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Efficacy of high-dose intravenous methylprednisolone therapy for ocular myasthenia gravis

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ABSTRACT

High-dose intravenous methylprednisolone (IVMP) is often used as a treatment for generalized myasthenia gravis (MG); however, little is reported about the efficacy of IVMP in ocular MG. We evaluated the efficacy and safety of IVMP therapy and compared results with those of conventional oral prednisolone (PSL) treatment in ocular MG. We retrospectively studied 18 patients with ocular MG. Clinical course and safety during 6 months in 10 patients who were treated with IVMP were compared with those of 8 who were treated with PSL. IVMP (1000 mg/day) was administered one to three times within 6 months, whereas oral PSL was administered at the dose of 5–10 mg/day. The score for MG activities of daily living profile (MGADL) was assessed at baseline and at 1, 3, and 6 months after treatment. Patients who received IVMP showed faster improvements than those receiving PSL; the median changes in the ocular scores on the MGADL was −2 versus 0 at 1 month ($p = 0.03$), −3 versus −1 at 3 months ($p = 0.07$), and −3 versus −2 ($p = 0.86$) at 6 months. No patient in either group developed initial worsening of symptoms or generalized weakness. In conclusion, IVMP results in more rapid improvement than oral PSL therapy and can be a treatment option for ocular MG.

1. Introduction

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease of the neuromuscular junction, characterized by muscular weakness with fatigability. The target of the autoimmune attack in most cases of MG is the skeletal muscle acetylcholine receptor (AChR) and occasionally muscle-specific receptor tyrosine kinase [1]. Oral corticosteroid therapy is the established treatment for MG, but there are some concerns, such as the slowness of improvement, the risk of initial worsening, reducing of quality-of-life score, and adverse effects. High-dose intravenous methylprednisolone (IVMP) has been reported to produce clinical improvement in several neuroimmunological disorders such as multiple sclerosis, neuromyelitis optica [2,3], neurosarcoidosis, [4], and MG [5]. In moderate to severe MG, IVMP therapy seems to have an advantage in terms of rapid improvement, which may allow a reduction in maintenance prednisolone (PSL) doses and adverse effects [5–7], although caution is required to protect the patient from a transient initial worsening. Regarding oral steroid therapy, in one study, approximately 26% of patients with MG developed initial worsening after starting PSL; high PSL dose was one of the risk factors [8].

The symptoms of ocular MG are limited to ptosis, diplopia, and facial weakness and do not include impairment of the limb and truncal muscles. Therefore, the severe initial worsening of symptoms and MG crisis are rare in cases of ocular MG, in comparison with generalized MG [6,9–11]. Although IVMP is often used as a treatment for ocular MG, detailed analysis of its effects has been lacking. The aim of this study was to compare the efficacy and adverse effects of IVMP treatment with those of conventional treatment with oral PSL in patients with ocular MG.

2. Materials and methods

2.1. Patients

The diagnosis of MG was based on the following criteria: (1) typical clinical history of MG with fluctuating weakness of muscles and either (2) positive serum findings of anti-AChR or muscle-specific receptor tyrosine kinase antibodies or (3) a positive result of an edrophonium test or an abnormal result of an electrophysiological test (repetitive nerve stimulation or single-fiber electromyography). We retrospectively

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reviewed data from patients with anti-AChR antibody-positive MG who visited our hospital from January 2011 to March 2018 with ocular symptoms alone at first examination. No patients had received immunotherapy at baseline. We included patients with ocular MG who were treated with only IVMP and those treated with only oral PSL; we excluded patients who were treated both IVMP and oral PSL and those also used immunosuppressants concomitantly. In principle, PSL was started at a dosage of 5 to 10 mg/day in this study; then it was increased or decreased depending on patients' symptoms. Peak dose of prednisolone in our protocol was essentially lower than 10 mg/day to avoid side effects by long-term use of oral steroids. IVMP (1000 mg for 1 day) was administered and repeated monthly if patients could not achieve minimal manifestations. These treatments procedures were decided by physicians who expertise MG based on patients' symptoms.

To evaluate the severity of ocular symptoms, we used scores on the ocular segments (the evaluation of diplopia and ptosis) of the Myasthenia Gravis Activities of Daily Living profile (MGADL) (range: 0 to 6 points) [12]. We checked data such as gender, age at onset, immunotherapy (IVMP, oral PSL or others), anti-AChR antibody titers, MGADL score, MG-related symptoms, and adverse events at baseline and 1, 3, and 6 months after starting immunotherapy. The "E-L-T classification" was used to identify patients with early-onset MG (age at onset $\leq$49 years), late-onset MG (age at onset $\geq$50 years), and thymoma-associated MG [13]. In addition, we employed the ΔMGADL score (the change in MGADL scores over time) to evaluate the improvement in MG symptoms.

2.2. Statistical analysis

We performed Fisher's exact test to compare categorical outcomes and the Mann-Whitney *U* test to compare results of non-paired continuous measures. A p value of < 0.05 was considered statistically significant.

3. Results

3.1. Clinical profiles before immunotherapy

We used data from 10 patients who were treated with IVMP (IVMP group) and 8 patients who were treated with oral PSL (PSL group). All 18 patients had been given pyridostigmine (the dose was 60 to 180 mg/day). Their clinical characteristics were as follows: 4 patients (22.2%) were female; mean age at onset was 60.6 years (standard deviation [SD]: 15.6 years; range: 19 to 79 years); mean age at starting treatment was 64.4 years (SD: 11.8 years; range: 40 to 87 years); and 4 patients were early-onset MG, 13 were late-onset MG, and 1 was thymoma-associated MG. Table 1 summarizes the clinical difference between the 10 patients who received IVMP and the 8 who received PSL before immunotherapy. Clinical features such as age at onset, gender, anti-AChR antibody titers, and ocular MGADL scores of the two groups were similar.

Table 2 summarizes the course of treatment for ocular MG during 6 months. One patient (case 7) underwent IVMP treatment twice within a month because his ocular symptoms were severe. In contrast, only one IVMP treatment was needed to minimize symptoms in another patient (case 1).

3.2. Clinical course after immunotherapy

Table 3 summarizes the clinical difference between the IVMP group (n = 10) and the PSL group (n = 8) at 1, 3, and 6 months after treatment. There was no significant difference between the two groups in ocular MGADL scores (1, 3, and 6 months: p = 0.32, p = 0.22, and p = 0.21, respectively). However, ΔMGADL scores of the IVMP group, especially in the early phase, tended to be higher than those of the PSL group (1, 3, and 6 months: p = 0.03, p = 0.07, and p = 0.86, respectively; Fig. 1). ΔMGADL scores for diplopia in the IVMP group also tended to be better than those of the PSL group, especially in the early phase (1, 3, and 6 months; p = 0.07, p = 0.04, and p = 0.33, respectively). On the other hand, the change in ptosis in ΔMGADL was less significant than that of diplopia between IVMP and PSL groups (1, 3, and 6 months: p = 0.08, p = 0.49, p = 0.20).

During an observation period of 6 months, no patient in either group experienced initial worsening of symptoms or developed generalized weakness; however, only Case 6 developed generalized symptom within 2 years. Patients visited our hospital every 1 to 2 months and underwent one blood test on average during 6 months. One patient (case 3) who had been treated by IVMP experienced an exacerbation of psoriasis vulgaris. In the PSL group, two patients (cases 16 and 18) experienced exacerbations of diabetes mellitus, and one patient (case 13) showed urinary glucose positivity and an abnormality in lipid metabolism.

4. Discussion

In this study, we compared the efficacy of and adverse events caused by IVMP with those of oral PSL in patients with ocular MG. Although there was no significant difference in patients' background, ΔMGADL scores (indicating the improvement in MG symptoms) at 1 and 3 months were higher for the IVMP group than for the PSL group. Notably, the efficacy of IVMP treatment was stronger for diplopia than for ptosis. Therefore, IVMP treatment appears to have been more effective and to have worked faster than oral PSL treatment, especially for diplopia in ocular MG. Although, one patient (Case 6) in IVMP group have become generalized, generalized rate within 2 years was similar between two groups (p = 1.00). As to safety, during 6 months after the start treatment, 3 patients in the PSL group experienced exacerbation of metabolic disorders such as diabetes and dyslipidemia. On the other hand, one patient in IVMP group experienced an exacerbation of

Table 1
The clinical profiles of IVMP recipients and PSL recipients at baseline.

	IVMP recipients (n = 10)	PSL recipients (n = 8)	p Value
E-L-T classification (EOMG, LOMG, TAMG)[a]	2:7:1	2:6:0	1.00
Age (years) at onset (mean ± standard deviation)[b]	60.1 ± 16.95	61.1 ± 14.85	1.00
Age (years) at starting immunotherapy (mean ± standard deviation)[b]	64.6 ± 9.16	64.1 ± 15.25	0.89
Gender (male/female)[a]	7:3	7:1	0.59
Median anti-AChR antibody titres (nmol/L) before treatment (range)[b]	5.6 (1.1–50)	16 (4–91)	0.37
Median ocular MGADL score (range)[b]	3.5 (2–6)	3.5 (1–4)	0.38
Median MGADL score with diplopia (range)[b]	2 (0–3)	1.5 (0–2)	0.48
Median MGADL score with ptosis (range)[b]	2 (1–3)	2 (0–3)	0.28

AChR: acetylcholine receptor; EOMG: early-onset myasthenia gravis (MG); IVMP: high-dose intravenous methylprednisolone; LOMG: late-onset MG; MGADL: Myasthenia Gravis Activities of Daily Living profiles; PSL: prednisolone; TAMG: thymoma-associated MG.

[a] Fisher exact test.

[b] Mann-Whitney test.

Table 2
Course of treatment for ocular myasthenia gravis during 6 months.

Treatment	Patient	Month						
		0	1	2	3	4	5	6
IVMP	Case 1	IVMP						
	Case 2	IVMP		IVMP				
	Case 3	IVMP	IVMP					IVMP
	Case 4	IVMP			IVMP		IVMP	
	Case 5	IVMP			IVMP			
	Case 6	IVMP						IVMP
	Case 7	IVMP (2 times)		IVMP				
	Case 8	IVMP	IVMP					
	Case 9	IVMP					IVMP	IVMP
	Case 10	IVMP	IVMP	IVMP				
Oral PSL	Case 11	5 mg/day	10 mg/day	→	→	→	9 mg/day	→
	Case 12	5 mg/day	→	→	→	→	→	→
	Case 13	10 mg/day	→	8.5 mg/day	7.5 mg/day	6.5 mg/day	5.5 mg/day	4.5 mg/day
	Case 14	5 mg/day	→	→	→	→	→	→
	Case 15	5 mg/day	→	→	→	→	→	3.75 mg/day
	Case 16	5 mg/day	10 mg/day	→	8.75 mg/day	→	→	7.5 mg/day
	Case 17	5 mg/day	→	→	→	→	→	→
	Case 18	10 mg/day	→	→	→	→	→	8.75 mg/day

IVMP, intravenous methylprednisolone; MG, myasthenia gravis; PSL, prednisolone.

Table 3
Clinical course during 6 months in IVMP recipients and PSL recipients.

	IVMP recipients (n = 10)	PSL recipients (n = 8)	p value
1 month after treatment	Mean 1.4 times	7.5 ± 2.7 mg/day	
Median ocular MG-ADL score (range)	1.5 (0 to 5)	3 (0 to 5)	0.32
Median MGADL score (diplopia) (range)	0 (0 to 2)	1.5 (0 to 2)	0.26
Median MGADL score (ptosis) (range)	1 (0 to 3)	2 (0 to 3)	0.55
Median ΔMGADL score (range)	−2 (−4 to 0)	0 (−3 to 2)	0.03*
Meidan ΔMGADL score (diplopia) (range)	−1 (−2 to 0)	0 (−1 to 2)	0.07
Median ΔMGADL score (ptosis) (range)	−1 (−3 to 0)	0 (−2 to 0)	0.08
3 month after treatment	Mean 1.9 times	7.0 ± 2.3 mg/day	
Median ocular MGADL score (range)	1 (0 to 3)	2 (0 to 4)	0.22
Median MGADL score (diplopia) (range)	0 (0 to 1)	1.5 (0 to 2)	0.02*
Median MGADL score (ptosis), median (range)	1 (0 to 3)	1 (0 to 2)	0.96
Median ΔMGADL score (range)	−3 (−6 to 0)	−1 (−3 to 1)	0.07
Median ΔMGADL score (diplopia) (range)	−1.5 (−3 to 0)	0 (−1 to 2)	0.04*
Median ΔMGADL score (ptosis) (range)	−1 (−3 to 0)	−1 (−2 to 0)	0.49
6 month after treatment	Mean 2.4 times	5.9 ± 2.2 mg/day	
Median ocular MGADL score (range)	1 (0 to 4)	0 (0 to 4)	0.21
Median MGADL score (diplopia) (range)	0 (0 to 2)	0 (0 to 2)	0.43
Median MGADL score (ptosis) (range)	1 (0 to 3)	0 (0 to 2)	0.03*
Median ΔMGADL score(range)	−3 (−6 to 1)	−2 (−4 to 0)	0.86
Median ΔMGADL score (diplopia) (range)	−2 (−3 to 1)	0 (−2 to 0)	0.33
Median ΔMGADL score (ptosis) (range)	−1 (−3 to 1)	−2 (−3 to 0)	0.20

Mann-Whitney test.
IVMP: High-dose intravenous methylprednisolone; MGADL, Myasthenia Gravis Activities of Daily Living profile; PSL: prednisolone (conventional).
* $p < 0.05$.

psoriasis vulgaris; however, no patient experienced metabolic disorders. Although we consider the adverse events might be less occurred patients in IVMP group than in PSL group, this study was retrospective one using relatively small number of participants. To establish the difference of adverse event between IVMP group and PSL group, further prospective analysis is needed.

In general, cholinesterase inhibitors, such as pyridostigmine and neostigmine, are the first choice of therapy and are widely used for ocular MG. The advantages of cholinesterase inhibitors are that they are fast acting, less of long-term adverse effects, and have a good effect on ptosis. However, treatment with cholinesterase inhibitors by themselves cannot always achieve remission for the ocular symptoms in ocular MG; in those cases, immunosuppressive treatment is suggested [14]. Although the efficacy of oral PSL treatment for ocular MG has been reported in double-blind, placebo-controlled trials [10], some experts mentioned that steroid treatment should be performed for only occasional cases of ocular MG (e.g., in patients who are cosmetically distressed by myasthenic symptoms or in patients who suffer severe symptoms) because of the potential long-term adverse effects of steroid therapy [15]. Originally, there are wide variations of efficacious corticosteroid regimens used in treatment of MG. For generalized MG, British guidelines recommends PSL should be started 10 mg on alternate days and increased by 10 mg every three doses until symptoms improve (Maximum dose is 100 mg or 1.5 mg/kg on alternative days) [16]. For ocular MG, Kupersmith [9] and Benatar [10] recommended that the dairy PSL should be started 10 mg daily or every other day, and then increased to peak dose (40–60 mg/day) in their study. After that, prednisolone gradually reduced to 2.5–10 mg/alternate day. On the other hand, Japanese clinical guidelines for MG describe that high-dose oral steroids utilizing dose escalation and de-escalation are effective

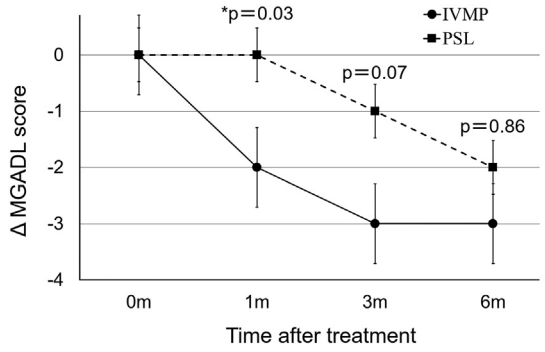

Fig. 1. Sequential changes in the scores on the Myasthenia Gravis Activities of Daily Living profile (ΔMGADL). Patients who received intravenous methylprednisolone (IVMP) tended to have higher ΔMGADL scores in the early phase than did patients who received conventional oral prednisolone (PSL). *p < 0.05.

against MG, but long-term use of oral steroids above a certain dosage level is known to involve a number of problems [17]. So this approach is now being reconsidered and high-dose oral steroids require careful consideration given the other treatment options available. Azathioprine or calcineurin inhibitors (Cyclosporine A and tacrolimus) are recommended because they not only improve symptoms, but also have steroid-sparing effects [14,16]. IVMP is often used for moderate to severe generalized MG [5,7], but not for ocular MG [14,16]. On the other hand, there are some reports that IVMP had efficacy for diplopia [6,18] and was a safer treatment alternative to oral PSL [6,11]; thus they believed that IVMP might be usable in patients with ocular MG [17]. In previous studies, protocols of IVMP treatment varied widely; one protocol consisted of 30 mg/kg/day of methylprednisolone during 3 days of every 7 days for two to three cycles [6]. Another protocol consisted of 500 to 1000 mg/day of methylprednisolone during 3 days in 1 cycle for up to three cycles [17]. Our protocol, 1000 mg of IVMP for 1 day per month, seemed to be more acceptable to outpatients than previous ones. Therefore, in our institution, when symptoms do not adequately improve using an oral prednisolone dose of 10 mg/day, we usually consider adding other immunosuppressants or IVMP.

The precise mechanisms of action by corticosteroids on MG are still uncertain. Komiyama and colleagues [6] suggested that the acute effect of corticosteroids may be due to an increase in acetylcholine, which assuages myasthenic ocular symptoms dramatically but transiently. Furthermore, they described the difference between neuromuscular junction's composition of rectus and oblique extraocular muscles and that of levator muscle, which might be contributed to the different effects of IVMP on diplopia and ptosis. Soltys and colleagues reported that neuromuscular junction of extraocular muscles are more susceptible to complement-mediated injury than that of other muscles in active experimental autoimmune MG [19]. These immunological properties may explain the efficacy of IVMP therapy in ocular MG.

Several limitations of our study should be mentioned. First, the treatments were given in an unblinded method, and there was no control group. Second, to prevent adverse events, the peak dose of oral prednisolone was relatively low in this study. Third, the number of patients in this study was small. Last, long-term evaluation for adverse events was insufficient. Therefore, we need to carefully interpret the results and could not make firm comparative conclusions only from this study. Further large-scale and prospective studies are needed to address these issues.

5. Conclusion

We showed the effectiveness and safety of IVMP in treating ocular MG. Because of its quick action, IVMP therapy seems to be an efficacious treatment for ocular MG.

Conflicts of interest

None.

Funding

None.

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