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Five-year follow-up with low-dose tacrolimus in patients with myasthenia gravis

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ABSTRACT

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease of the neuromuscular junction, and prednisolone (PSL) and immunosuppressive drugs are available for treatment. Tacrolimus, a macrolide that suppresses the immune system, is used as a second-line treatment for MG. There have been several reports of the effects of tacrolimus over a few years of follow-up. Here, we report data from 9 patients with steroid-dependent generalized MG treated with low-dose tacrolimus (2–3 mg/day) for 5 years. Following treatment with tacrolimus, mean MG-activities of daily living score improved from 4.6 at baseline to 3.3 at 5 years after initiation of treatment. Mean dose of PSL could also be reduced, from 24.0 mg/day at baseline to 10.2 mg/day at 5 years, although there were no cases of total withdrawal of PSL. By contrast, 5 of the 9 patients experienced exacerbation of symptoms and transient increases in PSL dose during the 5-year period. Tacrolimus is an important option for treatment of MG; however, careful management is needed for long-term treatment with this drug.

1. Introduction

"Myasthenia gravis (MG) is a chronic autoimmune disorder of the neuromuscular junction characterized by fatigable weakness. The target of the autoimmune attack is the skeletal muscle acetylcholine receptor (AChR) in most cases; however, in some, non-AChR components of the neuromuscular junction are targeted instead. Current treatments for MG include several immunosuppressive agents and, for use as chronic immunosuppressive agents for MG, corticosteroids are still the first-line therapy [1]. However, not all patients respond to treatment with corticosteroids alone, and many adverse events are related to treatment with these agents [1]. Advances in the treatment of MG have reduced mortality rates due to the disease, and several types of drugs are now available, including non-steroidal immunosuppressive agents such as cyclosporine and azathioprine. Cyclosporine has shown more rapid efficacy for MG compared to azathioprine; however, the risk of high serum creatinine levels was increased with long-term use of cyclosporine [2]. In Japan, tacrolimus (FK506), a macrolide immunosuppressant derived from *Streptomyces tsukubanesis* [3], has been approved since 2000 for systemic use in MG patients with insufficient response to corticosteroids. The maximum dose of tacrolimus for MG is 3 mg/day in Japan, which may be low compared to that in other countries [4–6]. The addition of tacrolimus to corticosteroids for post-thymectomy treatment in MG patients provided substantial clinical benefits compared with the use of prednisolone (PSL) alone in terms of improvement of muscular strength shortly after surgery and a substantially shorter time in the estimated median follow-up to obtain complete stable remission [7]. Furthermore, tacrolimus facilitated the reduction of the dose of PSL or discontinuation of steroid treatment, which can reduce the serious side effects associated with long-term steroid treatment [7]. However, the efficacy and safety of long-term tacrolimus treatment for MG have not been established. There have been several early reports of the effects of tacrolimus, including studies in Japan; however, these studies only evaluated short-term effects, for example over 16 weeks [8,9]. We report here the efficacy and safety of long-term treatment with tacrolimus (5-year follow-up) in 9 patients.

2. Patients and methods

2.1. Patients

Study participants were 9 patients (6 female and 3 male; mean age of 50.7 years, and a range of 33–64 years) who were diagnosed with MG according to history, signs and symptoms, positive responses to the edrophonium test, positive serum anti-AChR antibody titer, and decrement in response to repetitive nerve stimulation, and were treated with tacrolimus for 5 years between 2001 and 2008. We collected patients' clinical and laboratory data retrospectively. Disease severity evaluated by MG-activities of daily living (ADL) score [10], dose of oral steroids, and rate of anti-AChR antibody were compared at baseline and after 5 years in all patients. This study was approved by the local ethics committee of Hokkaido Medical Center.

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2.2. Statistics

Data were analyzed using the Wilcoxon signed-rank test. Statistical significance was set at $P<0.05$.

3. Results

3.1. Clinical features of MG patients at baseline

The clinical profiles of all 9 patients at baseline are shown in Table 1. Mean age at onset of MG was 41.4 years (range 33–64 years), and mean disease duration before treatment with tacrolimus was 109 months (range 6–264 months). Eight of the 9 patients underwent thymectomy. Pathology of the removed thymus in the 8 patients included hyperplasia ($n=5$), invasive thymoma ($n=2$), and non-invasive thymoma ($n=1$). Anti-AChR antibody was positive in all 8 patients. The most severe disease classification according to the Myasthenia Gravis Foundation of America (MGFA) before the administration of tacrolimus was >3 in 6 patients, and 4 patients were treated with immunoadsorption under membrane plasmapheresis (IAP) at least once before initiation of tacrolimus. After treatment with tacrolimus for 5 years, the mean drug dose was 2.6–2.9 mg/day in the 9 patients.

3.2. MG-ADL score and clinical symptoms

The MG-ADL scores before tacrolimus treatment were 2 to 7 points (mean 4.6) and the scores gradually decreased during the first 3 months after initiation of tacrolimus treatment (Fig. 1). The MG-ADL scores remained reduced during the 5 years of follow-up; however, statistical analysis showed no significant decrease in MG-ADL score at any point compared to baseline. Two patients who had suffered with MG for more than 10 years had four or six relapses during the 3 years before treatment with tacrolimus, and their relapses were significantly reduced to one during the 5 years after the initiation of treatment. During 5 years of follow-up, no patients received IAP therapy.

3.3. Dose of oral steroids

The mean dose of oral PSL was 24.0 mg/day (range 5–50 mg/day) before initiation of tacrolimus treatment. The dose of PSL was tapered 6 months after initiation of treatment (Fig. 2). The mean doses of PSL were 13.9, 12.8, and 10.2 mg/day at 12, 24, and 60 months, respectively. The dose of PSL at 12 months was significantly lower compared to the dose at baseline ($P<0.05$). However, 5 patients experienced exacerbation and increased PSL dose during the 5 years of follow-up.

3.4. Anti-AChR antibody

The ratio of anti-AChR antibody was calculated from the data at each time point divided by the value at baseline. The ratio was not reduced at 3 months but was decreased to 0.556, 0.599, and 0.453 at 12, 24 and 36 months, respectively (Fig. 3) ($P<0.05$). Thereafter, the ratio did not change significantly. During the 5 years of follow-up, 3 patients had an increased titer of anti-AChR, and they experienced a worsening of symptoms during this period.

3.5. Adverse events

Table 2 shows adverse events for which therapies were needed during the 5-year follow-up. Most of these events were considered to be associated with steroid use, such as bone disease and infection. Three of the 9 patients developed kidney stones. There were no severe adverse effects in any of the patients.

Table 1
Clinical characteristics of the 9 patients at baseline.

Pt No.	Age at start of tacrolimus treatment (years)	Gender	Age at MG onset (years)	Duration between onset and start of tacrolimus treatment (months)	Duration between onset and thymectomy (months)	Maximum severity before administration of tacrolimus (MGFA)	Severity at baseline (MGFA)	Pathology of thymus	Dose of PSL (mg/day)	AChR Ab (nmol/l)	IAP before administration of tacrolimus	Reasons to introduce tacrolimus
1	58	M	56	18	8	3a	3a	Hyperplasia	50	<0.2	No	Difficulty in reducing PSL
2	42	F	38	54	46	5	3b	Hyperplasia	5	33	Yes	Worsening DM
3	33	F	11	264	246	5	3a	Hyperplasia	25	760	No	Worsening symptoms of MG
4	62	F	47	168	165	2b	2a	Hyperplasia	15	35	No	Worsening DM
5	44	M	25	234	221	3a	2b	Hyperplasia	22.5	43	Yes	Worsening symptoms of MG
6	56	F	41	182	0	1	1	None	23.8	210	No	Patient's request
7	46	M	41	46	46	3b	3b	Invasive thymoma	20	19	No	Worsening symptoms of MG
8	52	F	51	8	1	4b	2a	Non-invasive thymoma	35	15	Yes	Worsening DM
9	64	F	63	6	1	4b	3b	Invasive thymoma	20	7.9	Yes	Worsening DM

MGFA; Myasthenia Gravis Foundation of America, IAP; immunoadsorption under membrane plasmapheresis, PSL; predonisolone, DM; diabetes mellitus, and MG; myasthenia gravis.