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Immunotherapy for ocular myasthenia gravis: an observational study in Japan

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Abstract

Background: Treatment for ocular myasthenia gravis (OMG) has not yet been well established. Few reports have been published on the clinical practice and outcomes of OMG.

Objectives: We investigated treatment of OMG and its outcomes in Japan.We investigated treatment of OMG and its outcomes in Japan.

Design: We performed a retrospective cross-sectional survey of OMG patients from eight hospitals in Japan.

Methods: Clinical information, including sex, age at onset, initial symptoms, autoantibodies, clinical course, treatment history, complications, and outcomes, was obtained. In addition, we recorded the total number of patients with MG and OMG separately.

Results: In total, 135 patients with OMG (67 men, 68 women) were included. Treatment of OMG was not simple and involved various immunotherapeutic strategies. Eight patients went into remission spontaneously without immunotherapy. A total of 117 patients showed improvements after treatment, whereas 10 patients showed refractory responses to treatment. Overall outcomes were good; however, symptoms persisted in 60.7% of patients even after treatment. Among 90 patients who received immunotherapy, only two showed a refractory response. Meanwhile, for 45 patients who did not receive immunotherapy, 8 were refractory. Thus, the rate of refractory disease in the group with immunotherapy was significantly lower ($p = 0.001$, u-test) than in the group without immunotherapy. The proportion of generalized MG patients among all MG cases was low in medical centers where immunotherapy for OMG was frequently performed.

Conclusion: Although the overall prognosis for patients with OMG was good, symptoms remained in more than half of the patients. Immunotherapy, including corticosteroids, may be beneficial for patients with OMG.

Plain language summary

Is immunosuppressive therapy beneficial for myasthenia gravis patients with ocular symptoms only?

Patients with ocular myasthenia gravis (OMG) have only eye symptoms for more than 2 years. Whether this condition is an initial stage of the disease before eventually progressing to generalized myasthenia gravis (gMG) is still uncertain. Different from gMG, OMG is not life-threatening. But eye symptoms often cause troublesome problems in life. Doctors have treated OMG patients similarly to patients with gMG. There is no standard clinical practice for OMG. In this study, we examined how patients with OMG were treated at eight different specialist centers in Japan. In 135 patients with OMG, 8 patients became symptom free without treatment, 117 patients showed improvements

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after treatment, whereas 10 patients did not get well. Overall outcomes were good, but symptoms remained in 60.7% of patients even after treatment. Among 90 patients who received one or more immunotherapies, only 2 did not get well. Meanwhile, for 45 patients who did not receive immunotherapy, 8 remained ill. We found that treatment of OMG was not simple and often needed multiple immunotherapies. Administering immunotherapy, including corticosteroids, may be beneficial for patients with OMG.

Keywords: blepharoptosis, corticosteroid, diplopia, myasthenia, outcomes

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Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies against neuromuscular junctions. Antibodies specific to acetylcholine receptor (AChR) act on the postsynaptic membrane to reduce the amount of AChR or function, resulting in variable weakness of the ocular, bulbar, respiratory, and limb muscles. Less frequently, this also occurs with antibodies to muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein-4 (LRP4). MG is classified as ocular or generalized MG (OMG and gMG, respectively) depending on the distribution of weakness. More than half of the patients with MG develop ocular symptoms, such as ptosis and diplopia, from an early stage of the disease.[1,2] Subsequently, approximately 80% develop generalized symptoms and are classified as having gMG, while those with only ocular symptoms for more than 2 years are diagnosed with OMG.[2–5] Whether OMG is an initial stage of the disease before eventual progression to gMG is still controversial. Fifty-five percent of OMG transforms to gMG.[6] OMG seems to consist of heterogeneous subgroups, and at least a few OMG subtypes have characteristics different from those of gMG in terms of antibody titers and age of onset.[7–10]

OMG is not life-threatening and is generally recognized as a mild disease, but diplopia and ptosis often cause troublesome problems in activities of daily living and quality of life. Patients with OMG have been treated similarly to patients with gMG without established evidence.[1,4,5,11,12] Moreover, details about clinical practice and outcomes in patients with OMG have seldom been documented. Randomized clinical trials (RCTs) are ideal to prove the efficacy of common immunosuppressive therapies; however, there have been few RCTs for OMG. Since OMG is a rare disease, it is often difficult to enroll an adequate number of patients in clinical trials,[13] and thus, sufficient evidence-based treatment options have not been sufficiently established.

The European Federation of Neurological Society/European Neurological Society (EFNS/ENS) guidelines for the treatment of OMG recommend that treatment should initially be started with pyridostigmine.[14] Several studies[15–22] have reported that corticosteroid administration or immunotherapy was effective in preventing progression of OMG to gMG, but this conclusion was not supported in a previous systematic review.[13] The updated formal consensus guidance of international MG experts recommends that ophthalmoparesis or ptosis in ocular MG that does not respond to anticholinesterase agents should be treated with immunosuppressive agents if symptoms are functionally limiting or troublesome to the patient.[23] In this study, we investigated the treatment of OMG in Japan and its outcomes, focusing on the application of immunotherapy to provide sufficient information for the establishment of evidence-based treatment options. We hypothesized that OMG had similar autoimmune etiologies as gMG and, thus, could be treated with the same treatment course, namely, immunotherapy.

Methods

Patients

Subjects were patients with OMG who visited hospitals in the MG group of 'Evidence-based Early Diagnosis and Treatment Strategies for

Neuroimmunological Disease', from 1 January to 31 December 2015. To reduce patient selection bias, we selected eight hospitals that see more than 40 MG patients annually and excluded hospitals specializing in pediatrics. MG was diagnosed based on clinical findings and amelioration of symptoms after intravenous administration of acetylcholinesterase inhibitors or the presence of anti-AChR antibodies. We excluded other disorders that caused ptosis and/or diplopia through various examinations, especially in anti-AChR-negative patients. The diagnostic criterion for OMG was as follows: MG patients who showed ocular symptoms such as ptosis, diplopia, and extraocular muscle paralysis for more than 2 years after onset. The inclusion criteria were: (1) patients who satisfied the diagnostic criteria of OMG and were diagnosed at one of the eight specialized medical institutions advocating neurology in Japan and (2) patients who received any treatment, including immunotherapy, within 2 years of onset. The exclusion criteria were: (1) patients who showed generalized symptoms throughout the course, (2) patients with thymoma, and (3) patients who did not provide consent for this study. We obtained the total number of patients with MG (including OMG) and the number of patients with OMG alone at each medical center.

Clinical assessments

We obtained further clinical information about patients with OMG, including sex, age at onset, initial symptoms, autoantibody profile, clinical course, treatment history, complications, and outcomes. The status of each patient at the end of the study was ranked into four grades with reference to the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) by one of the authors of each hospital: Grade 1: Complete stable remission (CSR), the patient with no symptoms or signs and no therapy for MG, including spontaneous remission; Grade 2: Pharmacological remission/minimal manifestations (PR/MM), in remission or no symptoms of functional limitations after some form of therapy for MG; Grade 3: Improved (I), symptoms improved, but remain; Grade 4: Unchanged/Worse (U/W), unresponsive to treatment, or had unchanged or worsened symptoms after treatment.

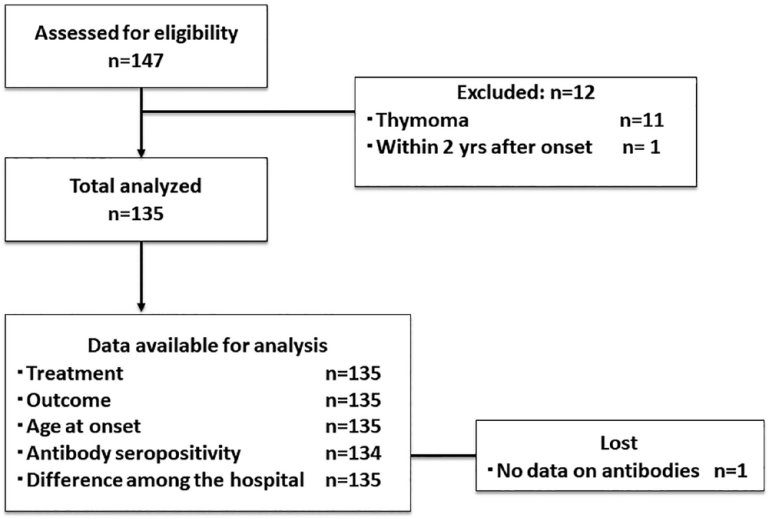

Figure 1. Patient inclusion flow chart.

Statistical analyses

Commercially available statistical software (SigmaPlot®; SPSS, Inc., Chicago, IL, USA) was used to analyze the data. When comparing the treatment administered and clinical findings, one-way analysis of variance (ANOVA) on ranks was applied. For all analyses, statistical significance was set at $p < 0.05$.

Results

We obtained data from 147 participants. Among them, 12 were excluded as 11 patients were found to have thymoma and 1 was within 2 years after onset. We finally included 135 patients with OMG (67 men and 68 women) from eight hospitals. All data, except AChR antibody titers, from these 135 patients were available for analyses (Figure 1). The mean age was age 58.7 ± 15.2 years, age at onset was 1–83 years, and duration of illness was 2–52 years (median = 10.5 years, average = 14.3 years). In total, 64 patients experienced both ptosis and diplopia, 49 had ptosis alone, and 22 had diplopia alone.

Treatment of OMG

A total of 120 patients were treated with ChE-Is, and 90 were treated with at least one or more immunotherapeutic strategies (Figure 2). Several different types of immunotherapy were administered to these 90 patients, with the majority being

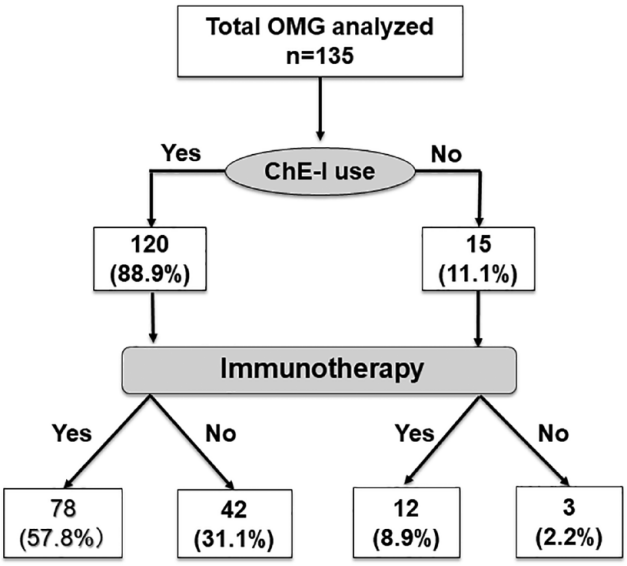

Figure 2. Overview of treatment for patients with ocular myasthenia gravis. ChE-I, cholinesterase inhibitor; OMG, ocular myasthenia gravis.

oral prednisolone (PSL) ($n=75$) with ($n=49$) or without ($n=26$) another immunotherapy (Table 1). Intravenous administration of methylprednisolone (IVMP) was performed in 37 patients. Calcineurin inhibitors (CNIs) were also used rather frequently ($n=33$, tacrolimus, 31; or cyclosporine A, 2). To improve eye symptoms, three patients received intravenous immunoglobulin administration (IVIg) (two patients did one course, the other did five) and another was treated with four sessions of plasma exchange (PLEX). Thymectomy was performed in 11 patients. Surgical therapy, in the form of ptosis and/or eye muscle surgery, was not investigated in this study. Within the three outcome groups (PR/MM, I, and U/W), amelioration (PE/MM + I) was significantly associated with the use of immunotherapy ($p<0.001$, ANOVA on ranks).

Outcomes of treatment in patients with OMG

Of the 135 patients, 8 were CSR, of whom 6 received a short-term medication of ChE-I, and 2 improved spontaneously. A total of 117 patients showed improvements, but 72 still had symptoms as ranked into I. Furthermore, 10 of the 135 patients were U/W (Table 1) and were all positive for anti-AChR; of these, 8 received only ChE-I, but no immunotherapy, and the others were treated with a low dose of PSL (5–10 mg daily) with or without ChE-I.

Among the 45 patients who had never received any immunotherapy, 8, 10, 20, and 8 were CSR, PR/MM, I, and U/W, respectively. Among the 90 patients who received immunotherapy, none were CSR, 35 PR/MM, 53 I, and only 2 U/W. The refractory response (U/W) rate in the group with immunotherapy was lower ($p=0.001$, u-test) than that in the group without immunotherapy.

Moreover, 37 patients treated with IVMP had successful outcomes, and none were U/W, although 33 patients were treated with one or more supplemental immunotherapeutic strategies. In addition, 33 patients treated with CNIs showed good outcomes, including 27 patients who received supplemental immunotherapy. Two of three patients who received IVIg were I and the other PR/MM. Another patient treated with PLEX resulted in PR/MM.

Thymectomy was performed in 11 patients whose outcomes appeared to be successful: seven patients were PR/MM and four were I. The histology of the thymus was reported as follows: normal thymus, three; hyperplasia, one; thymic cyst, two; atrophy, two; and unknown, three.

Age at onset and treatment

In total, 67 of 135 patients had a late-onset of OMG (onset at $\geqslant 50$ years). Among early-onset patients (onset at <49 years), 24 were juvenile-onset patients (onset at <15 years). No significant difference was found in the choice of treatment based on the age at onset (Table 2).

Even in patients with juvenile-onset OMG, immunotherapy, including PSL, IVMP, and CNIs, was selected for early- and late-onset groups. Notably, in the juvenile-onset group, none of the 24 patients were CSR, while 6 patients were U/W, representing a higher proportion than that in other age groups. Among them, four patients had not received any immunotherapy, and two were treated with oral PSL alone as immunotherapy.

In the early-onset group, CSR was rare (only one), and 59 responded to treatment (PR/

Table 1. Treatment of patients with ocular myasthenia gravis and its outcomes.

		n	Status at the end of study			
			Complete stable remission (CSR) (%)	Pharmacologic remission /Minimal manifestations (PR/MM) (%)	Improved (I) (%)	Unchanged/ Worse (U/W) (%)
Total		135	8 (6.0)	45 (33.3)	72 (53.3)	10 (7.4)
Immunotherapy (–)		45	8 (17.8)	10 (22.2)	19 (42.2)	8 (17.8)
Immunotherapy (+)		90	0(0.0)	35 (38.9)	53 (58.9)	2 (2.2)
Immunotherapy (+)	PSL	75	—	33 (44.0)	40 (53.3)	2 (2.7)
	PSL alone	26	—	11 (42.3)	13 (50.0)	2 (7.7)
	PSL + others	49	—	22 (44.9)	27 (55.1)	0 (0.0)
	IVMP	37	—	15 (40.5)	22 (59.5)	0 (0.0)
	IVMP alone	4	—	1 (25.0)	3 (75.0)	0 (0.0)
	IVMP + PSL	17	—	8 (47.1)	9 (52.9)	0 (0.0)
	IVMP + CNIs	3	—	1 (33.3)	2 (66.7)	0 (0.0)
	IVMP + PSL + CNIs	8	—	2 (25.0)	6 (75.0)	0 (0.0)
	IVMP + PSL/CNIs + others	5	—	3 (60.0)	2 (40.0)	0 (0.0)
	CNIs	33	—	9 (27.3)	24 (72.7)	0 (0.0)
	CNIs alone	6	—	0 (0.0)	6 (100.0)	0 (0.0)
	CNIs + PSL/IVMP	22	—	7 (31.8)	15 (68.2)	0 (0.0)
	CNIs + PSL/IVMP + others	4	—	2 (50.0)	2 (50.0)	0 (0.0)
	CNIs + thymectomy	1	—	0 (0.0)	1 (100.0)	0 (0.0)
	PLEX	1	—	1 (100.0)	0 (0.0)	0 (0.0)
	IVIg	3	—	1 (33.3)	2 (66.7)	0 (0.0)
	Thymectomy	11	—	7 (63.6)	4 (36.4)	0 (0.0)

CNI, calcineurin inhibitor; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; *n*, number of patients; PLEX, plasma exchange; PSL, prednisolone.

MM + I) but 8 did not. In contrast, outcomes were considerably better in the late-onset group than in the early-onset group: 7 patients were CSR, 58 showed improvements (PR/MM + I), and only 2 were U/W. Furthermore, the rate of CSR among the four outcomes was significantly higher in the late-onset group than that in the early-onset group ($p = 0.004$, u-test).

Antibody seropositivity and treatment

The data regarding AChR antibodies in one patient was not available. Data from the remaining 134 patients with OMG were analyzed (Table 3). Anti-AChR antibodies were detected in 104 patients. Tests for the detection of antibodies against MuSK were conducted in only 15 patients, none of whom tested positive. Antibodies

Table 2. Outcomes of treatment for patients with ocular myasthenia gravis and age of onset.

		n	Status at the end of study			
			Complete stable remission (CSR) (%)	Pharmacologic remission /Minimal manifestations (PR/MM) (%)	Improved (I) (%)	Unchanged /Worse (U/W) (%)
⩾50 years: Late-onset		67	7 (10.4)	26 (38.8)	32 (47.8)	2 (3.0)
⩾50 years	Oral PSL	30	—	18 (60.0)	12 (40.0)	0 (0.0)
	IVMP	13	—	6 (46.2)	7 (53.8)	0 (0.0)
	CNIs	14	—	4 (28.60	10 (71.4)	0 (0.0)
	Thymectomy	4	—	3 (75.0)	1 (25.0)	0 (0.0)
	Immunotherapy (–)	26	7 (26.9)	7 (26.9)	10 (38.5)	2 (7.7)
<49 years: Early-onset		68	1 (1.5)	19 (27.9)	40 (58.8)	8 (11.8)
<49 years	Oral PSL	43	—	15 (34.9)	26 (60.5)	2 (4.7)
	IVMP	23	—	9 (39.1)	14 (60.9)	0 (0.0)
	CNIs	17	—	5 (29.4)	12 (70.6)	0 (0.0)
	Thymectomy	7	—	5 (71.4)	2 (28.6)	0 (0.0)
	Immunotherapy (–)	19	1 (5.3)	3 (15.8)	9 (47.4)	6 (31.6)
<15 years: Juvenile-onset		24	0 (0.0)	5 (20.8)	13 (54.2)	6 (25.0)
<15 years	Oral PSL	18	—	5 (27.8)	11 (61.1)	2 (11.1)
	IVMP	8	—	2 (25.0)	6 (75.0)	0 (0.0)
	CNIs	6	—	0 (0.0)	6 (100.0)	0 (0.0)
	Thymectomy	1	—	0 (0.0)	1 (100.0)	0 (0.0)
	Immunotherapy (–)	6	0 (0.0)	0 (0.0)	2 (33.3)	4 (66.7)

CNI, calcineurin inhibitor; IVMP, intravenous methylprednisolone; *n*, number of patients; PSL, prednisolone.

against Lrp-4 were not measured in the patients of this study.

Of the 134 patients with OMG, 30 tested negative for anti-AChR antibodies. Among them, 22 had received immunotherapy, including oral PSL ($n=17$), IVMP ($n=10$), and tacrolimus ($n=4$). Twenty-nine patients improved with treatment, including 10 who were PR/MM. Unexpectedly, remission was observed in one patient.

Of the 104 patients who were positive for anti-AChR, 65 received immunotherapy, including oral PSL (55), IVMP (27), tacrolimus (26), and cyclosporine A (3), and seven patients were in remission. There were no significant differences among the four outcome statuses between the antibody-positive and antibody-negative groups ($p=0.263$, ANOVA on ranks). The refractory response rate was higher in the antibody-positive group, but the difference was not statistically significant. Among patients who received some immunotherapy, anti-AChR titers before treatment were available in 65; there was no correlation between the titers and outcomes after immunotherapy.

Anti-AChR titers of the 10 patients in U/W ranged from 1.5 to 310 nmol/L, whereas none of

Table 3. Anti-acetylcholine receptor antibody seropositivity, titers, and outcomes of treatment.

		n	Status at the end of study			
			Complete stable remission (CSR) (%)	Pharmacologic remission /Minimal manifestations (PR/MM) (%)	Improved (I) (%)	Unchanged/ Worse (U/W) (%)
Total		134	8 (6.0)	44 (32.8)	72 (53.3)	10 (7.4)
AChR Abs (–)		30	1 (3.3)	10 (33.3)	19 (63.3)	0 (0.0)
AChR Abs (+)		104	7 (6.7)	34 (32.7)	53 (51.0)	10 (9.6)
AChR Abs (+) in nmol/L	0.2–0.9	27	4 (14.8)	6 (22.2)	17 (63.0)	0 (0.0)
	1.0–9.9	39	3 (7.7)	13 (33.3)	17 (43.6)	6 (15.4)
	10.0 – 99.9	24	0 (0.0)	7 (29.2)	14 (58.3)	3 (12.5)
	100 –	8	0 (0.0)	5 (62.5)	2 (25.0)	1 (12.5)
	Titer unavailable	6	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)

AChR Abs, anti-acetylcholine receptor antibodies.

the patients with titers below 1.0 nmol/L or negative for anti-AChR were U/W. In contrast, anti-AChR titers were significantly lower in the CSR group ($p = 0.045$, ANOVA on rank). Furthermore, the titers of eight patients in CSR were less than 2.0 nmol/L, ranging from 0 to 1.7 nmol/L (median 0.8 nmol/L), except in one patient (6.7 nmol/L). There were no differences in other therapeutic effects between the two groups regarding the presence or absence of anti-AChR.

Differences among hospitals

Treatment options selected by each hospital varied considerably (Table 4). Immunotherapy was actively used in some hospitals and infrequently in others. Some hospitals often used IVMPs, while others used CNIs. The percentage of patients with OMG among those with MG also differed considerably, ranging 7–36% among the hospitals. Interestingly, there was a significant correlation ($r = 0.58$) between the ratio of OMG to MG and the frequency of immunotherapy for OMG at each medical center (Figure 3(a)). The more frequently that immunotherapy for OMG was administered, the larger the OMG/MG ratio. Consequently, the gMG/MG ratio tended to decrease. We also found a significant correlation ($r = 0.56$) between the frequency of corticosteroid therapy for patients with OMG and OMG/MG ratio at each medical center (Figure 3(b)). There was no significant correlation between other modalities of immunotherapy (IVMP and tacrolimus) and the OMG/MG ratio (data not shown).

Discussion

Our multicenter cross-sectional survey included the treatment profiles and therapeutic outcomes of 135 patients with OMG in Japan. The main results are summarized as follows. (1) Outcomes of patients with OMG who received any immunotherapy seemed better than those of patients who did not. (2) Treatment with corticosteroids, including IVMP, is commonly used and seems effective in patients with OMG. (3) Eight of 10 patients with unfavorable outcomes had never received any immunotherapy. (4) While the overall outcomes were good in OMG, symptoms persisted in more than 60% of patients. (5) Treatment of OMG is not simple and varies among medical centers in Japan. (6) Among all MG cases, the proportion of patients with gMG was low in medical centers that frequently performed immunotherapy for OMG.

In this study, the outcomes of patients with OMG who received immunotherapy were better than

Table 4. The number of patients with myasthenia gravis and the treatment options selected in each hospital.

	Total MG (*n*)	OMG (*n*)	OMG (%)	Immunotherapy (%)	Corticosteroids (%)	CNIs (%)	IVMP (%)
A	74	9	12	67	67	0	0
B	40	8	20	88	88	0	63
C	135	21	16	81	62	29	48
D	149	29	19	59	52	34	28
E	45	19	42	79	79	16	32
F	71	5	7	40	40	40	0
G	70	11	16	64	27	55	18
H	278	33	12	55	42	15	18

A–H, individual medical center; CNIs, calcineurin inhibitors; IVMP, intravenous methylprednisolone; MG, myasthenia gravis; OMG, ocular myasthenia gravis; OMG%, number of OMG/number of total MG.

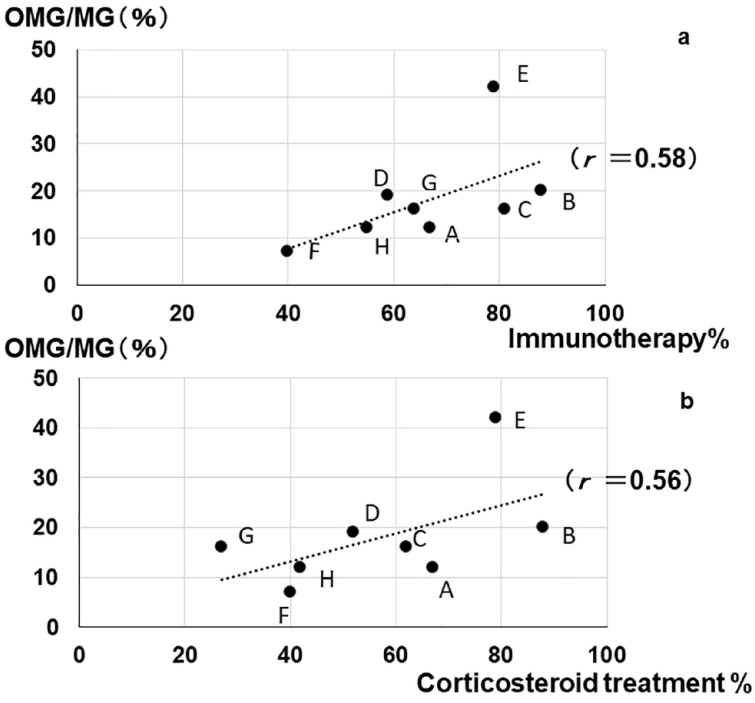

Figure 3. Relationship between the ratio of patients with ocular myasthenia gravis (OMG) to all patients with myasthenia gravis (MG) and the (a) proportion of immunotherapy or (b) steroid treatment for OMG at each medical center. *R*, correlation coefficient.

those of patients who did not. Surprisingly, 80% of patients with unfavorable outcomes had not received any immunotherapy. We did not investigate the exact reasons why these eight patients had not received immunotherapy. Four had onset in childhood, and the other person at the age of 81. We speculate that the age of onset may be related to not using immunosuppressants. Weighing the risks and benefits of each immunotherapy modality used in the treatment of OMG is important, and while we do not draw any conclusions about treatment selection, our findings suggest that immunotherapy may help avoid these troublesome sequelae.

Furthermore, we demonstrated that oral PSL is the most commonly used and effective treatment. A few RCTs relevant to the use of steroids in treating OMG have been conducted.[11,24,25] In one trial, the period of treatment seemed too short to draw any conclusions regarding the efficacy of steroid therapy.[24] In the EPITOME study,[25] which demonstrated a clinically and statistically significant benefit of prednisone compared with placebo in patients with OMG, the sample size was very small. In addition, eight non-randomized observational studies have been conducted,[21,22,26–31] six of which suggested a possible benefit of steroids in reducing the risk of progression to gMG[21,22,26–28,30] and three suggested a favorable symptomatic effect.[21,22,31] Our observation may support the EPITOME results as well as other reports.

In this study, IVMP was the second most common treatment for OMG. All patients treated with IVMP, with or without another immunotherapy, showed good outcomes. Repeated IVMP, in addition to oral PSL, was effective for OMG.[32,33] This suggests that IVMP may be an important option when choosing the appropriate immunotherapy for OMG treatment.

In general, OMG is considered a mild disease, and lack of general muscle weakness often leaves patients without sufficient treatment or with only symptomatic treatment. Notably, overall outcomes of OMG in this study appeared to be good, but only 39.3% of patients became symptom free (CSR and PR/MM), and the remaining other patients (I + U/W) still suffered from ocular symptoms. This insufficiency may account for the need for multiple immunotherapeutic strategies in several patients.

As part of the natural progression of the disease, 11–30% of patients with OMG achieved spontaneous, long-lasting remission without immunosuppression or pyridostigmine.[3,34,35] Juvenile-onset MG patients showing only eye symptoms were occasionally reported to have spontaneous remission in East Asia, including Japan.[7,8,36] These facts may be another reason why some of the OMG patients were observed without immunotherapy. In our study, however, spontaneous remission was rare. In contrast to previous studies, few patients with CSR and a higher rate of refractory response than the other age groups were observed in the juvenile-onset MG group. This result may be attributed to the fact that we missed patients who were in remission or had improved and did not visit the hospital for follow-up and may also be related to our finding of only one CSR in anti-AChR-negative OMG.

Another surprising finding was that the proportion of patients with late-onset OMG accounted for approximately half of the total patients with OMG in our study and had a higher rate of remission. There has been a continuous increase in the incidence of late-onset MG.[36–38] Our finding showing a higher incidence of late-onset OMG is consistent with these reports.

Unexpectedly, antibody seropositivity did not appear to have a significant influence on the treatment strategy. One reason is that nearly half of the patients with OMG had low anti-AChR titers (<1.0 nmol/L) or negative results. Second, anti-AChR titers were not generally associated with disease severity. However, our results suggest that anti-AChR titers were associated with OMG prognosis. Most patients with OMG with low titers (<1.0 nmol/L) showed good outcomes. In contrast, when the anti-AChR titers were apparently positive (≥ 1.0 nmol/L), the number of U/W increased.

We showed that treatment for OMG varies considerably in Japan among medical centers with expert neurologists for MG. Since this study included cases that were followed for a long period, we presumed that the latest treatment strategy of each institution was not reflected in the data we collected. Perhaps, each treatment was influenced by the treatments that were noted at the time of diagnosis. We noticed that the proportion of patients with gMG was lower at medical centers where patients with OMG were frequently treated with immunotherapy and corticosteroids. These results also suggest that immunotherapy, including corticosteroids, at the stage of ocular symptoms might suppress progression to gMG.

In previous reports, OMG and gMG were shown to have different characteristics in terms of age distribution and positivity for anti-AChR antibodies.[1,5–10,39] OMG may be heterogeneous and consist of several subgroups. Accordingly, a portion of patients with OMG might have a different pathophysiology from that of typical gMG, some of whom might show spontaneous remission and others may not respond to immunotherapy. Nevertheless, it should be noted that the majority of our cohort responded well to immunotherapy,

which might prevent progression to gMG. In addition, most patients with low or undetectable anti-AChR titers had good outcomes. This finding suggests that most OMG characteristics are pathophysiologically similar to those of acquired autoimmune diseases and that OMG possibly constitutes an early and mild stage of gMG.[40,41] Therefore, immunotherapy may be considered during the early stages of the disease, consistent with recently presented guidelines for OMG.[23] Similarly, the good outcomes of our cohort who had undergone thymectomy is intriguing because the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisolone Therapy (MGTX) study suggested thymectomy benefits patients with autoimmune MG.[23,42–44]

This study has several limitations. Due to the retrospective nature of this study, we could not elucidate the effects of each immunotherapy modality used on the OMG outcome. Second, we did not collect information on dosages or duration of individual immunotherapy, and it was unknown how these affected the outcomes. Finally, we enrolled patients who had received immunotherapy within 2 years of OMG onset. Hence, it is possible that patients whose disease might progress to gMG were included in our cohort. The definition of OMG itself may not be practical because it is often difficult to follow the course of OMG in patients who receive symptomatic treatment alone for 2 years after onset. Further studies are required to clarify these issues.

As shown in Table 1, the treatment of OMG is often complicated, and it is necessary to make full use of various immunotherapeutic strategies. Thus, treating OMG clinically is difficult, and appropriate guidelines would be helpful for clinicians. Further investigation is necessary to establish the standard treatment for OMG and to elucidate whether immunotherapy suppresses progression of OMG to gMG in a larger prospective cohort.

In conclusion, the overall prognosis for patients with OMG was good in our study; however, the outcomes of some patients, especially those who did not receive immunotherapy was unfavorable. Immunotherapy appears to be beneficial for patients with OMG.

Declarations

Ethics approval and consent to participate

We obtained approval from the Ethics Committee of the Nagasaki Kawatana Medical Center (#2016-02) and permission from the directors of each participating institution for this study. Written informed consent was obtained from all patients before participation in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data set used during the study will be made available by the corresponding author upon request from qualified researchers (i.e. affiliated with a university or research institution/hospital). Data are not publicly available because they include patient data that could compromise the privacy of the participants.

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