Neurol Sci (2014) 35:891–896
DOI 10.1007/s10072-013-1621-4

ORIGINAL ARTICLE

Intravenous immunoglobulin for prophylaxis of acute exacerbation in Myasthenia Gravis

Mine Hayriye Sorgun · Huseyin Ozden Sener · Canan Yucesan · Nezih Yucemen

Received: 1 August 2013 / Accepted: 24 December 2013 / Published online: 8 January 2014

Abstract Intravenous immunoglobulin (IVIg) treatment for acute exacerbations of Myasthenia Gravis (MG) was shown in several open-label studies. There are only two studies demonstrating the efficiency of regular intermittent IVIg therapy on MG patients who are not in their acute attack periods. Thirteen patients who had displayed an inadequate clinical response to immunosuppressive treatments, or who were not appropriate for immunosuppressive treatment due to the age factor and thus were given regular IVIg therapy, were retrospectively investigated. Moreover, the pre- and post-treatment attack frequencies were also evaluated. The mean number of attacks was 0.0960 attacks/year before IVIg therapy, and 0.0056 attacks/year after IVIg therapy ($p = 0.002$). The number and severity of the attacks were decreased in all patients. Eight patients (62 %) had used steroids; among them, steroid was completely stopped in two patients following the regular IVIg therapy, and the dose was decreased by 50 % in the other six patients. The requirement for pyridostigmine did not decrease in four patients, whereas this need decreased by 20–50 % in nine patients. IVIg can produce repeated beneficial effects in patients with MG and may be useful as an adjunct in the management of MG. IVIg has minimal adverse effects and ability to reduce corticosteroid dose. These results suggest that intravenous immunoglobulin maintenance therapy is a valid modality in patients with resistant treatment MG.

Keywords Myasthenia Gravis · Intravenous immunoglobulin · Clinical response · Immunosuppressive treatment

M. H. Sorgun (✉) · H. O. Sener · C. Yucesan · N. Yucemen
Department of Neurology, Ankara University School of Medicine, İbni Sina Hospital, Samanpazarı, Ankara, Turkey
e-mail: drmsorgun79@yahoo.com.tr

H. O. Sener
e-mail: Ozden.Sener@medicine.ankara.edu.tr

C. Yucesan
e-mail: cyucesan@yahoo.com

N. Yucemen
e-mail: nezihyucemen@mynet.com

Introduction

Myasthenia Gravis (MG) is a well-defined autoimmune disease characterized by weakness and fatigue. Antibodies to the acetylcholine receptor (AchR) of skeletal muscle can be detected in 80–90 % of patients with generalized MG [1]. Acute exacerbations of MG need effective and urgent life-saving treatment. Life-threatening hypoventilation is the utmost threat. Plasma exchange (PE) or intravenous immunoglobulin (IVIg) is effective for acute MG [2]. Immunoactive drugs such as prednisone, mycophenolate mofetil, methotrexate, azathioprine, cyclosporine A, rituximab, tacrolimus have an effect linked to pathogenesis, and the effect usually needs some time before it becomes manifest [3].

IVIg treatment was first used for MG by Gajdos et al. in 1984 [4]. After that, the efficacy of IVIg treatment for acute exacerbations of MG was shown in several open-label studies [1–3, 5–9].

Arsura et al. [10] determined that patients who were given IVIg therapy in their attack periods, had a long well-being period, and suggested that intermittent IVIg therapy could prevent attacks for a considerable period of time. There are only two studies demonstrating the efficiency of regular intermittent IVIg therapy on MG patients who are not in their acute attack periods. It has been shown with these studies that the clinical well-being condition of these

MG patients continued and the dose of other drugs were reduced [11, 12]. Gajdos et al. [8] mentioned that studies on this issue were very few in number and insufficient.

In this study, 13 patients who had displayed an inadequate clinical response to immunosuppressive treatments, or who did not want to take any immunosuppressive treatment due to their side effects and thus were given regular IVIg therapy, were retrospectively investigated. Moreover, the pre- and post-treatment attack frequencies were also evaluated.

Materials and methods

Patients who were followed-up with the diagnosis of MG at Ankara University Medical Faculty Neurology Department between 1995 and 2012, and who were given regular IVIg therapy for attack prophylaxis for at least 1 year, were included in the study. The diagnoses had been made with clinical characteristics, Ach receptor antibodies, electrophysiological tests, and pharmacological tests. Thymic abnormalities were assessed by computed tomography (CT). Acute severe exacerbations of MG were defined as diffuse extremity paresis, dysarthria, dysphagia, or shortness of breath any of which affects daily living activities significantly. A regular IVIg therapy was given to the patients who had severe attacks causing clinically moderate to severe functional loss, who did not give an adequate response to standard therapies, and who could not receive corticosteroid or immunosuppressive treatments due to their side effects or did not want to take any immunosuppressive treatment due to their side effects. Regular PE was not preferred because of necessity of intravenous catheter during treatment sessions. Periods of IVIg administration were empirically decided according to the severity of attacks and persistent symptoms during remission. If patients needed mechanical ventilation and/or nasogastric feeding in their attacks or patients had symptoms such as severe diplopia or proximal limb weakness during their remission periods, IVIg treatment was used in short intervals such as once a month or every 2 months. The dates of diagnoses, types, severity, durations and dosages of all treatments, and the clinical situations of all the patients were recorded. The severity of MG was graded using a modified Osserman scale [13]. The effect of IVIg in the patients was retrospectively investigated.

Statistics

The group rates were compared using the Chi-square test and the means were compared using the Student's t test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS 11.5 version (SPSS Inc. Chicago, Illinois, USA).

Results

Thirteen MG patients were determined to be on regular IVIg therapy. Ten (77 %) were female, and three (23 %) were male. The mean age of the patients was 62 ± 18 (range 25–93). The mean duration of the disease was 10 ± 4 (range 4–17) years. The mean follow-up period before regular IVIg therapy was 2.5 (range 1–6) years. Five patients had Anti-AChR-Ab and one patient had Anti-MuSK-Ab (Table 1). The mean duration of regular IVIg therapy was 7.5 (range 1–13) years. The mean number of attacks was 0.0960 attacks/year before IVIg therapy, and 0.0056 attacks/year after IVIg therapy ($p = 0.002$). The median modified Osserman scale was 4 ± 0.7 (range 3–5) and 1.25 ± 0.45 (range 1–2) at the start of IVIg treatment and at the last visit, respectively ($p < 0.001$). The mean number of attacks in patients without thymectomy was 0.139 attacks/year before regular IVIg therapy, and 0.005 attacks/year after IVIg therapy ($p = 0.001$) (Fig. 1). Twelve patients had severe bulbar and respiratory involvement (Table 2). Some patients [3, 10, 11] had two attacks in first 2–3 years from MG onset and before IVIg treatment. These patients had severe dysarthria, dysphagia, and shortness of breath and needed nasogastric feeding in their attacks and persistent proximal limb weakness during remission. Three patients needed mechanical ventilation before IVIg therapy. All attacks were treated by PE before regular IVIG therapy. Only one patient required mechanical ventilation, which appeared just after ceasing prednisolone administration; the other patients had only moderate dysarthria and dysphagia in their attacks after IVIg treatment.

Five patients underwent thymectomy. Thymus pathologies were reported such as thymoma in two patients, atrophic thymus in two patients and thymic lymphoid follicular hyperplasia in one patient (Table 1). The mean number of attacks before thymectomy was 0.48 attacks/year, whereas it was 0.06 attacks/year after thymectomy ($p = 0.053$). The duration of remission was 1/2–5 years in the post-operative period. No attacks were observed in two patients after thymectomy, and the duration of remission for these patients was 3–5 years. The mean number of attacks in patients with thymectomy was 0.005 attacks/year before a regular IVIg therapy, whereas this was 0.006 attacks/year after IVIg therapy ($p = 0.093$) (Fig. 1).

Five patients (patient nos.: 1, 3, 6, 8, 9) had received azathioprine or mycophenolate mofetil therapies before regular IVIg therapy. Azathioprine could not be continued in patient no. 9 due to the development of severe lymphopenia. Liver function tests were elevated in patient no. 8, and this patient did not benefit from azathioprine or mycophenolate mofetil treatments. The other three patients (patient nos.: 1, 3, 6) did not respond to azathioprine. Eight patients did not want to take any immunosuppressive

Table 1 Demographic features of MG patients

Patient no.	Age	Sex	Antibody status	Steroid	Immunosuppressant	Thymectomy	Thymic histological features
1	42	F	–	D	Azathioprine	+	Atrophic thymus
2	57	M	–	D		–	
3	25	F	–	P	Azathioprine	–	
4	93	F	Anti-AChR-Ab+	–		–	
5	72	F	Anti-AChR-Ab+	P		–	
6	66	F	–	D	Azathioprine	+	Thymoma
7	52	F	Anti-AChR-Ab+	D		+	LFH
8	53	F	–	P	Azathioprine mycophenolate mofetil	+	Atrophic thymus
9	51	F	Anti-AChR-Ab+	–	Azathioprine	+	Thymoma
10	79	M	–	–		–	
11	66	F	Anti-MuSK-Ab+	–		–	
12	72	F	Anti-AChR-Ab+	–		–	
13	78	M	–	D		–	

P prednisone, *D* deflazacort, *LFH* thymic lymphoid follicular hyperplasia

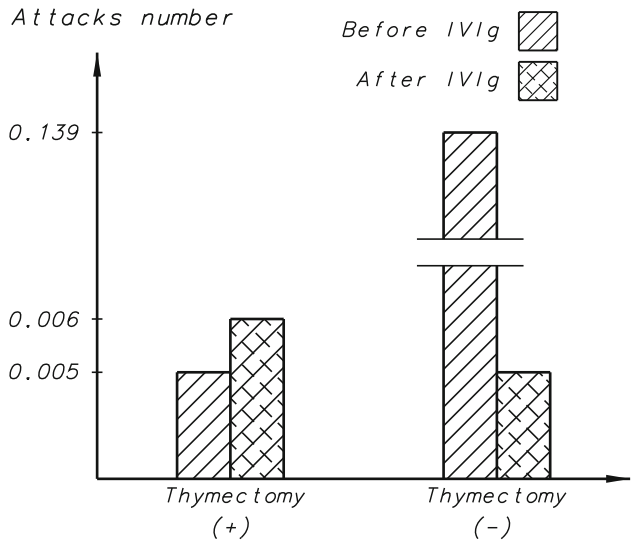

Fig. 1 The mean number of attacks

treatment due to their side effects. Thus, 13 patients were given regular IVIg therapy. The therapy was applied as a standard of 400 mg/kg for 5 days. This 5-day therapy was repeated between once a month and once in up to 6 months depending on the need of the patients. The mean IVIg administration frequency was 2.8 months. Other drugs were applied regularly in proper doses during this period. The mean duration of IVIg therapy was 7.5 years. None of the patients were applied PE during this time. The frequencies of attacks were observed to decrease in all the patients after IVIg therapy. At the time of cessation of prednol, only one patient (no. 8) needed mechanical ventilation. Eight patients (62 %) had used steroids; among them, steroid was completely stopped in patient no. 3 and 6 following the regular IVIg therapy, and the dose was decreased by 50 % in the other six patients. The requirement for pyridostigmine did not decrease in four patients, whereas this need decreased by 20–50 % (mean = 30 %) in nine patients. No serious side effects related to IVIg therapy were recorded. Patient no. 2 died during coronary by-pass surgery. Patient no. 12 died due to a post-pneumonia sepsis, which was not related to myasthenic respiratory distress. Her myasthenia was in remission at that time.

Discussion

IVIg treatment has been used in the acute exacerbation of MG [1–3, 5–9]. Arsura et al. started IVIg therapy on 12 generalized MG patients in their attack periods, and obtained a clinical well-being of 106.6 days in these patients. They suggested that intermittent IVIg therapy can be useful in such patients [10]. There are only two studies demonstrating the efficacity of intermittent IVIg therapy on MG patients with frequent attacks, which could not be reduced by immunosuppressive treatments [11, 12]. Achiron et al. reported ten patients with generalized myasthenia who did not respond to corticosteroid, cyclosporine, or azathioprine therapies. These patients responded to IVIg therapy performed at 6-week intervals. Muscle strength, fatigue and respiratory function tests were evaluated. IVIg treatment was effective in continuity of remission and provided a reduction in the doses of immunosuppressive

Table 2 Demographic features and disease and treatment-related parameters of MG patients

Patient no.	Modified Osserman scale		Total number of attacks (disease duration, years)		Intervals of IVIg administration	Daily pyridostigmine need (mg)		Daily steroid need (mg)		MV need		Total number of attacks (disease duration, years)	
	Before IVIg	Last visit	Before IVIg	After IVIg		Before IVIg	After IVIg	Before IVIg	After IVIg	Before IVIg	After IVIg	Before thymectomy	After thymectomy
1	4	1	3 (6)	0 (7)	2	240	180	D, 90	D, 4.8	–	–	1 (1)	2 (12)
2[a]	4	1	3 (5)	0 (3)	2	360	180	D, 90	D, 45	–	–		
3	3	1	2 (3)	0 (1)	1	240	240	P, 64	–	–	–		
4	4	1	2 (1)	1 (8)	3	240	180	–	–	–	–		
5	5	2	3 (1)	0 (7)	1/5[b]	300	240	P, 64	P, 12	1	–		
6	4	1	7 (1)	2 (13)	3	360	240	D, 90	–	–	–	3 (0.5)	6 (13.5)
7	5	1	3 (4)	0 (7)	2	300	240	D, 45	D, 8	1	–	1 (1)	2 (10)
8	5	5[c], 2[d]	4 (1)	1 (11)	2	360	360	P, 64	P, 32	1	1[c]	4 (1)	1 (11)
9	4	1	8 (6)	2 (11)	3	360	240	–	–	–	–	2 (1)	8 (16)
10	3	1	2 (2)	0 (5)	3	300	240	–	–	–	–		
11	3	1	2 (2)	0 (7)	6	360	360	–	–	–	–		
12[a]	4	2	3 (2)	1 (12)	3	240	180	–	–	–	–		
13	4	1	2 (1)	0 (4)	2	240	240	D, 60	D, 30	–	–		
Total			44 (35)	7 (96)								11 (4.5)	19 (62.5)

MV mechanic ventilation, *P* prednisone, *D* deflazacort

[a] Exitus

[b] First year every month, then every 5 months

[c] When prednisone ceased

[d] Other time

drugs such as prednisolone, pyridostigmine or azathioprine [11]. Hilkevich et al. reported 11 generalized MG patients with bulbar involvement. IVIg therapy was performed monthly for 20.3 months. Clinical improvement was observed following the start of IVIg therapy. Furthermore, the doses of prednisolone and pyridostigmine were decreased [12].

Achiron et al. performed regular IVIg therapy on their patients once every 6 weeks. The therapy was begun with a dose of 400 mg/kg/day for 5 days and continued with a dose of 400 mg/kg once every 6 weeks [11]. IVIg therapy was performed once in a month in the study of Hilkevich et al. Similar to the previous study, it was begun with a dose of 400 mg/kg/day for 5 days and continued with a dose of 400 mg/kg once in a month [12]. Improvement was observed in all patients receiving regular IVIg therapy [11, 12]. In our study, IVIg was begun at a dose of 400 mg/kg/day for 5 days and repeated at a dose of 400 mg/kg for 5 days at intervals of once in a month to once every 6 months. The mean IVIg requirement was observed as approximately once every 3 months. The attack severity and frequencies were seen to be improved in all patients.

Thymectomy has generally been accepted as the standard therapy combined with the use of corticosteroid, immunosuppressive, and/or anticholinesterase agents for the treatment of MG. The response to thymectomy is not evident for several months and is maximal in most cases by 3 years [1]. Maggi et al. [14] found that the best remission rate in patients is seen during the 5- to 10-year post-operative period. Takanami et al. [15] showed that the best complete or pharmacological remission rate was seen over 7 years after thymectomy. Our five patients underwent thymectomy after 1 year of the diagnosis of MG. Remission was observed between 6 months and 5 years after thymectomy. Patient no. 6 had four attacks in first 6 months after thymectomy and only two attacks in following 13.5 years, while IVIg treatments were administered. One attack was observed before thymectomy and two attacks in first 2 years after thymectomy, and then no attack recorded in patient no. 7. Whether these two patients had benefited from thymectomy or regular IVIg therapy, or both, is unclear; therefore, thymectomy effect could be relevant in these patients. Due to the fact that our groups were small in size, it is difficult to state that thymectomy alone can provide complete remission in patients, without the effect of IVIg. Five patients who had undergone thymectomy had more frequent attacks than the other eight patients in the first 5 years. However, after 5 years, the number of attacks was similar in both groups.

Eight patients (62 %) in our trial had used steroids. Steroid was completely stopped in two out of eight patients, and the dose was reduced at least 50 % in the other six patients following the beginning of IVIg treatment. Long-term possible side effects of steroid include Cushing's syndrome, truncal weight gain, osteoporosis, glaucoma and cataracts, type II diabetes mellitus, and depression in MG [16]; our patients have not had any serious side effects that could be related to steroids. IVIg treatment seems to be effective for reducing or totally ceasing steroids for a long term.

There are only a few studies regarding regular IVIg therapy on generalized MG patients who do not respond to conventional treatments. There are two studies investigating the prevention from the attacks via IVIg therapy. However, the decrease in the frequency of attacks was not evaluated in these studies. Our study is the first to consider the frequency of attacks. The sample size was small as the other studies. However, the follow-up periods of the patients were longer, and the decrease in the frequencies of attacks could be observed. The mean age in all patients was similar to the study of Hilkevich et al., but older compared to the study of Archiron et al. No side effect related to long-term regular IVIg therapy was reported in these studies, and in our study [10–12].

There are several limitations of this study: first, this was a retrospective study. The dosages and the periods of IVIg therapy and other treatments were not constant, and this study had a rather small sample size.

In summary, IVIg can produce repeated beneficial effects in patients with MG and may be useful as an adjunct therapy in the management of MG. IVIg has minimal adverse effects and ability to reduce corticosteroid dose for years. These results suggest that intravenous immunoglobulin maintenance therapy is a valid modality in patients with resistant treatment MG.

Conflict of interest None.

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