ORIGINAL COMMUNICATION

Usefulness of subcutaneous immunoglobulin therapy in the management of myasthenia gravis: a retrospective cohort study

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Abstract

Introduction To describe the efficacy of subcutaneous immunoglobulin (SCIg) in patients with myasthenia gravis (MG).
Methods This was a retrospective study conducted in the neuromuscular referral center of Bordeaux (between January 1, 2014 and March 31, 2021) with MG patients treated with SCIg. The main outcome was SCIg efficacy assessed by the before and after SCIg Myasthenia Gravis Foundation of America (MGFA) clinical classification, the duration of hospitalization and the number of days of orotracheal intubation (OTI).
Results Sixteen patients were included in the study (11 females; 5 males). Nine patients were still treated with SCIg at the end of the study (March 31, 2021) and then underwent prospective follow-up. The average age of the patients was 56.1 (19–83) years. The median duration of MG at onset of SCIg was 37.4 months. Eight patients (50%) remained stable (4 in stage MGFA-IV and 4 in MGFA-III). Eight patients (50%) improved: 3 from MGFA-IV to MGFA-III, 1 from MGFA-IV to MGFA-II, 1 from MGFA-IV to MGFA-I, 2 from MGFA-III to MGFA-II and 1 from MGFA-III to MGFA-I (no patient worsened). The duration of disease progression did not appear to affect the response to SCIg therapy. The number of hospital days per month was significantly reduced after SCIg compared to before, and the number of days in intensive care unit and the number of days of OTI were also reduced. Only minor adverse effects were noted, and 80% of patients were in favor of continuing SCIg.
Conclusions SCIg is a well-tolerated and useful treatment in MG, offering interesting perspectives in the management of MG patients. However, further large-scale prospective studies are needed to confirm these results.

Keywords Myasthenia gravis · Subcutaneous immunoglobulin · Management · SCIg · Treatment

Abbreviations

AChT	Anticholinesterase therapy
anti-AChR	Antibodies against acetylcholine receptor
anti-MuSK	Antibodies against muscle-specific kinase
A-SCIg	Period after using SCIg (after SCIg)
B-SCIg	Period before using SCIg (before SCIg)
CI	Confidence interval
IQR	Interquartile range
IVIg	Intravenous immunoglobulin
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis activities of daily living
MGFA	Myasthenia Gravis Foundation of America Score
MG-Qol-15	Myasthenia gravis quality of life 15-item scale
OTI	Orotracheal intubation
PLEX	Plasma exchange
SCIg	Subcutaneous immunoglobulin

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Introduction

Myasthenia gravis (MG) is caused by pathogenic autoantibodies to components of the postsynaptic muscle endplate, mainly against acetylcholine receptor (anti-AChR) and muscle-specific kinase (anti-MuSK). Clinically, MG is characterized by fatigable muscle weakness, worsened by exertion and improved by rest, and the most common symptoms are binocular diplopia and ptosis [1]. MG is a treatable disease,

but treatment may occasionally result in significant morbidity and even mortality. The management of acquired autoimmune MG remains challenging, as a majority of patients require long-term therapy based on the use of symptomatic drug treatment (pyridostigmine) and immunosuppressive drug treatment if MG cannot be treated with symptomatic treatment alone; supportive treatment and thymectomy are also useful. In patients with acute severe MG, when a rapid response is crucial, short-term treatments are proposed, including plasma exchange (PLEX) and intravenous immunoglobulin [1].

Preparations of exogenous human immunoglobulins, either intravenous (IVIg) or subcutaneous (SCIg), are currently used in various autoimmune neuromuscular disorders [2]. Class I evidence indicates that IVIg can improve clinical status in MG worsening or acute exacerbations; it is a safe and well-tolerated drug with comparable effectiveness to PLEX [3, 4]. However, the data focusing on SCIg in MG are limited. We identified only 2 prospective open-label trial (23 patients) [5–7], 2 retrospective studies (9 patients [8]—34 patients [9]) and 3 published case reports [10–12]. Although SCIg treatment seems to be an interesting alternative treatment to IVIg and a complementary treatment to immunosuppressants, there is no official recommendation for its use as a chronic maintenance therapy in MG due to a lack of data and studies. The main objective of our study was therefore to evaluate the efficacy of SCIg in MG by comparing the severity of disease symptoms before and after the initiation of SCIg.

Methods

Study design and participants

This was a retrospective chart review of patients with MG (followed in the University Hospital of Bordeaux from January 1, 2014 to March 31, 2021 treated or under treatment (for at least 1 consecutive month) with SCIg. Then, if possible, patients still being treated with SCIg at the time of the study were followed prospectively during a dedicated consultation to assess perceived efficacy and satisfaction with the treatment using validated scales (Fig. 1). The inclusion criteria were adults (18 years or older) with a clinical diagnosis of generalized MG who were treated with SCIg.

MG diagnosis was made previously through clinical evaluation by a neuromuscular expert (F.D.) and by meeting two of the following supportive criteria: abnormal Tensilon test, abnormal repetitive nerve stimulation studies, abnormal single-fiber electromyography, elevated serum anti-AChR or anti-MuSK antibodies, or prior response to anticholinesterase therapy (AchT). All participants were screened for commonly accepted exclusion criteria, including the use of immunoglobulins, including renal insufficiency, abnormal liver function (transaminase elevation greater than 2.5 times the upper limit of normal), history of thrombotic events in the past year or established high risk of thrombosis.

Clinical examination of the patients was performed according to the modified Osserman scale [13]. Disease severity was graded according to the 'MG-activities of daily living' (MG-ADL) score [14]. The therapeutic response was evaluated by comparing the Myasthenia Gravis Foundation of America (MGFA) clinical classification [15] before and after SCIg. We collected the duration of hospitalization and the number of days of orotracheal intubation (OTI) to evaluate the severity of the disease: the total number of days of hospitalization included both IVIg treatment duration as well as hospitalization in the department of neurology and in the intensive care unit (ICU). The quality of life of patients was evaluated using the myasthenia gravis quality of life 15-item scale (MG-QoL-15) [16]; we also used the following single validated question: "What percentage of normal do you feel regarding your MG?" [17].

The Health Research Ethics Board at the University Hospital of Bordeaux approved the study and its use of human subjects. All patients provided informed, written consent prior to study participation.

Statistical analysis

Statistics were performed using IBM® SPSS v.23. For continuous variables, the results were expressed as the means ± standard deviation (SD) or as medians (with their minimum and maximum values). In each group, including the before SCIg (B-SCIg) and after SCIg (A-SCIg) groups, the normal distribution of the variables was assessed using the Shapiro–Wilk test. In the case of a normal distribution, Student's t test was applied for paired samples. In the case of a nonnormal distribution, we used the Wilcoxon signed ranks test. Given the small size of our population, most of the tests were nonparametric. Given that the MGFA score is an ordinal quantitative variable, its distribution in the B-SCIg and A-SCIg groups was compared using a Wilcoxon signed ranks test. For categorical variables, the results were expressed as the number of patients and percentages. Intergroup comparisons of the B-SCIg and A-SCIg groups were performed with a McNemar test, which is an alternative to the chi-square test for paired samples. For all these tests, a p value of < 0.05 was considered statistically significant.

Given that the duration of follow-up in the B-SCIg and the A-SCIg (especially) groups varied within and between patients, the number of days of hospitalization and the number of days of OTI were reported as the number of days per month to obtain comparable values. For AchT, because some patients were treated with either pyridostigmine or ambenonium chloride, we chose to compare the number of tablets
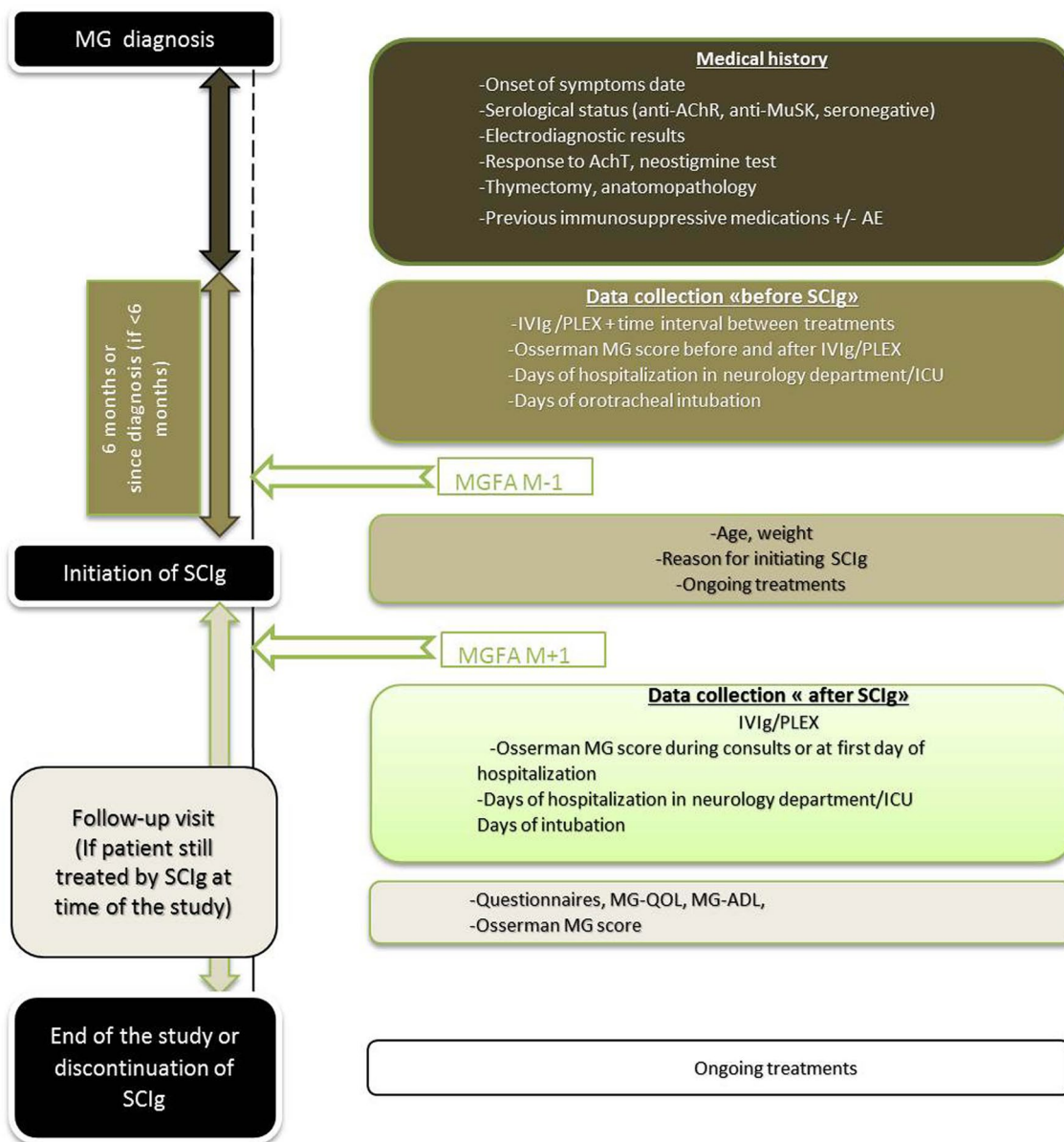
Fig. 1 Study design. *AChT* anticholinesterase therapy, *AE* adverse effect, *ICU* intensive care unit, *IVIg* intravenous immunoglobulin, *MG* myasthenia gravis, *MG-ADL* myasthenia gravis activities of daily living, *MGFA* myasthenia gravis foundation of America score, *MG-Qol-15* myasthenia gravis quality of life 15-item scale, *PLEX* plasma exchange, *SCIg* subcutaneous immunoglobulin

per day (pyridostigmine extended-release tablets were considered equivalent to 2 immediate-release tablets). Finally, the Kaplan–Meier estimator was used to assess the time to

occurrence of a refill IVIg course while accounting for differences in follow-up time.

Results

Clinical features of MG patients

Sixteen patients (11 females, 5 males) were included in the study. Eleven patients had the final follow-up visit, but only 9 patients were still treated with SCIg at the end of the study (March 31, 2021: IgSC was discontinued between January 2021 and March 2021 for 2 patients). The average age of the patients was 56.1 (19–83) years. The median duration of MG at onset of SCIg was 37.4 months. A thymectomy was performed in 5 patients (Table 1).

Table 1 Characteristics of patients at onset of subcutaneous immunoglobulin treatment

Sex	
Female/male	11/5
Percentage of female	68.8%
Age (years)	
Average ± standard deviation	56.1 ± 19,9
Median (minimum–maximum)	52.5 (19–83)
Categories of patients (n, %)	
18–65 years	9 (56.3%)
> 65 years	7 (43.8%)
Medical history (*n*, %)	
At least one medical history (*n*, %)	14 (87.5%)
At least one medical history of autoimmune disorder (*n*, %)	7 (43.8%)
Weight at onset of SCIg (kg)	
Average ± standard deviation	66.8 ± 14.6
Median (minimum–maximum)	64.5 (42–102)
Duration of the disease at onset of SCIg (months)	
Average ± standard deviation	76.5 ± 109.3
Median (minimum–maximum)	37.4 (2.1–375.5)
Serological status	
Anti-ChR	9 (56.3%)
Anti-MuSK	1 (6.3%)
Seronegative patients	6 (37.5%)
Electrodiagnosis	
RNS with decremental response ≥ 10% (*n* = 14)	12 (85.7%)
Abnormal SFE (*n* = 3)	3 (100%)
Either RNS with decremental response ≥ 10% or abnormal SFE ≥ 10% (*n* = 15)	13 (86.7%)
Efficacy of acetylcholinesterase inhibitor (AchI)	
Neostigmine efficacy (*n* = 6)	5 (83.3%)
Oral AchI efficacy (*n* = 11)	10 (90.9%)
Either neostigmine or oral ACHI efficacy (*n* = 12)	12 (100%)
Thymus	
Thymectomy	5 (31.3%)
Histopathological study (*n* = 5)	
Normal thymus	2 (40%)
AB subtype thymoma	1 (20%)
B1 subtype thymoma	1 (20%)
B2 subtype thymoma	1 (20%)
Delay between thymectomy and onset of SCIg (months)	
Average ± standard deviation	72.8 ± 116.4
Median (minimum–maximum)	14.4 (3.0–257.9)

anti-ChR antibodies against acetylcholine receptor, *anti-MuSK* antibodies against muscle-specific kinase, *n* number, *RNS* repetitive nerve stimulation, *SCIg* subcutaneous immunoglobulin, *SFE* single-fiber electromyography

Treatments

Thirteen patients were undergoing at least one immunosuppressive treatment at the onset of SCIg (4 patients had only 1 immunosuppressant, 5 patients had 2 immunosuppressants and 4 patients had 3 immunosuppressants): corticosteroids (9 patients), azathioprine (8 patients), rituximab (5 patients), mycophenolate mofetil (2 patients) and methotrexate (2 patients). All patients were treated with several courses of IVIg (average delay between each IVIg treatment: 35.9 days) within the 6 months before the onset of SCIg. The first administration of SCIg was systematically preceded by a last course of IVIg (at a total dose of 2 g/ kg). The average dose of SCIg at initiation was 0.40 g/kg/ week. This dose was then increased in 37.5% of patients, reaching an average of 0.46 g/kg/week. This change was motivated either by a low serum immunoglobulin level (60%) or by the lack of significant clinical improvement (40%). The reasons for the cessation of SCIg are indicated in Table 2. The adverse effects observed after SCIg included subcutaneous nodules (8 patients), erythema at the puncture site (4 patients), headache (4 patients), pruritus (2 patients), diarrhea (1 patient), hematoma at the puncture site (1 patient), local extravasation of SCIg (1 patient), asthenia (1 patient), and pulmonary embolism (1 patient).

Table 2 Data concerning the treatment with subcutaneous immunoglobulins

	Patients ($n = 16$)
Duration of data collect before SCIg (month)	
Average ± standard deviation	5.1 ± 1.9
Median (minimum–maximum)	6.0 (1.1–6)
Reason for iniation of SCIg	
IVIg dependence	13 (81.3%)
Difficult venous access	8 (50%)
Contraindication to immunosuppressive treatment	2 (12.5%)
Poor tolerance of IVIg	1 (6.3%)
Initial dosage of SCIg (g/week)	
Average ± standard deviation	26.6 ± 9.0
Median (minimum–maximum)	26 (16–48)
Initial dosage of SCIg (g/kg/week)	
Average ± standard deviation	0.40 ± 0.09
Median (minimum–maximum)	0.38 (0.25–0.58)
Necessary increase in dosage of SCIg	
Number of patients (%)	6 (37.5%)
Maximum dosage of SCIg (g/week)	
Average ± standard deviation	30.9 ± 8.6
Median (minimum–maximum)	30 (16–48)
Maximum dosage of SCIg (g/kg/week)	
Average ± standard deviation	0.46 ± 0.10
Median (minimum–maximum)	0.45 (0.25–0.64)
Total duration of SCIg treatment (month)	
Average ± standard deviation	28.4 ± 23.0
Median (minimum–maximum)	22.5 (2.1–78.0)
Cumulative dose of SCIg (g)	
Average ± standard deviation	3391.2 ± 3976.3
Median (minimum–maximum)	1928.0 (254.3–16,144.0)
Reason for stopping SCIg (n, %)	
Inefficiency	3 (18.8%)
Poor tolerance	1 (6.3%)
Patient's request	1 (6.3%)
Subcutaneous access temporarily unavailable	1 (6.3%)
Stabilization of myasthenia gravis	1 (6.3%)
SCIg supply interruption	4 (25.0%)

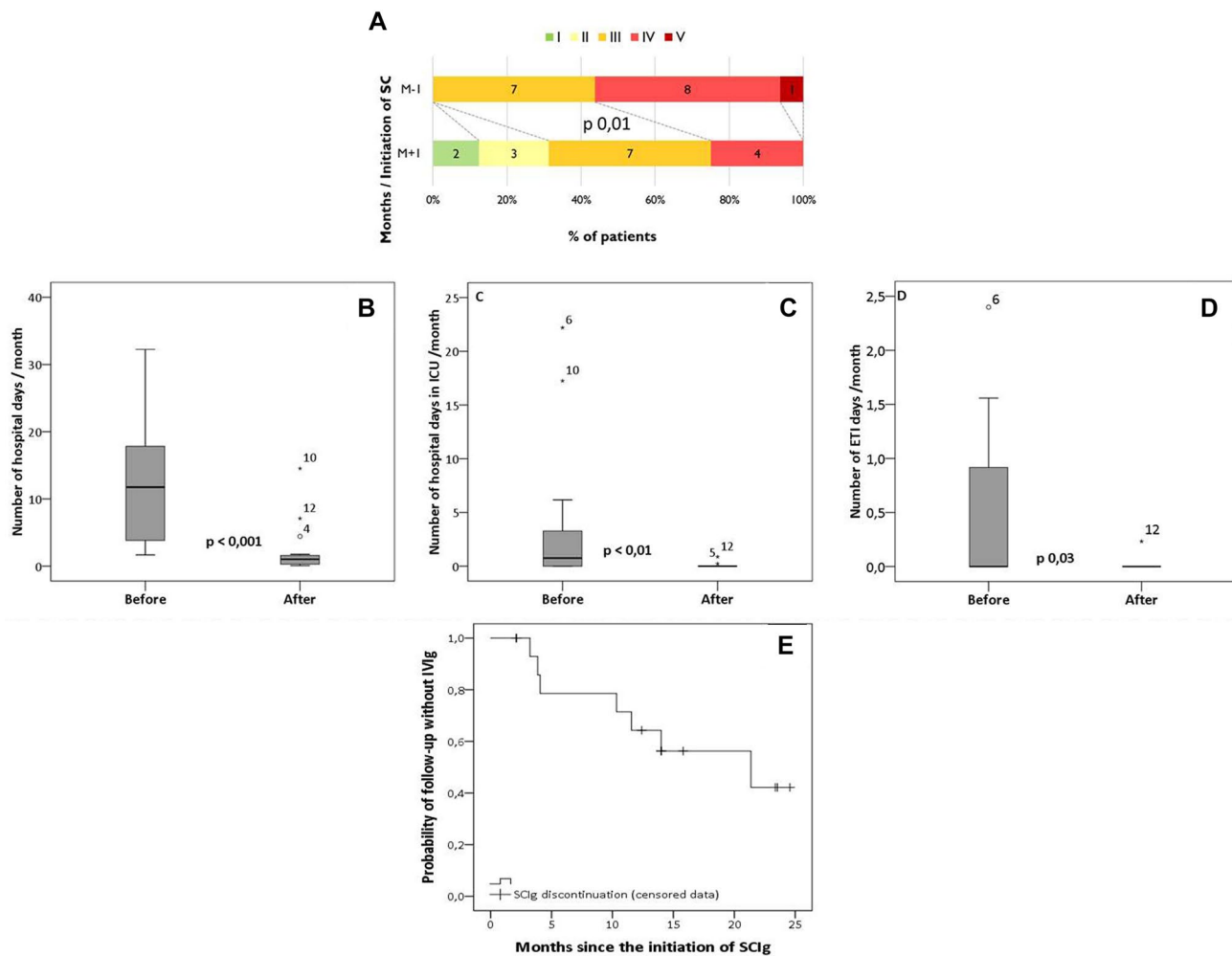*g* gram, *n* number, *SCIg* subcutaneous immunoglobulin

Fig. 2 Efficiency of subcutaneous immunoglobulin (SCIg). **A** Distribution of the MGFA score 1 month before and 1 month after the initiation of SCIg (statistical test: Wilcoxon test). **B** Number of hospital (days/month) before and after SCIg (statistical test: Wilcoxon test). **C** Number of days in intensive care unit (days/month) before and after SCIg (statistical test: Wilcoxon test). **D** Number of days of endotracheal intubation (days/month) before and after SCIg (statistical test: Wilcoxon test). **E** Probability of being treated with subcutaneous immunoglobulin (SCIg) without requiring intravenous immunoglobulin (IVIg) treatment (Kaplan–Meier estimator)

Efficacy of SCIg

Using the MGFA score, eight patients (50%) remained stable (4 in stage IV and 4 in stage III). Eight patients (50%) improved: 3 from stage IV to stage III, 1 from stage IV to stage II, 1 from stage IV to stage I, 2 from stage III to stage II and 1 from stage III to stage I. No patient worsened (Fig. 2A). The duration of disease progression did not appear to affect the response to SCIg therapy. The number of hospital days per month was significantly reduced after SCIg compared with that noted before ($p < 0.001$; Fig. 2B), and the number of days in the intensive care unit ($p < 0.01$; Fig. 2C) and the number of days of OTI ($p = 0.03$; Fig. 2D) were also significantly reduced.

The average number of daily treatments by AChT was not significantly different before and after SCIg ($p = 0.66$). The median number of immunosuppressant treatment(s) was 2 at the onset of SCIg (range: 0–3; IQR: 1.5) compared with 1.5 (range: 0–2; IQR: 1) at the end of SCIg; this difference was not significant ($p = 0.25$). However, as shown in Table 3, the dosage of corticosteroids was significantly reduced after SCIg treatment ($p = 0.04$). The proportion of patients treated with azathioprine decreased (not significantly) from the start of SCIg to the end of treatment, whereas the median number of course(s) of rituximab significantly increased ($p < 0.01$).

Although the duration of the A-SCIg period was longer for collecting data than that of the B-SCIg period, the average number of myasthenic crises decreased, requiring less use of IVIg and PLEX (Table 4). A total of 7 patients (43.8%) required at least one course of IVIg during their follow-up (while they were treated with SCIg). For the remaining 9 patients, treatment was interrupted or data

Table 3 Immunosuppressive medications before and after treatment with subcutaneous immunoglobulin therapy

Treatments	At onset of SCIg	At end of SCIg	*p* value
Corticosteroids			
Treated patients (*n*, %)	9 (56.3%)	8 (50%)	–
Median dose (minimum–maximum)	20 (10–60)	12,5 (0–30)	*0.04*
Azathioprine			
Treated patients (*n*, %)	8 (50%)	3 (18.8%)	*0.13*
Methotrexate			
Treated patients (*n*, %)	2 (12.5%)	0 (0%)	–
Mycophenolate mofetil			
Treated patients (*n*, %)	2 (12.5%)	2 (12.5%)	-
Rituximab			
Treated patients (*n*, %)	5 (31.3%)	9 (56.3%)	*0.13*
Median number of course(s) of rituximab (minimum–maximum)	1 (0–1)	2 (1–4)	*<0.01*

The value are significant if *p*<0.05

n number, *SCIg* subcutaneous immunoglobulin

Table 4 Treatment with intravenous immunoglobulin and plasma exchange before and after using subcutaneous immunoglobulin therapy

	Before SCIg	After SCIg
Duration of data collect (months)		
Average ± standard deviation	5.1 ± 1.9	28.4 ± 23.0
Median (minimum–maximum)	6.0 (1.1–6.0)	22.5 (2.1–78.0)
IVIg (number of course) (*n* = 16)		
Average ± standard deviation	4.5 ± 2.2	1.6 ± 3.0
Median (minimum–maximum)	4 (2–9)	0 (0–11)
PLEX (number of course) (N = 4)		
Average ± standard deviation	5.0 ± 2.5	2.3 ± 4.5
Median (minimum–maximum)	5 (2–8)	0 (0–9)

IVIg intravenous immunoglobulin, *PLEX* plasma exchange, *SCIg* subcutaneous immunoglobulin

collection was stopped before they required IVIg. According to the Kaplan–Meier estimator, the median duration of treatment with SCIg before requiring a course of IVIg was 21.4 months (CI: 95%; range: 5.1–37.6) (Fig. 2E).

Tolerance and quality of life under treatment with SCIg (follow-up)

Among the 11 patients remaining treated with SCIg at the time of the study, 10 participated in the follow-up visit (Table 5). Eight patients (80% of patients) were in favor of continuing SCIg. One patient wanted to alternate SCIg treatments at home and IVIg treatments in the hospital given the reassurance provided by hospitalizations, and 1 patient wished to resume SCIg, considering IVIg to be more effective but with more adverse effects. One patient emphasized

the interest of applying lidocaine patches before the injection of SCIg to improve comfort.

Discussion

We describe the successful management of MG patients using SCIg, which was validated by MGFA classification, functional scales (MG-ADL, MG-QoL-15), ICU hospitalizations and the use of OTIs in 16 patients. The demographic data concerning our patient population are consistent with those in the medical literature, such as the female predominance. The high proportion of elderly patients can be explained by a lack of satisfactory venous access (which can be observed in this age group) but also by difficulties in using immunosuppressants in patients with numerous comorbidities. Among all our patients, 37.5% were seronegative, which is consistent with other data in the medical literature [5, 8, 9]; this high proportion can be explained in part by the absence of systematic research of low affinity anti-AChR antibodies and the unavailability of anti-LRP4 (low-density lipoprotein receptor-related protein) antibody assays in France. In our study, the mean duration of evolution was 76.5 months (6.4 years), which was comparable to the study by Beecher et al. (77 months) [5]. In contrast, the mean duration of evolution was much higher in the studies of Alcantara et al. (14.5 years) [9], Bourque et al. (11.8 years) [8] and in the case reported by Garnero et al. (22 years) [10].

In this retrospective study, we chose the MGFA score as the primary endpoint rather than other scales. We observed that the distribution of this score was significantly improved 1 month after the start of SCIg treatment. This score was chosen as the primary endpoint only in Bourque et al.'s study [8]. The proportion of patients whose MGFA score

Table 5 Data collected during the follow-up visit

Item	Résultats
Time between the onset of IgSC and the follow-up visit (month)	
Average ± standard deviation	33.5 ± 25.3
Median (minimum–maximum)	22.2 (13.9–77.6)
Osserman myasthenic score (n = 8)[a]	
Average ± standard deviation	83.0 ± 21.7
Median (minimum–maximum)	92.5 (38–100)
MG-ADL (n = 10)	
Average ± standard deviation	4.0 ± 3.7
Median (minimum–maximum)	2.5 (1–10)
MG-QoL-15 (n = 10)	
Average ± standard deviation	19.8 ± 12.6
Median (minimum–maximum)	16.5 (4–43)
Percentage of normal state (n = 10)	
Average ± standard deviation	68.0 ± 23.9
Median (minimum–maximum)	65 (30–100)
Score of satisfaction, out of 10 (n = 9)[b]	
Average ± standard deviation	8.6 ± 1.7
Median (minimum–maximum)	9 (5–10)
Beneficial effects of SCIg treatment (n = 10)	
Reduction of hospitalizations; n (%)	7 (70%)
Stabilization of symptoms; n (%)	8 (80%)
Don't know; n (%)	2 (20%)
Other; n (%)	6 (60%)
Patient's wishes for further care (n = 10)	
Continuation of SCIg; n (%)	8 (80%)
Resumption of IVIg; n (%)	1 (10%)
Alternate treatment between SCIg and IVIg; n (%)	1 (10%)

MG-ADL myasthenia gravis activities of daily living, *MG-Qol-15* myasthenia gravis quality of life 15-item scale, *SCIg* subcutaneous immunoglobulin, *IVIg* intravenous immunoglobulin, *n* number

[a]Two patients were reviewed by teleconsultation

[b]One patient did not want to answer the question

was improved or stable after SCIg was similar in both studies (44.4% and 55.6% in Bourque et al.'s study and 50% and 50% in our study, respectively). However, in Bourque et al.'s study, the duration of SCIg treatment before re-evaluation of the MGFA was random with a mean time significantly longer than ours (6.8 months) [8]. On the other hand, we set the time of evaluation of the MGFA at 1 month before and 1 month after the initiation of SCIg, allowing us to homogenize the data collection for all patients. We are aware that this choice may have contributed to underestimating the efficacy of SCIg in some patients, especially those with severe bulbar involvement (which may require several months of well-managed treatment to improve). Moreover, several limitations are inherent to our choice of primary endpoint, including the partly subjective evaluation (especially for intermediate grades II and III). In addition, the statistical analysis did not differentiate between grades A and B (even though the presence of bulbar or respiratory disorders

represented a poorer prognosis for the patients). The reassessment of the MGFA at 1 month was sufficiently early to not completely avoid a possible residual effect of the IVIg treatment performed before the initiation of the SCIg. Based on these reasons, the number of days of hospitalization and OTI appeared to be important criteria for a good evaluation. Thus, the monthly number of days of hospitalization, especially in the ICU, and the monthly number of days of OTI were significantly reduced after SCIg. Interestingly, no published study on SCIg in MG patients has looked at this endpoint. The number of days of hospitalization and OTI are an indirect image of the severity of the disease as well as the reduction in myasthenic crisis and the use of IVIg and PLEX in patients treated with SCIg. In our study, the reduction in total hospital days and ICU days was particularly significant with robust results (even after excluding extreme values). This reduction in hospitalizations could contribute to the improvement of the quality of life of MG

patients. The reduction in hospitalizations was cited as a beneficial effect of the treatment by 70% of the patients in our cohort, whereas 30% emphasized the gain in autonomy offered by SCIg. Another point is that, in terms of health economics, the switch to SCIg could be particularly interesting. Although we do not have a French study comparing the cost of IVIg in hospitals with that of SCIg at home, a recent study by Le Masson et al. (2018) showed that the annual cost of treatment in a cohort of French patients treated with IVIg for dysimmune peripheral neuropathy was estimated at 91,798 € in hospitals versus 48,189 € at home [18]. This cost reduction was primarily related to hospitalization costs and, to a lesser extent, fewer commutes.

While SCIg appeared to be of value in the management of MG, the average number of AChT (taken per day) and the total number of required immunosuppressive treatments were not significantly altered at the end of the A-SCIg period. However, given the severity of the disease in the patients included in our study (median MGFA grade 4), it was expected that the dosage of AchT and immunosuppressants could not be modified by SCIg. On the other hand, corticosteroid tapering is notable, especially as 75% of our population experienced at least one complication associated with long-term corticosteroid therapy.

The clinical evaluation at the follow-up visit was very satisfactory overall with patients favoring SCIg treatment. MG-ADL averaged 4/24, which is similar to that observed at 6 weeks of follow-up in the study of Beecher et al. (4.6/24) [5]. The mean MG-QoL-15 was higher (i.e., less favorable) in our study (19.8/60) compared with Bourque et al.'s study (13.7/60) [8]; however, it would be more interesting to compare the longitudinal evolution of this score before and after SCIg in each patient. In our study, satisfaction with SCIg was excellent with an average of 9/10 patients reporting satisfaction with treatment. In Beecher et al.'s study, satisfaction was assessed by the 'Treatment Satisfaction Questionnaire for Medication' (79.6%) [5]. In Bourque et al.'s study, patients assessed their disease control by means of a visual analog scale. A significant improvement was observed given that they estimated an average of 5.8/10 before SCIg compared to 8.2/10 under SCIg (however, the questionnaire was administered only once, and this a posteriori assessment therefore included a possible memory bias) [8]. Eighty percent of our patients wished to continue SCIg. This rate is consistent with Alcantara et al.'s (90%) [9] and Bourque et al.'s (100%) [8] studies. The most frequently reported adverse events were minor local skin reactions at the injection sites and headache. Despite a much higher average cumulative dose than in previously published studies, this safety profile remains similar to that reported in the medical literature [5, 8, 9].

Small number of included patients and the retrospective design of the study were the main limitation. Nevertheless, our cohort was of similar or even larger size than those published. Specifically, two studies included between 20 and 30 patients [5, 9], one study included less than 10 patients [8], and three publications were case reports [10–12]. In addition, our sample included patients with various profiles in terms of age, duration of disease progression, type of antibodies, and number of immunosuppressants tried. The high proportion of seronegative patients can be explained by the age of the diagnosis, with less efficient techniques, but all seronegative patients had a decrement and/or a response to AChT. The monocentric nature of our study may have been the cause of recruitment bias. The University Hospital of Bordeaux is a referral center for neuromuscular diseases, and we probably included more severe patients. Despite this limitation and as already discussed in previous studies, the use of SCIg seems to offer interesting perspectives in the management of MG patients, but there is still no official recommendation for its use as a chronic maintenance therapy in MG. Therefore, the launch of a large-scale prospective study (in terms of size and duration of follow-up) should be considered. In fact, more importantly, we need to standardize recommendations for the pattern of initiation and use of SCIg in MG. For example, in our cohort, the initiation of SCIg was systematically preceded by a course of IVIg at 2 g/kg. Thereafter, treatment was initiated at a monthly dose equivalent to the usual monthly dose of IVIg (at the rate of 2 injections per week), and then the SCIg dose was increased in cases of ineffectiveness or insufficient serum IgG levels. In Alcantara et al.'s study, the IVIg dose was increased by a factor of 1.37 [9], and the dosage of SCIg was then adjusted according to clinical response. In Bourque et al.'s study, the calculated weekly dose of SCIg was 120% of the corresponding weekly IVIg dose (in immunoglobulin-naive patients, treatment was started at 20 g per week). Finally, the current coronavirus pandemic has highlighted the problems of human immunoglobulin supply encountered for several years in parallel with the multiplication of their indications in neurology [19]. This situation is illustrated in our cohort by the discontinuation of SCIg motivated, among other factors, by supply shortages in 4 patients. This problem is likely to recur in the future, underlining the need to carefully select patients who can benefit from the treatment.

Declarations

References

1. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J (2019) Myasthenia gravis. Nat Rev Dis Primers 5(1):30
2. Bayry J, Thirion M, Misra N, Thorenoor N, Delignat S, Lacroix-Desmazes S, Bellon B, Kaveri S, Kazatchkine MD (2003) Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. Neurol Sci 24(Suppl 4):S217–S221
3. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V (2011) Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 76(23):2017–2023
4. Karelis G, Balasa R, De Bleecker JL, Stuchevskaya T, Villa A, Van Damme P, Lagrange E, Heckmann JM, Nicolle M, Vilciu C, Bril V, Mondou E, Griffin R, Chen J, Henriquez W, Garcia B, Camprubi S, Ayguasanosa J (2019) A phase 3 multicenter, prospective, open-label efficacy and safety study of immune globulin (human) 10% caprylate/chromatography purified in patients with myasthenia gravis exacerbations. Eur Neurol 81(5–6):223–230
5. Beecher G, Anderson D, Siddiqi ZA (2017) Subcutaneous immunoglobulin in myasthenia gravis exacerbation: a prospective, open-label trial. Neurology 89(11):1135–1141
6. Putko BN, Beecher G, Siddiqi ZA (2020) Pharmacodynamic properties of subcutaneous immunoglobulin in myasthenia gravis: sub-analyses from an open-label trial. Front Neurol 11:921
7. Dimachkie M, Bril V, Levine T, Trivedi J, Silvestri N, Milind P, Saperstein D, Nations S, Katzberg H, Wolfe G, Herbelin L, Higgs K, Heim A, McVey A, Rico G, Statland JM, Barohn R, Pasnoor M (2019) Subcutaneous immunoglobulin in myasthenia gravis: results of a North American open label study (N4.002). Neurology 92(Suppl 15):N4.002
8. Bourque PR, Pringle CE, Cameron W, Cowan J, Chardon JW (2016) Subcutaneous immunoglobulin therapy in the chronic management of myasthenia gravis: a retrospective cohort study. PLoS ONE 11(8):e0159993
9. Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V (2021) Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol 28(2):639–646
10. Garnero M, Fabbri S, Gemelli C, Benedetti L, Mancardi GL, Schenone A, Grandis M (2018) Subcutaneous immunoglobulins are a valuable treatment option in myasthenia gravis. J Clin Neurol 14(1):98–99
11. Kovacs E, Danko K, Nagy-Vince M, Csiba L, Boczan J (2017) Long-term treatment of refractory myasthenia gravis with subcutaneous immunoglobulin. Ther Adv Neurol Disord 10(11):363–366
12. Yoon MS, Gold R, Kerasnoudis A (2015) Subcutaneous immunoglobulin in treating inflammatory neuromuscular disorders. Ther Adv Neurol Disord 8(4):153–159
13. Osserman KE, Genkins G (1971) Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 38(6):497–537
14. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ (1999) Myasthenia gravis activities of daily living profile. Neurology 52(7):1487–1489
15. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB (2000) Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 55(1):16–23
16. Burns TM, Conaway MR, Cutter GR, Sanders DB (2008) Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. Muscle Nerve 38(2):957–963
17. Abraham A, Breiner A, Barnett C, Katzberg HD, Bril V (2018) The utility of a single simple question in the evaluation of patients with myasthenia gravis. Muscle Nerve 57(2):240–244
18. Le Masson G, Solé G, Desnuelle C, Delmont E, Gauthier-Darnis M, Puget S, Durand-Zaleski I (2018) Home versus hospital immunoglobulin treatment for autoimmune neuropathies: a cost minimization analysis. Brain Behav 8(2):e00923
19. Hartmann J, Klein HG (2020) Supply and demand for plasma-derived medicinal products—a critical reassessment amid the COVID-19 pandemic. Transfusion 60(11):2748–2752