Journal of Neurology (2021) 268:3871–3877
https://doi.org/10.1007/s00415-021-10544-3

ORIGINAL COMMUNICATION

Chronic low-dose intravenous immunoglobulins as steroid-sparing therapy in myasthenia gravis

Adi Wilf-Yarkoni[1,2,3] · **Itay Lotan**[1,2,3] · **Israel Steiner**[1,3] · **Mark A. Hellmann**[1,2,3]

Received: 13 February 2021 / Revised: 1 April 2021 / Accepted: 1 April 2021 / Published online: 7 April 2021

Abstract

Introduction Intravenous immunoglobulin (IVIg) has been proven beneficial in myasthenic crisis, but their role as maintenance therapy is unclear. The aim of this study was to determine if maintenance therapy with low-dose IVIg improves clinical outcome and may be used as a steroid-sparing agent in myasthenia gravis (MG).

Methods We retrospectively reviewed charts of all MG patients treated with IVIg from January 2006 to December 2019. Long-term treatment response to IVIg was assessed by improvement in the Myasthenia Gravis Foundation of America (MGFA) clinical classification scale as primary end point, as well as the ability to reduce the time-weighted average required dose of prednisone as secondary end-point, in a follow-up period of 36 months.

Results 109 patients were treated with IVIg. The mean follow-up time was 34.03 ± 5.5 months. Sixty-seven patients (61.4%) responded to therapy with at least one-point improvement of the MGFA scale. There was no statistical difference in demographic and clinical characteristics between IVIg responders and non-responders. The mean prednisone dose decreased significantly from 33.1 ± 14.5 mg at baseline to 7.2 ± 7.8 mg after 36 months of IVIg treatment ($P < 0.0001$), with the greatest effect after 6 months (33.1 ± 14.5 mg Vs. 17.9 ± 11.7 mg; $P < 0.0001$). In the follow-up period of 36 months, most patients (92.5%) remained clinically and pharmacologically stable under chronic IVIg treatment.

Conclusion This retrospective study demonstrates that chronic low-dose IVIg treatment in patients with MG improves clinical outcomes and has a prolonged and significant steroid-sparing effect over a period of 3 years.

Keywords Myasthenia gravis · Intravenous immunoglobulin · Chronic Immunotherapy · Steroid sparing

Introduction

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease against components of the postsynaptic neuromuscular junction of striated muscle [1–3]. The clinical manifestations of MG include muscle weakness, which can be localized to the extraocular muscles (i.e., ocular MG) or involve bulbar and skeletal muscles (i.e., generalized MG) [3]. Antibodies against acetylcholine receptor (AChR) [4], muscle-specific kinase (MuSK) [5] and lipoprotein-related protein 4 (LRP-4) [6] can be found in about 90% of generalized MG patients [2].

Treatment of MG includes symptomatic treatment using acetylcholinesterase inhibitors, thymectomy and immunotherapy. While corticosteroids remain the mainstay of immunotherapy, dose-dependent side effects and inadequate response often require the addition of other immunotherapies, including azathioprine, methotrexate, mycophenolate, cyclophosphamide, and cyclosporine [7]. These immunotherapies may have severe long-term side effects. Moreover, about 20 percent of patients with MG are refractory to these treatments [8–10]. Therefore, there is a need for safe and effective long-term therapies. In the last few years, rituximab and eculizumab have emerged as potential therapies in refractory MG [11, 12].

Intravenous immunoglobulin (IVIg) has shown a beneficial therapeutic effect in MG exacerbations [13–16]. In randomized controlled trials, IVIg was found to be as effective as plasmapheresis and superior to placebo for the treatment of

✉ Adi Wilf-Yarkoni
adi.wilf@gmail.com

1 Department of Neurology, Rabin Medical Center, Beilinson Campus, 49100 Petach Tikva, Israel

2 Neuroimmunology Unit, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel

3 Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

MG exacerbations [17]. The plausible mechanism of action of IVIg in the treatment of MG includes neutralization of autoantibodies by anti- idiotypic antibodies, downregulation of antibody production, inhibition of complement, prevention of membranolytic attack complex formation and suppression of pathogenic cytokines involved in B and T cell activation [17]. Another action of IVIg may be the competition with endogenous autoantibodies access to the neonatal Fc receptor leading to accelerated autoantibody degradation [18, 19].

Chronic IVIg maintenance therapy in MG has been shown to improve clinical function in uncontrolled and open clinical trials [20–23]. In a previous retrospective analysis, we reported clinical improvement in 52 patients treated with chronic low-dose IVIg [22]. In another recent study, similar results were reported in 30 patients who were treated with the standard dose of chronic maintenance IVIg of 1 g/kg, followed by subcutaneous chronic IVIg therapy. This study demonstrated a significant reduction in the number of immunosuppressive medications and in prednisone and pyridostigmine doses, suggesting a clear steroid-sparing effect of IVIg [21]. However, the frequency and dosage of this treatment regimen are expensive and may limit its use in clinical practice.

In this study, we performed a retrospective analysis of patients treated with low-dose (0.4 g/kg) IVIg to determine the response rate to therapy with this therapeutic regimen and to identify which MG patients are more likely to respond. The response was measured according to clinical improvement and steroid-sparing effect.

Methods

Patients and study design

We performed a retrospective chart review of MG patients treated with IVIg, followed in our neuro-immunology clinic at the Rabin Medical Center, Petach Tikva, Israel, between January 2006 and December 2019. The study protocol was approved by the Rabin Medical Center Institutional Review Board for human experiments (Helsinki Committee, No. 0361-20).

Inclusion criteria were: age > 18 years, established diagnosis of MG based on a combination of clinical presentation confirmed by repetitive nerve stimulation, single-fiber electromyography, and/or positive anti-AChR or anti-MuSK antibodies. We included only patients that were treated with IVIg.

Baseline demographic and clinical data included sex, age, age at MG onset, age at IVIg initiation, duration of disease at IVIg initiation, history of thymectomy, anti-AChR and anti-MuSK antibody status, and all medications used. Patients were classified according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification from class I to V [24]. We collected data at several time points: at baseline, at 3 months intervals during the first year, and then at six months intervals up to 36 months. The follow-up was stopped in patients who had MG crisis or started another immunosuppressant drug while on IVIg treatment. Data included MGFA score, MGFA post-intervention status (PIS) [24], and immunosuppressant dose (including prednisone, azathioprine, and mycophenolate mofetil).

Treatment protocol and clinical outcome measures

IVIg treatment protocol included a loading dose of 2 g/Kg given over 5 days, followed by a maintenance dose of 0.4 g/Kg every 3–4 weeks. Patients that did not experience clinical improvement after a loading dose and two maintenance doses of IVIg were defined as non-responders. We compared the clinical characteristics of patients who responded to IVIg to non-responders. Long-term treatment response to IVIg in our study was assessed based on 2 parameters: 1. Improvement in the MGFA clinical classification scale and MGFA post-intervention status (PIS) [24, 25]. An improvement from class IV to III or from class III to II was defined as a mild improvement, while an improvement from class V to class III or from class IV to class II was defined as a moderate improvement. 2. The ability to reduce the time-weighted average required dose of prednisone.

Statistical analysis

Clinical and demographic data are presented as means ± standard deviation. Paired t tests were performed for continuous variables, and the Fisher's exact test was used to analyze categorical variables between the groups. A repeated measures Brown–Forsythe and Welch ANOVA were used to compare the longitudinal changes in prednisone doses. All tests were two-tailed, and a p value < 0.05 was considered statistically significant. Statistical analysis and the graphical representation of the data were performed with GraphPad Prism (version 9.0.0. GraphPad Software, San Diego, CA, USA).

Results

Group characteristics (Table 1)

A total of 109 patients were treated with IVIg. The group consisted of 61 females and 48 males, the average age at disease onset was 47.5 ± 18.5 years, and the average disease duration at IVIg treatment initiation was 5 ± 7.5 years. At baseline, 102 (93.5%) patients suffered from moderate/severe

Table 1 Demographic and clinical characteristics of the patients at baseline

	Total ($n=109$)	Good response to IVIg treatment ($n=67$)	No responder to IVIg treatment ($n=42$)	*p Value
Female sex	61 (56%)	37 (55%)	24 (57%)	0.67
Age at onset, y**	47.5 ± 18.3	48.8 ± 19.1	45.4 ± 18.1	0.35
Age (at IVIg treatment initiation)—y	52.5 ± 18.3	54.6 ± 17.9	49.3 ± 18.7	0.14
Disease duration (at IVIg treatment initiation)—y	5 ± 7.5	5.79 ± 8.2	3.9 ± 6.5	0.2
IVIg initiation in the first year after diagnosis		29 (43%)	0	$p<0.0001$
Thymectomy	33 (30%)	19 (28%)	14 (33%)	0.6
Thymic hyperplasia	14 (13%)	10 (14%)	4 (9.5%)	0.5
Thymoma	19 (17%)	9 (13%)	10 (24%)	0.1
Double seronegative	16 (15%)	8 (12%)	8 (19%)	0.4
Anti-Musk	3 (2.7%)	1 (1.4%)	2 (4.7%)	
*MGFA****				
I	3 (2.7%)	1 (1.4%)	2 (4.7%)	
IIa	4 (3.6%)	0	4 (9.4%)	
IIb	0	0	0	
IIIa	48 (44%)	28 (41%)	20 (47%)	
IIIb	9 (8.3%)	7 (10%)	2 (4.7%)	
IVa	33 (30%)	26 (39%)	7 (16.6%)	
IVb	6 (5.5%)	4 (6%)	2 (4.7%)	
V	6 (5.5%)	1 (1.4%)	5 (11.2%)	

Data are presented as n (%) or mean ± SD. Good response was defined as a clinical improvement by at least one class of the MGFA. **P-value* for between-group comparison is based on paired t-tests for continuous variables, and a Fisher exact test was used to analyze categorical variables between the groups. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. ***y* = years. ***Myasthenia Gravis Foundation of America (MGFA) class I indicates ocular weakness, class II indicated mild generalized weakness, class III moderate generalized weakness, class IV severe generalized weakness, and class V defined by intubation. A notation of "a" denotes predominantly limb or axial weakness and "b" predominantly bulbar weakness

symptoms defined as MGFA clinical score of III/IV/V. Three patients had severe pure ocular MG. Ninety patients (82%) were positive for anti-AChR antibodies, 3 patients were positive for anti-MuSK antibodies, and 16 patients were double seronegative. Thirty-three patients (30%) underwent thymectomy; thymic hyperplasia was present in 14 patients (13%) and thymoma in 19 patients (17%) (Table 1). The mean follow-up duration was 34.03 ± 5.5 months. Fifty-nine patients had finished the 36 months follow-up period. One patient had a follow-up period of 30 months. The follow-up period was only 18 months in 7 patients; 2 patients had only started IVIg 18 months previously, in three more, IVIg was replaced by other immunosuppressant therapy, one had a myasthenic crisis and one a COPD exacerbation that required treatment change.

Clinical response to therapy (Table 1)

A beneficial clinical response was defined as an improvement in the MGFA clinical scale of at least one point. Sixty-seven patients (61.4%) had a beneficial response, and 42 (38.5%) did not improve with IVIg treatment (e.g., non-responders). Ninety patients were positive for AChR antibodies in our study, of which 58 (64%) had a beneficial response to IVIg, whereas only 8/16 (50%) patients who were negative for both AChR and MuSK antibodies, had a beneficial response to IVIG therapy. ($p<0.28$). There was no statistical difference in gender, age of onset, thymic pathology, and serology status between IVIg responders and non-responders (Table 1). Median time between thymectomy and the beginning of IVIg treatment was 6.7 ± 10.1 years in the responders group and 3.14 ± 6.1 years ($P<0.25$) in the non-responders group. We did not observe any difference between the groups in baseline MGFA score nor in the percentage of patients with a bulbar presentation. However, a significant difference in the response rate was found between patients that received IVIg during the first year of diagnosis (29 responders compared to 0 non-responders; $p<0.0001$, Table 1).

Treatment response to other therapies among the non-responders patients was also examined. Treatment failure was defined as no clinical benefit or side effects that required therapy switching. Twenty of the 42 non-responders to IVIg (48%) responded to other treatments (Including rituximab, plasma exchange, azathioprine, and mycophenolate mofetil). However, 22/42 patients (52%) had treatment failure with

other therapies: 11 patients experienced treatment failure with one drug and 11 patients (26%) with two or more drugs in addition to IVIg and were therefore defined as refractory MG [8].

Improvement in the MGFA scale and PIS (Fig. 1)

Sixty-seven (61.4%) MG patients improved by at least one MGFA class after loading treatment and subsequent maintenance dose. Of these, 55 (82%) MG patients had a mild response to IVIg treatment (one-point improvement on MGFA scale); 20 MG patients improved from MGFA scale of IV to III, and 35 MG patients improved from MGFA scale of III to II. Eleven (16.5%) MG patients had a moderate response to IVIg treatment (two-point improvement on MGFA scale); 10 MG patients improved from MGFA scale of IV to II and one MG patient from V to III (Fig. 1). One patient with severe pure ocular MG improved clinically with IVIg treatment. Fifty-nine (88%) MG patients demonstrated clinical improvement of at least one point on the MGFA scale at 3 months post-IVIg initiation. Seven more patients (10%) improved at 6 months' follow-up. Sixty-two (92.5%) patients had a minimal manifestation of their disease after 12 months, according to the MGFA PIS. Despite the clinical improvement, only two patients achieved pharmacological remission, defined as no need for symptomatic therapy with acetylcholine esterase inhibitors according to the MGFA PIS. In the follow-up period of 36 months, most MG patients (92.5%) in our study remained clinically stable under chronic IVIg treatment. One MG patient suffered an MG crisis, and another patient had respiratory deterioration from COPD exacerbation. Three MG patients had worsening of their symptoms that required an adding of another medication to IVIg treatment.

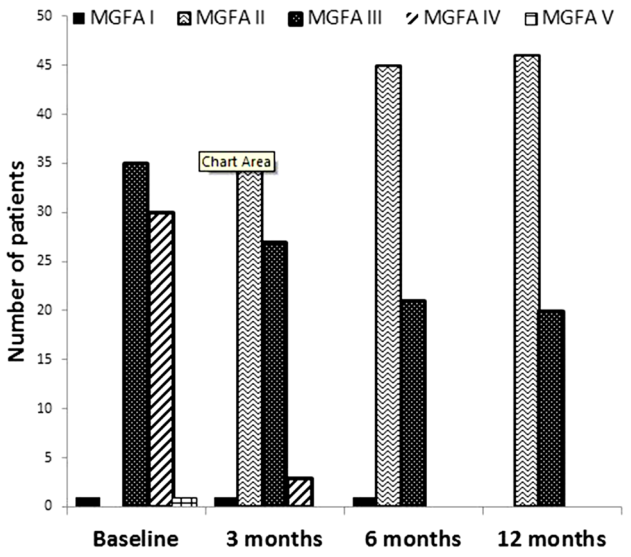

Fig. 1 Clinical response to treatment. Change in disease severity according to the MGFA classification scale at the time of diagnosis and at 3, 6, and 12 months. Each bar represents the number of patients at the corresponding MGFA score. Myasthenia Gravis Foundation of America (MGFA) class I indicates ocular weakness, class II indicates mild generalized weakness, class III moderate generalized weakness, class IV severe generalized weakness, and class V defined by intubation

Side effects of IVIg treatment included headache and infusion-related reactions. Two patients suffered from a myocardial infarction during the follow-up period.

Decrease in average daily prednisone dose (Fig. 2a)

Thirteen MG patients were treated only with IVIg, 39 patients with IVIg and prednisone, and 15 patients received IVIg with other immunosuppressant treatments. Fourteen MG patients were treated with azathioprine and one patient with mycophenolate mofetil. In five patients (33.3%), it was possible to taper off azathioprine or mycophenolate mofetil during the follow-up period. The pyridostigmine doses were held relatively constant throughout the period of treatment with IVIg.

Overall, there were 48 MG patients that were treated with prednisone during the IVIg treatment period. The average daily prednisone dose was calculated at 9 different time points: at the time of the IVIg initiation (0) and at the clinical visits at 3, 6, 9, 12, 18, 24, 30 and 36 months. Prednisone taper was dictated by the treating physician based upon MG clinical manifestations. There was a significant reduction in mean prednisone dose after 36 months (33.1 ± 14.5 mg compared to 7.2 ± 7.8 mg; $P < 0.0001$, Fig. 2a). Significant reduction in mean daily prednisone dose was already observed after 6 months (33 ± 14 mg compared to 17.9 ± 11.7 mg; $P < 0.0001$; Fig. 2a). Multiple comparison analysis revealed no statistical difference in daily prednisone dose from the 9th month onwards. From a total of 41 patients that started treatment with IVIg while on prednisone, 34 (83%) were on a prednisone dose lower than 10 mg/day at the end of the follow-up period (36 months). Of these, 15 patients (36.5%) were free from prednisone treatment at the end of the follow-up period.

Nine MG patients were treated with azathioprine in addition to prednisone at the time of IVIg initiation. To neutralize the azathioprine effect on prednisone tapering, a sub-group analysis was performed with MG patients that were treated solely with prednisone at the time of IVIg initiation. There was a significant decrease in mean prednisone dose after 36 months (31.1 ± 14.1 mg compared to 5.5 ± 5.8 mg; $P < 0.0001$; Fig. 2b). A significant reduction in prednisone mean dose was already observed after 6 months (31.1 ± 14.1 mg compared to 16.12 ± 10.75 mg; $P < 0.0001$; Fig. 2b). Moreover, the daily prednisone dose was stable from 12 months until the end of the follow-up period.

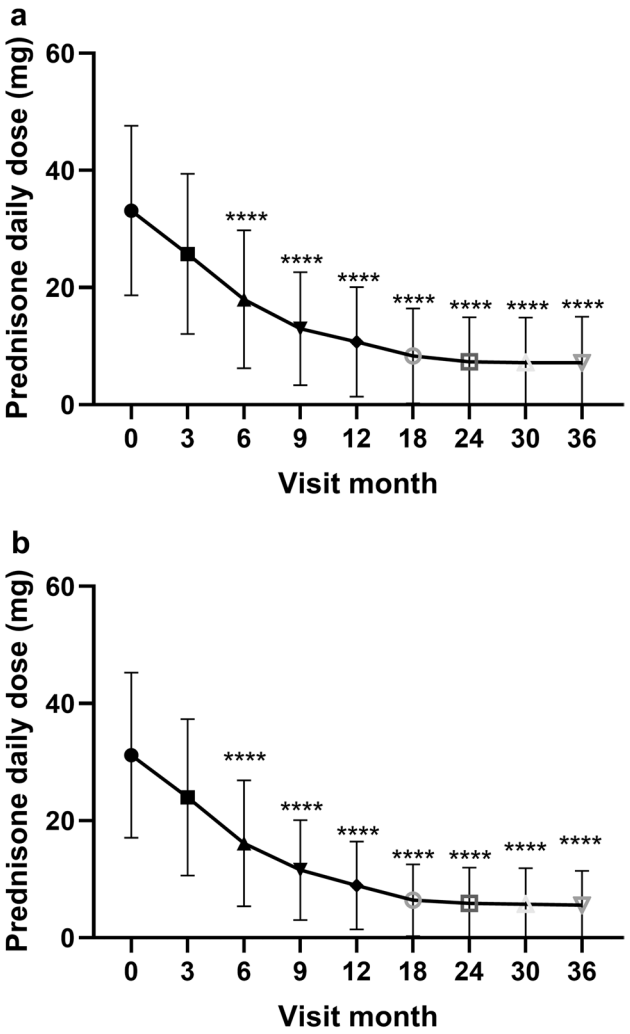

Fig. 2 Time-weighted average prednisone daily dose. Mean prednisone daily dose ± SD before and during chronic low dose IVIg treatment in patients treated with IVIg combined with immunosuppressants (a) and in patients treated with IVIg alone (b). Repeated measures Brown-Forsythe and Welch ANOVA was used to compare the longitudinal changes in prednisone doses. The Asterisk represents the *p* values of multiple comparisons of each visit month compared to baseline. **** $p < 0.0001$

Discussion

This study provides evidence supporting the use of chronic low-dose IVIg treatment for improving clinical outcomes and reducing the need for prednisone therapy in patients with MG. 61.4% of MG patients in our study had a good clinical response to IVIg treatment. With chronic IVIg treatment, these patients demonstrated a significant improvement in MGFA score and MGFA PIS for a period of 3 years, with a significant reduction in prednisone daily dose.

IVIg has been shown to be an effective treatment for acute MG exacerbation [13–16]. However, there are few studies addressing the place of IVIg as a chronic, maintenance therapy in patients with MG. In a previous study with a smaller sample size, we showed that IVIg given at regular intervals improves the clinical status of MG patients but that this is dependent on regular cycles of therapy [22]. Out of 52 patients in our previous study, 37 improved with maintenance IVIg and there was a greater tendency to respond in older patients with seropositive disease who had bulbar onset [22]. However, in this larger cohort, clinical characteristics, such as age, sex, thymic pathology, clinical onset, and seropositivity, for acetylcholine receptor antibodies were not associated with a more beneficial response. These results are supported by a recent study where improvement in MG patients treated with chronic IVIg was consistent regardless of the demographic and clinical characteristics of patients [21]. We could only include 3 anti-MuSK antibodies positive patients in our study, so we cannot draw any conclusions about the effectiveness of IVIg in this population. 43% of the responders received IVIg in the first year after diagnosis, compared to none from the non-responders group. In addition, 52% of MG patients that were non-responders had treatment failure to other therapies as well, and 26% were defined as refractory MG. Therefore, IVIg may be considered as chronic therapy in any MG patient that is uncontrolled on other therapies, independent of the type of myasthenia and thymic pathology. To optimize the chance for IVIg success, treatment should probably be started in the first year after MG diagnosis. After 1 year, refractory MG patients are less likely to respond to chronic IVIg treatment.

The decision to treat MG patients with chronic IVIg should take into consideration the likelihood of a response to therapy compared to other agents. Our cohort included 109 patients, 67 of which (61.4%) showing a treatment response to IVIg therapy. Treatment response was achieved after 3 months in 88% of the patients. This treatment response is important when considering augmentation with a steroid-sparing agent in MG patients whose disease is uncontrolled on steroids and pyridostigmine alone. The response rate of other therapies, such as azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus, is slightly higher, about 70–80% [26]. However, these therapies carry significant disadvantages, including delayed treatment response of several months and the side effects of prolonged immunosuppression.

The goal of MG treatment is to achieve a maximal clinical benefit with a minimal immunosuppressant dose to lower the risk of adverse effects from prolonged immunosuppression. In our study, we demonstrated a significant reduction in the average daily prednisone dose with improved clinical scores. The main reduction was observed in the first 6 months of treatment, and this was then sustained and augmented with continued therapy. Other studies have similarly demonstrated a reduction in prednisone dose following IVIg treatment [20–23]. Although these are all retrospective analyses,

it seems that the steroid-sparing effect is consistent and significant. While corticosteroids are very effective in the treatment of MG, the burden of dose-related side effects means that steroid-sparing agents improve patients' quality of life.

The dose given for maintenance therapy in our study was 0.4 g/kg given at a 3- to 4-week intervals. The traditional dose of IVIg in chronic maintenance therapy by neurologists is adopted from experience gained in chronic inflammatory demyelinating polyneuropathy, where guidelines recommend a maintenance dose defined between 0.6 and 1 g/kg every 3–8 weeks and 0.4 and 1.2 g/kg every 2–6 weeks [27, 28]. A reduction of IVIg maintenance dose in chronic neurological diseases has been shown to improve the cost/benefit ratio [29]. The lower dose used in our study was due to regulatory requirements in Israel in an attempt to lower the cost of IVIg therapy. A lower dose has the advantage of reducing side effects and a lower burden on health services. The 0.4 g/kg can be given over a few hours as opposed to 1 g/kg, which requires a much longer duration of infusion and sometimes the need to give the infusion over two separate days. Despite this lower dose, we showed a clear clinical benefit and steroid-sparing effect. This may encourage the use of a lower dose of IVIg in the maintenance therapy of MG.

With new therapies available, the place of chronic IVIg therapy in MG patients that are uncontrolled on steroids, pyridostigmine, and immunosuppressive therapies is unclear. Over the past few years, more therapeutical options for MG have emerged. The B cell depletion agent rituximab is effective in refractory MG, especially in patients with anti-MUSK antibodies [30]. The complement inhibitor, eculizumab is now approved for therapy in refractory MG, though its cost may limit its use [12, 31]. Even in the era of these new therapies, low-dose maintenance IVIg may be a useful bridging therapy until a response from the immunosuppressive agent occurs or until one of these new therapies is used.

One of the limitations of our study is its retrospective design. It could be argued that the improvement in clinical function on chronic IVIg is attributed in part to concomitant immunotherapies and not solely to IVIg. However, we established clinical improvement in MG patients that were treated with IVIg alone. Moreover, the long-term follow-up period of this study allows us to demonstrate a prolonged clinical stability after prednisone tapering.

In conclusion, this retrospective study shows that chronic low-dose IVIg in patients with MG over a period of 3 years can act as a steroid-sparing agent with good and prolonged clinical effect. A prospective randomized controlled clinical trial of chronic IVIg therapy in myasthenia gravis is needed to confirm our results.

Author contributions Adi Wilf-Yarkoni and Mark A. Hellmann contributed to the study conception and design. Material preparation, data collection and analysis were performed by Adi Wilf-Yarkoni and Mark A. Hellmann. The first draft of the manuscript was written by Adi Wilf-Yarkoni and Mark A. Hellmann. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work did not receive any funding.

Availability of data and material The data presented in this report will be made available to bona fide investigators upon request to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All data gathered after approval by the Ethics Committee of Rabin Medical Center and therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

Consent to participate The Institutional Review Board for human experiments waived informed consent.

References

1. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B (2014) Diagnostic and clinical classification of autoimmune myasthenia gravis. J Autoimmun 48–49:143–148
2. Gilhus NE (2016) Myasthenia Gravis. N Engl J Med 375:2570–2581
3. Gilhus NE, Verschuuren JJ (2015) Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14:1023–1036
4. Vincent A, Newsom-Davis J (1985) Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. J Neurol Neurosurg Psychiatry 48:1246–1252
5. Evoli A, Tonali PA, Padua L et al (2003) Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain J Neurol 126:2304–2311
6. Zisimopoulou P, Evangelakou P, Tzartos J et al (2014) A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. J Autoimmun 52:139–145
7. Souto EB, Lima B, Campos JR, Martins-Gomes C, Souto SB, Silva AM (2019) Myasthenia gravis: State of the art and new therapeutic strategies. J Neuroimmunol 337:577080
8. Farrugia ME, Goodfellow JA (2020) A practical approach to managing patients with myasthenia gravis-opinions and a review of the literature. Front Neurol 11:604
9. Engel-Nitz NM, Boscoe A, Wolbeck R, Johnson J, Silvestri NJ (2018) Burden of illness in patients with treatment refractory myasthenia gravis. Muscle Nerve 58(1):99–105
10. Silvestri NJ, Wolfe GI (2014) Treatment-refractory myasthenia gravis. J Clin Neuromuscul Dis 15:167–178
11. Beecher G, Anderson D, Siddiqi ZA (2018) Rituximab in refractory myasthenia gravis: Extended prospective study results. Muscle Nerve 58:452–455
12. Muppidi S, Utsugisawa K, Benatar M et al (2019) Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. Muscle Nerve 60:14–24

13. Gajdos P, Chevret S (2008) Treatment of myasthenia gravis acute exacerbations with intravenous immunoglobulin. Ann N Y Acad Sci 1132:271–275
14. Gajdos P, Chevret S, Toyka KV (2012) Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 12:Cd002277
15. Karelis G, Balasa R, De Bleecker JL et al (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 81:223–230
16. Zinman L, Ng E, Bril V (2007) IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology 68:837–841
17. Dalakas MC (2019) Immunotherapy in myasthenia gravis in the era of biologics. Nat Rev Neurol 15:113–124
18. Hansen RJ, Balthasar JP (2002) Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. Thromb Haemost 88:898–899
19. Norris PAA, Kaur G, Lazarus AH (2020) New insights into IVIg mechanisms and alternatives in autoimmune and inflammatory diseases. Curr Opin Hematol 27:392–398
20. Achiron A, Barak Y, Miron S, Sarova-Pinhas I (2000) Immunoglobulin treatment in refractory Myasthenia gravis. Muscle Nerve 23:551–555
21. Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V (2020) Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol 28(2):639–646
22. Hellmann MA, Mosberg-Galili R, Lotan I, Steiner I (2014) Maintenance IVIg therapy in myasthenia gravis does not affect disease activity. J Neurol Sci 338:39–42
23. Hilkevich O, Drory VE, Chapman J, Korczyn AD (2001) The use of intravenous immunoglobulin as maintenance therapy in myasthenia gravis. Clin Neuropharmacol 24:173–176
24. Jaretzki A, Barohn RJ, Ernstoff RM et al (2000) Myasthenia gravis: recommendations for clinical research standards. Task force of the medical scientific advisory board of the myasthenia gravis foundation of america. Neurology 55:16–23
25. Roda RH, Doherty L, Corse AM (2019) Stopping oral steroid-sparing agents at initiation of rituximab in myasthenia gravis. Neuromuscul Disord 29:554–561
26. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J (2019) Myasthenia gravis. Nat Rev Dis Primers 5:30
27. Hughes RA, Donofrio P, Bril V et al (2008) Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 7:136–144
28. Kuitwaard K, van Doorn PA (2009) Newer therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy. Drugs 69:987–1001
29. Dolezal O (2014) Intravenous immunoglobulin treatment in chronic neurological diseases: do we have maintenance dose right? Autoimmune Dis 2014:962530
30. Hehir MK, Hobson-Webb LD, Benatar M et al (2017) Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review. Neurology 89:1069–1077
31. Howard JF Jr, Utsugisawa K, Benatar M et al (2017) Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol 16:976–986