patient would be assigned to the “not taking an SSI” group. Group assignment at 4 years was independent from group assignment at 2 years. Similar rules were applied at 6 years. Using these rules, the same patients were assigned to groups at 2, 4 and 6 years. The time frame of twelve months of using an SSI was chosen as a criterion to include patients in the “taking an SSI” group because several studies have shown that SSIs may not have a clinically detectable effect before 12 months.(1–4) Additional sensitivity analyses were performed with more strict definitions for the “not taking an SSI” group, as described in the following section. A patient

who has been off SSI treatment for more than 3 months before the group assignment was assigned to the “not taking an SSI” group and was required to maintain an SR for an additional 6 months (for a total of 9 months of observation for washout) to be considered in the SR status. This is consistent with data from Kuks et al., who demonstrated that the effect of azathioprine dissipates over 4 to 9 months.(18)

Our general treatment paradigm was to start prednisone at 40 to 60 mg daily (Table 1). Once the patient reached remission or a minimal manifestation status, the prednisone dose was progressively tapered down to the lowest effective dose while maintaining remission or a minimal manifestation status. The taper down was according to the clinician’s discretion. If a patient’s symptoms recurred during the tapering period, the prednisone dose was increased to the previously effective dose. All patients had an opportunity to taper down the prednisone dose. SSIs were used at standard dosages to allow the oral prednisone dose to be reduced to the lowest effective dose, preferably under 10 mg daily. If the prednisone dose could not be tapered down, the SSI dose was increased.

The SR was defined as remission/minimal manifestation status maintained with 7.5 mg or less of daily prednisone for at least 6 months without worsening symptoms or receiving IVIG or PLEX.

The SR has several advantages when compared to the available terms in the literature. The SR is consistent with the goal of treatment in the international consensus of MG treatment as well as with remission, minimal manifestation status and improvement terms introduced by the MGFA. The added value of the SR is that it takes into account the dose of prednisone and the use of IVIG or PLEX.(14)

Outcomes

Primary outcome—The primary outcome was the percentage of generalized MG patients who were not taking SSIs and achieved an SR at 2, 4 and 6 years following symptom onset.

Sensitivity analyses—We conducted sensitivity analyses using five different definitions for the SR based on A) daily prednisone dose (5 mg and 10 mg), B) duration of SR (1 year) and C) two more strict definitions of “not taking an SSI”: (a) no exposure to any SSI at all and (b) 3 months exposure to an SSI.

Secondary outcomes—The SR% at 2, 4 and 6 years for the whole cohort and for the patients taking SSIs as well as the predictors of an SR were the secondary outcomes measured.

Assessment of confounding factors effect—To investigate whether the SR% was influenced by an unbalanced distribution of potential confounders, we compared crude and adjusted relative risk (RR) factors of the SR% for patients taking SSIs and those who were not taking SSIs. A change by more than 10% between the value of crude RR and adjusted RR indicate a presence of confounding effect. The impact of the confounding effect on SR% is proportionate to the change in the values between crude RR and adjusted RR. We adjusted for potential confounding effects from the following factors: onset severity, defined as the

maximum severity during the first year of the disease (mild versus moderate or severe), recent recurrent worsening (within the last 2 years), worsening with steroid tapering (within the last 2 years), the SR status 2 years earlier, the duration of treatment with >7.5 mg prednisone daily and the use of prednisone in the first year. Worsening was defined as needing IVIG, PLEX or a 10-mg increase in the prednisone dose. Worsening with steroid tapering included any reported symptoms that occurred after the prednisone dose was reduced and required increasing the prednisone dose or the use of IVIG or PLEX. Assessment of the confounding effect of receiving IVIG or PLEX prior to outcome assessment was included within the assessment of confounding effects for onset severity, as the patients who received IVIG or PLEX prior to outcome assessment were classified in the moderate to severe onset groups.

Statistical analysis

Baseline population characteristics were analyzed using the means, standard deviations, and frequencies. These data were compared using t-tests, chi-squared tests and Fisher's exact tests, as appropriate. The SR% was defined as the total number of patients who achieved SR divided by the total number of patients who were at risk (total number of patients with generalized MG at 2, 4 and 6 years from symptom onset). We calculated the RR using repeated measures Poisson regression analyses with a generalized estimating equation and robust standard error to account for autocorrelation within subjects.⁽¹⁹⁾ Factors with a p-value <0.1 were included in the multivariate model as candidate predictors. The final factors associated with the SR were selected by backward stepwise selection. Two-sided p-values <0.05 were considered statistically significant. Statistical testing was performed using STATA version 13 (Stata-Corp, College Station, TX).

Results

The databases revealed 427 patients of whom 81 fulfilled our inclusion criteria. Figure 1 shows a flow chart including the reasons for exclusion. Eighty-one patients were included at 2 years (45 were not taking an SSI and 36 were taking an SSI). Fifty-six patients and 32 patients were included at 4 and 6 years, respectively. The patients' characteristics were comparable between the "not taking an SSI" and "taking an SSI" groups including age of onset and the proportion of patients who underwent thymectomy (Table 1).

Treatment received prior to outcome (SR) assessment

As shown in (Table 1). Both groups were comparable in terms of thymectomy or no thymectomy. The "not taking an SSI" group had a lower proportion of patients taking prednisone in the 1st year and were on a lower starting dose than the "taking an SSI" group. There were more patients in the "taking an SSI" group who had prior trials of PLEX and IVIG. The unbalanced distribution of these two factors may have a confounding effect. We attempted to estimate the confounding effect of these two factors as described in the confounding effect estimation sections. None of the patients who were classified as having achieved an SR status were receiving IVIG or PLEX at the predefined period of SR outcome assessment.

Regarding the use of an SSI prior to achieving low dose prednisone, all patients in the “taking an SSI” group (n=36) have received > 12 months of azathioprine or mycophenolate or methotrexate. Among the “not taking an SSI” group (n=45), 31 patients never received an SSI at all, while the 14 patients who had limited exposure to SSI were excluded in two different sensitivity analyses.

Primary outcome

The percentage of AChR antibody-positive generalized MG patients who achieved an SR without an SSI was 44.4% at 2 years after symptom onset and increased to 64.7% and 58.8% at 4 and 6 years, respectively (Table 2).

Sensitivity analyses

The use of different definitions of the “not taking an SSI” group still revealed a similar SR %. When the “not taking an SSI group” was defined as patients with no exposure to an SSI at all, the SR% was 54.8%, 64.3% and 56.3% at 2, 4 and 6 years, respectively (Table 2). The SR% from the remaining sensitivity analyses was consistent with the SR% from the primary analysis, including when the “not taking an SSI” group was defined as patients with no exposure or <3 months of exposure to an SSI and when different cut-off values for LDP (5 and 10 mg daily) and a minimal duration of an SR (1 year) were considered. (Table 2).

Secondary outcomes

The percentages of generalized MG patients from the entire cohort who achieved an SR at 2, 4 and 6 years were 46.9%, 57.1% and 62.5%, while those in the SSI group were 50%, 45.5% and 66.7%, respectively (Table 2).

Assessment of confounding factors effect

We examined the stability of the relative risk by comparing the crude and adjusted relative risk of achieving SR between “taking an SSI” group versus “not taking an SSI” group. The relative risk has changed from 1.02 (crude relative risk) to 1.21 (adjusted relative risk) with an 18.6% difference (eTable 1, supplementary materials), implying that there was a confounding effect from the factors for which we adjusted.(20) For the rest of secondary outcomes, the differences between the crude and their respective adjusted relative risk varied between 1–22%; (eTable 2).

Predictors of SR

Relative risks of SR predictors are presented in (eTable 2). After multivariate adjustment, the factors of worsening with steroid tapering, duration of higher dose prednisone (>7.5 mg) for more than 18 months and recent (<2 years) recurrent worsening were inverse predictors of the SR (eTable 2). The SR% according to the presence and absence of the predictors are presented in eFigure 1.

Side effects

There were a total of 4 fractures (3 patients in the “taking an SSI” group and 1 in the “not taking an SSI” group), 2 gastrointestinal bleeds (both patients in the “taking an SSI” group)

and 11 cases of osteoporosis (8 patients in the “taking an SSI” group and 3 in the “not taking an SSI” group).

Discussion

We found that 44.4% of patients with AChR antibody-positive (seropositive) generalized MG who were not taking SSIs were able to achieve an SR at 2 years, and within the study limitations, this rate increased to >50% at 4 and 6 years. This finding was consistent across different cut-off values for low dose prednisone (5, 7.5 and 10 mg daily) and across different minimal durations of SR maintenance (6 months and 1 year; Table 2). Additionally, the sensitivity analysis that excluded any patient who had limited SSI exposure from the “not taking an SSI” group did not alter our results (Table 2). Our study is the first in the generalized MG literature to estimate the number of patients capable of achieving an SR on low dose prednisone without taking an SSI. Our reported SR% is higher than the previously reported 10–20% complete remission rate (with no prednisone and no pyridostigmine) and the 25–35% pharmacological remission rate (with no limit on the prednisone dose) because the SR in our study includes both remission and minimal manifestation categories.(12, 13) Our SR% in seropositive generalized MG is consistent with the 66% of patients who achieved minimal manifestation status or better in a study by Sanders and Evoli, which included both ocular MG and seronegative MG.(21) Our retrospective study design accounted for the effects of PLEX and IVIG use, since by design, those patients with symptoms worsening to the point of needing IVIG or PLEX were excluded from the SR status. More specifically, patients were excluded from the SR status if they had received IVIG or PLEX within a 6-month window of the follow-up mark (2, 4, or 6 years). This is one of the strengths of our study because prior studies that described remission rate have either excluded those patients who received IVIG or PLEX or did not attempt to distinguish the response to PLEX or IVIG from that to prednisone alone.(12, 13, 15)

Worsening with steroid tapering within the last 2 years inversely predicted the SR. This predictor has not been investigated before and may inform future clinical trial designs. This finding suggests that patients who experience worsening are likely to stay on a higher dose of prednisone or receive a maintenance treatment with IVIG or PLEX. Another predictive factor that we identified as being inversely correlated with an SR was a prednisone dose >7.5 mg for more than 18 months. However, the effect of this predictor was more prominent in the first 4 years of the disease course, and it diminished at the 6th year, although admittedly, we were limited by attrition and small sample size at these time points. This finding, however, is expected, as a longer disease duration increases the likelihood that a patient will achieve a satisfactory response.(12, 13, 17, 22) In contrast, the predictive value of worsening with steroid tapering in the last two years was maintained at 2, 4 and 6 years. This supports the clinical practice that steroid tapering should be attempted before initiating SSI treatment. Additionally, we propose that evidence of having failed a steroid taper in the last 2 years should be considered as part of the subject inclusion criteria for more rigorous generalized MG clinical trials that test SSIs. Thymectomy was not a predictor of achieving an SR in our study. However, thymectomy was effective in achieving favorable outcomes in a randomized clinical trial.(23)

The international consensus for MG management suggests that patients should initiate SSI treatment if certain indications are present and may terminate SSI treatment after 6 months to 2 years of stable symptoms.(14) This means that patients may switch back and forth between taking an SSI and not taking an SSI, which might not be as controlled for in retrospective studies as in prospective studies. Switching on and off SSI treatment has occurred in less than 24% of the patients in our cohort. This is one of the limitations of a retrospective study, as patients in the “not taking an SSI” group may have residual effects from SSI treatment if it was discontinued shortly before the assessment of outcomes. We addressed this issue by requiring that all patients, including those who were assigned to the “not taking an SSI” group, who discontinued SSI treatment more than three months prior to group assignment to demonstrate an additional 6-month period of a maintained SR, meaning an SSI washout period of 9 months in the primary analysis. Most symptoms of worsening related to the discontinuation of SSI treatment were demonstrated to occur within the first 4–9 months of medication cessation according to Kuks et al.(18) We extended this requirement to 15 months (3 months before group assignment and 12 months where the patients had to maintain an SR) in the sensitivity analysis, and the results were consistent (Table 2). However, if a patient discontinued SSI treatment within the last 3 months prior to group assignments, he/she was assigned to the SSI group. This occurred in a single patient at the 2-year follow-up, and he was on a 15-mg daily dose of prednisone before discontinuation of the SSI. The result of the sensitivity analysis where we excluded all patients who had any kind of exposure to SSI was similar to that of the primary analysis (Table 2).

The variability in the duration of SSI use represents another challenge during group assignment. We attempted to investigate this effect through study design and additional sensitivity analyses. We defined the “taking an SSI” group as taking an SSI for a duration of 12 months or more. This was based on several findings including the one by Palace et al who demonstrated that the separation between the placebo group and the azathioprine groups, in terms of prednisone dose reduction, occurred between 12 and 18 months, but both groups were able to reduce their prednisone dose by >50% at 12 months.(3) For mycophenolate mofetil (MMF), randomized clinical trials have not shown the superiority of MMF over a placebo at 36 weeks.(1, 4) Another study attributed the failure of two randomized trials to the fact that the clinical benefit of MMF begins after 36 weeks.(5) Similarly, the efficacy of a 12 months methotrexate usage in MG was not proven in a randomized clinical trial.(2) In our study, there were 14 out of 45 patients in the “not taking an SSI” group who have a limited exposure to SSI (10 patients had SSI exposure <6 months). In our sensitivity analyses, we excluded all patients (n=14) who had any kind of exposure to an SSI from the “not taking an SSI” group in one tier, and in a second tier, we excluded all patients who had been exposed to an SSI for longer than 3 months. The results were similar to those from the primary analysis (Table 2).

The major finding in our study is that approximately 50% of generalized MG patients achieved an SR on low dose prednisone without requiring an SSI. This highlights the need to exclude patients with a good response to low dose prednisone from clinical trials, as they will do well in both the placebo and the intervention groups, thereby diluting any treatment effect. Ideally, future prospective trials of SSIs should include failure to tolerate steroid tapering as an inclusion criterion, but this is complicated by the feasibility and ethics of

withholding the accepted standard of care treatment. Although several randomized trials did not prove an SSI effect on the outcome of MG, SSIs are still commonly used in clinical practice, and this practice is supported by international guidelines.(14) Our results suggests that the use of SSIs can be added for generalized MG patients if they failed to achieve satisfactory response without SSIs, since 50% of generalized MG patients can achieve satisfactory response without long term commitment to SSIs.

The main reasons to include the “taking an SSI” group in our study were to investigate whether the “not taking an SSI” group would have similar features as the other generalized MG patients and to assess the confounding effect of unbalanced variables. The “not taking an SSI” group and “taking an SSI” group were comparable in most variables, including age of onset and rate of thymectomy (Table 1). However, patients in the “taking an SSI” group were on larger prednisone doses in the first year of the disease and were more likely to have received maintenance IVIG or PLEX. This finding suggests that patients who used an SSI early on were more severe cases. To estimate the confounding effects of these factors, we compared the crude and adjusted relative risk of achieving SR between “taking an SSI” versus “not taking an SSI”. The relative risk changed from 1.02 to 1.21 with an 18% difference (eTable 1, supplementary materials), implying that there was a confounding effect.(20) Although relative risk can be used to compare the “taking an SSI” group to the “not taking an SSI” group, we did not make such comparison as a primary or secondary outcome because such a comparison is not accurate in retrospective studies where the distribution of confounders is unbalanced. Therefore, our data does not confer superiority of one therapy group over another.

The main limitations to this study include its retrospective, single-center design. Patients who experience worsening of symptoms are more likely to be treated with an SSI, and this may have a confounding influence despite our attempt to adjust for it. The small sample size may have influenced the statistical power, which may have prevented us from detecting a difference between groups based on disease severity and MGFA class. Even though MGFA class was comparable, patients not on an SSI may have had milder symptoms, as they were less likely to be on prednisone in the 1st year and took a lower starting dose than the patients in SSI group. Admittedly, this could have introduced bias to our analysis. Because our center is an MG referral center, our patients may be more severely affected or recalcitrant to first line therapies, particularly since 53% of patients were classified as MGFA class III to V. We focused on early-stage generalized MG, which is the most active period.(12, 13, 17, 22) This would likely result in a lower response frequency than that of the general MG population. Grob et al reported that 75% of MG patients experienced their maximum illness within 3 years and 85% experienced their maximum illness within 5 years.(17, 22) Our sample may therefore have included patients with more active disease states, as we excluded patients who were assessed at our center more than 3 years from symptom onset.(17, 22) We cannot exclude referral bias, since an argument can be made that patients presenting to academic centers more than 3 years after disease onset may represent “refractory MG” cases. We did not collect data regarding the rate of thymoma in our cohort; however, the thymectomy rate was comparable between groups. The rate of prednisone dose taper down could be different among different practicing neurologists this may have an influence on our results. We did not compare the SSI group and “not taking an SSI” group as a primary or secondary

outcome, since such comparison between groups is best carried out in a randomized clinical trial setting. However, we included patients taking an SSI for the purpose of assessing any confounding effect. In this retrospective study, there was an uneven distribution of three confounding factors: the onset severity, the use of prednisone in the first year and the use of PLEX and IVIG before outcome assessment, which we found to be more frequent in the “taking an SSI” group, suggesting more disease severity in the latter group.

Future prospective clinical trials may consider a design that calculates a sample size such that 44–65% of generalized MG patients may achieve an SR without SSI treatment. Inclusion of patients with favorable predictors would dilute any effect that would have otherwise been confirmed if only the generalized MG cases with less favorable predictors are included in research studies. Another secondary finding that might help future clinical trial planning is that 50–67% of patients in the “taking an SSI” group were able to achieve an SR status after being on an SSI for 12 months or more. However, we emphasize that disease onset was more severe in the “taking an SSI” group than in the “not taking an SSI” group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

MG	myasthenia gravis
SR%	satisfactory response rate
SR	satisfactory response
SSI	steroid-sparing immunosuppressant
LDP	low-dose prednisone
PLEX	plasma exchange

IVIG	intravenous immunoglobulin
MMF	mycophenolate mofetil
AChR	acetylcholine receptor
MGFA	Myasthenia Gravis Foundation of America
MRC	Medical Research Council
RR	relative risk

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Figure 1.

Flow chart following CONSORT (consolidating standards of reported trials) guidelines

Table 1

Baseline Characteristics.

	Whole cohort (n=81)	Not taking an SSI (n=45)	Taking an SSI (n=36)	P-value
Age (years), mean (SD)	60 (17.3)	59 (18.3)	61 (16.1)	0.64
Male (%)	65.4	64.4	66.7	0.83
DM (%)	24.7	26.7	22.2	0.64
HTN (%)	41.9	37.8	47.2	0.39
Heart disease (%)	16	20.0	11.1	0.28
Lung disease (%)	7.4	4.4	11.1	0.4 [*]
Mild onset (%; MGFA II) ^e	46.9	53.3	38.8	0.19
Moderate onset (%; MGFA III) ^e	38.2	35.5	41.6	0.57
Severe onset (%; MGFA IV, V) ^e	14.8	11.1	19.4	0.29
Prednisone exposure (%)	93	91	94	0.68 [*]
Started prednisone in the first year (%)	67.9	55.6	83.3	0.008
Started prednisone in the second year (%)	12.3	15.6	8.3	0.5 [*]
Years of start taking prednisone from onset, mean (SD)	1.5 (1.5)	1.8 (1.8)	1.1 (0.6)	0.034
Starting dose of prednisone (mg), mean (SD)	40 (24)	32 (21)	50 (25)	0.0006
Thymectomy (%)	25.9	28.8	22.2	0.49
IVIG or PLEX (%)	18.5	6.7	33.3	0.003

^e Myasthenia Gravis Foundation of America^{*} Fisher's exact test

Table 2

Outcomes.

	Whole cohort			Not taking an SSI			Taking an SSI		
	At 2 years N=81	At 4 years N=56	At 6 years N=32	At 2 years N=45	At 4 years N=34 ^e	At 6 years n=17 ^μ	At 2 years N=36	At 4 years N=22 ^e	At 6 years N=15
SR% n/N; if LDP 7.5 mg)	46.9(38/81)	57.1(32/56)	62.5(20/32)	44.4 [*] (20/45)	64.7(22/34)	58.8(10/17)	50.0(18/36)	45.4(10/22)	66.7(10/15)
Sensitivity analysis									
SR% (n/N; if LDP 10 mg)	58.0(47/81)	69.6(39/56)	68.7(22/32)	55.6(25/45)	71.0(24/34)	70.5(12/17)	61.1(22/36)	68.1(15/22)	66.7(10/15)
SR% (n/N; if LDP 5 mg)	43.2(35/81)	57.1(32/56)	56.3(18/32)	42.2(19/45)	64.7(22/34)	58.8(10/17)	44.4(16/36)	45.4(10/22)	53.3(8/15)
SR% (n/N) maintained for 1 year	43.2(35/81)	53.6(30/56)	59.4(19/32)	40.0(18/45)	61.8(21/34)	52.9(9/17)	47.2(17/36)	40.9(9/22)	66.7(10/15)
SR% (n/N) if "Not taking an SSI" group was defined as no exposure to an SSI at all	–	–	–	54.8(17/31)	64.3(18/28)	56.3(9/16)	50.0(18/36)	45.4(10/22)	66.7(10/15)
SR% (n/N) if "Not taking an SSI" group was defined as <3 months exposure to SSIs	–	–	–	52.8(19/36)	64.3(18/28)	56.3(9/16)	50.0(18/36)	45.4(10/22)	66.7(10/15)
Secondary outcomes									
Remission/minimal manifestation (%; n/N)	87.7(71/81)	89.3(50/56)	100(32/32)	86.7(39/45)	94.1(32/34)	100(17/17)	88.9(32/36)	81.8(18/22)	100(15/15)
No moderate or severe worsening (%; n/N)	97.5(79/81)	92.8(52/56)	96.9(31/32)	97.8(44/45)	94.1(32/34)	100(17/17)	97.2(35/36)	90.9(20/22)	93.3(14/15)

NA: not applicable, LDP: low-dose prednisone

^{*} primary outcome

^e At 4 years, 7 patients who were on "taking an SSI group" at 2 years switched to the "not taking an SSI group", while 6 patients were on "not taking an SSI group" at 2 years and switched to the "taking an SSI group".

^μ At 6 years: 1 patient who was on "taking an SSI group" at 4 years switched to the "not taking an SSI group". No patient switched from "not taking an SSI group" to the "taking an SSI group"