Long-term Treatment of Steroid-dependent Myasthenia Gravis Patients with Low-dose Tacrolimus

Akiko Nagaishi, Motohiro Yukitake and Yasuo Kuroda

Abstract

Objective  To examine the long-term effects of tacrolimus in steroid-dependent myasthenia gravis (MG) patients.

Patients and Methods  We administered tacrolimus at 3 mg/day to 10 generalized MG patients presented with clinical worsening by a reduction in dose of prednisolone. The effects of tacrolimus were assessed by using the MG activities of daily living (MG-ADL) profile and the post-intervention status criteria provided by the Myasthenia Gravis Foundation of America (PSC-MGFA).

Results  Seven patients were able to use tacrolimus without serious adverse effects for 1.0-5.1 years (mean 3.1 years). Further, its administration improved myasthenic symptoms to the level of pharmacologic remission or minimal manifestations of PSC-MGFA in 5 patients and made it possible to discontinue prednisolone administration in 4 of those 5. However, despite improvements caused by tacrolimus, the reduction in dose of prednisolone caused worsening of symptoms in another 2 patients. In addition, blood trough levels of tacrolimus lower than the recommended range were effective to maintain long-term improvements in 2 patients.

Conclusions  Administration of tacrolimus induced long-term improvements and enabled replacement of prednisolone in patients with intractable steroid-dependent MG.

Key words: myasthenia gravis, treatment, tacrolimus, corticosteroid, immunotherapy, prognosis


Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused mostly by antibodies (Abs) against the acetylcholine receptor (AChR) in neuromuscular junctions. A thymectomy procedure and corticosteroid administration are currently the primary choices for fundamental treatment of the disease. Tacrolimus, a new macrolide immunosuppressant, was approved for administration to MG patients in 2000, however, only for those who had previously received both a thymectomy and corticosteroids, and obtained little therapeutic benefit or developed serious medical problems such as adverse effects. Although there have been a number of reports on the beneficial effects of tacrolimus for steroid-dependent and resistant MG (1-8), the long-term dosage management protocols for tacrolimus and prednisolone have not been determined. Herein, we report findings obtained from long-term tacrolimus treatment of 7 patients with steroid-dependent generalized MG.

Patients and Methods

After obtaining informed consent, tacrolimus (Prograf®, Astellas, Tokyo, Japan) was prescribed at a dose of 3 mg/day, to be taken orally after dinner, to 10 MG patients, whose profiles are shown in Table 1. All were diagnosed with generalized MG of type IIb to IIIb (moderately severe generalized myasthenia, that is, severe skeletal and bulbar involvement but no crises; drug response less than satisfactory), according to the classification of the Myasthenia Gravis Foundation of America (MGFA) (9). The diagnosis of
MG was made based on typical history and neurological features, positive responses to edrophonium chloride, and decrement of muscle fiber potentials with repetitive nerve stimulation. Seven patients were positive for the anti-AChR Abs and 9 had undergone a thymectomy more than 5 years before receiving tacrolimus therapy. Nine patients had been receiving prednisolone 1 year or less (range, 0.1 to 1.0 year) after the diagnosis of MG, while the other (Patient 10) began prednisone therapy at 16 years after the initial diagnosis. Prednisolone was administered orally every day or every other day, with the dose gradually increased until obtaining clinical remission or minimal manifestations. The maximal dose for each patient ranged between 40 and 100 mg/day (when given daily) and was administered for more than 4 weeks in all patients except for 1 (Patient 7). The dose of prednisolone was then tapered in all patients, however, myasthenic symptoms in each patient were exacerbated by tapering. Additionally, the long-term treatment with prednisolone led to the development of adverse effects, such as diabetes mellitus, hyperlipidemia, and obesity. For these reasons, we decided to administer tacrolimus to these 10 patients.

The therapeutic effects of tacrolimus were assessed at each visit by using the myasthenia gravis activities of daily living (MG-ADL) scale (10), as it is known to correlate well with a quantitative MG score (9) and has been used as an assessment of MG severity in Japanese patients (11). The MG-ADL scale consists of a 4-point (0 to 3) assessment of 8 major MG-related symptoms that impair activities of daily living (ADL), which are talking, chewing, swallowing, brushing teeth or combing hair, raising from a chair, breathing, double vision, and eyelid droop (10). Changes in clinical status after tacrolimus administration were also assessed by the post-intervention status criteria of MGFA (PSC-MGFA) (9), which consists of complete stable remission (CSR), pharmacologic remission (PR), and minimal manifestations (MM). The level of MM was further divided into 4 stages from MM-0 (no treatment for at least 1 year) to MM-3 (requiring cholinesterase or other symptomatic therapy, and some form of immunosuppression for the past year). To precisely assess the effects of tacrolimus, we did not increase the daily dose of pyridostigmine, a cholinesterase inhibitor, throughout the observation period.

### Results

The results of tacrolimus administration in the present patients are summarized in Table 2. Of the 10 patients, 2 were unable to take 3 mg/day of tacrolimus for more than 1 month due to adverse effects, as 1 developed severe diarrhea and the other showed worsening of diabetes mellitus. Additionally, one patient voluntarily quit the follow-up visits. The remaining 7 patients were successfully given tacrolimus without serious adverse effects throughout the observation period (1.0-5.1 years, mean 3.1 years) (Table 2). Of these 7 patients, 5 patients (Patients 1, 2, 3, 6, and 7) showed improvements by 1 to 4 points (mean 3.0) on the MG-ADL scale after the first month of tacrolimus therapy and improvements of 4 to 12 points (mean 5.8) after 6 months (Fig. 1). Thereafter, each of those 5 patients continued to

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**Table 1. Profiles of 10 Patients with Steroid-Dependant MG**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Thymus Pathology</th>
<th>Follow-up Time (years)</th>
<th>Start of Tacrolimus (years)</th>
<th>Duration of Prednisolone (years)</th>
<th>Dose and Period of Prednisolone (mg/day, weeks)</th>
<th>Dose and Period of Tacrolimus (mg/day, weeks)</th>
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<tr>
<td>1 F</td>
<td>67</td>
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<td>Hyperplasia</td>
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<td>7.1</td>
<td>7.4</td>
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<td></td>
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<tr>
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<td></td>
<td>Hyperplasia</td>
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<td>7.0</td>
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<td>6.7</td>
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<tr>
<td>5 F</td>
<td>68</td>
<td></td>
<td>Non-Invasive Thymoma</td>
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<td>0.1</td>
<td>7.0</td>
<td>7.1</td>
</tr>
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<td>6 M</td>
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<td>Residual Thymus</td>
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<td>0.7</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
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<td>0.1</td>
<td>16.8</td>
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</tr>
<tr>
<td>8 F</td>
<td>51</td>
<td></td>
<td>(-)</td>
<td>33.0</td>
<td>(-)</td>
<td>16.0</td>
<td>(-)</td>
<td>17.0</td>
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<tr>
<td>9 F</td>
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<td>1.0</td>
<td>0.9</td>
<td>7.0</td>
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</table>

PSL: prednisolone
show a clinical status score of 0 or 1 point on the MG-ADL scale (Fig. 1), which led us to taper prednisolone. Tapering of the daily dose of prednisolone by 1 to 5 mg at time intervals of 2 to 4 weeks succeeded in obtaining its discontinuation after 7 to 21 months (mean 13.2 months) in 4 of the patients (Patients 1, 2, 3 and 6) while the dosage in the other (Patient 7) was reduced by 30% of dosage, with no worsening of myasthenic symptoms seen in any patient (Fig. 1). Each of these 5 patients finally reached a PSC-MGFA status of PR or MM-3.

The continuation of good status after withdrawal of prednisolone led us to attempt to taper tacrolimus in Patients 1 and 2. Based on a report of occurrence of myasthenic crisis by the abrupt cessation of tacrolimus therapy (12), tacrolimus was administrated at 3 mg/day for at least 1 year and then decreased to 2 mg/day, which was shown to be adequate to maintain the same MM status in both patients (Fig. 1). An additional decrease of tacrolimus to 1 mg/day was attempted in Patient 1 after 1 year and the same MM status was maintained (Fig. 1).

As for Patients 4 and 5, administration of tacrolimus also improved the clinical status of MG-ADL by 1 and 4 points, respectively (Fig. 2). We attempted to taper prednisolone in these 2 patients from 6 months after starting tacrolimus therapy and were able to reduce its dose by 50% after 24 months in Patient 4 and 27 months in Patient 5 (Fig. 2). However, the reduction in dose of prednisolone gradually led to a deterioration of clinical symptoms, which finally required a dosage increase. At the end of the follow-up period, each patient had MG-ADL scores of 3 points, and was receiving tacrolimus at 3 mg/day and prednisolone at 10 mg/day (Fig. 2).

As for changes in anti-AChR Abs titers, 3 patients (Patients 2, 4, and 5) showed an increase during the very early stage of tacrolimus therapy without a worsening of myasthenic symptoms (Patient 4) or with obvious improvement of MG (Patients 2 and 5) (Figs. 1, 2). Although anti-AChR Abs titers declined continuously in these 3 patients thereafter, the reduction in dose of prednisolone resulted in increases in the anti-AChR Abs titer and worsening of myasthenic symptoms in Patients 4 and 5 (Fig. 2). Each of these 3 patients had a past history of thymoma (Table 1).

Although the administration of 3 mg/day of tacrolimus resulted in improvements in all of our patients, the blood trough levels of tacrolimus varied and had no correlation with its dose or grade of therapeutic efficacy (Table 2). For example, in Patient 1, the blood trough level of tacrolimus remained between 5.1 and 6.4 ng/ml even after decreasing the dose to 1 mg/day from 3 mg/day (data not shown). Further, Patients 4 and 6, who received 3 mg/day of tacrolimus continuously, had lower blood trough levels than Patient 1 (Table 2). Nevertheless, we were able to withdraw prednisolone in 2 patients who had blood trough levels of tacrolimus lower than the recommended value (Patient 3: 2.7 to 7.5 ng/ml, mean, 5.0 ng/ml and Patient 6: 1.7 to 4.5 ng/ml, mean, 2.9 ng/ml).

**Discussion**

Herein, we report results of long-term (mean 3.1 years) tacrolimus therapy in 7 patients with intractable generalized MG. The purpose of this study was to establish a safe and

<table>
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<th>patient</th>
<th>follow up time after entry (year)</th>
<th>PSL (mg/day) at entry</th>
<th>PSL (mg/day) final visit</th>
<th>tacrolimus (mg/day) at entry</th>
<th>tacrolimus (mg/day) final visit</th>
<th>plasma trough level of tacrolimus (ng/ml) mean range</th>
<th>MG-ADL at entry</th>
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MG-ADL: myasthenia gravis activities of daily living profile
PSL: prednisolone
MGFA: Myasthenia Gravis Foundation of America
MM: minimal manifestation*
PR: pharmacologic remission**

*No symptoms of functional limitations from myasthenia gravis but some weakness on examinations of some muscle.
**Remission under some form of therapy for myasthenia gravis without cholinesterase inhibitors.
Figure 1. Changes in clinical variables after tacrolimus administration in Patients 1, 2, 3, 6 and 7. Improvements were observed from 1 month after beginning administration.

effective method to maintain long-term remission in intractable MG patients receiving prednisolone. Recently, concurrent administration of low-dose tacrolimus with prednisolone has been reported to result in improvements of various degrees in steroid-dependent MG patients (1-8). Tacrolimus is an immunosuppressant that inhibits activation of helper T cells, mainly through the suppression of interleukin-2 (IL-2) production (13). However, the therapeutic mechanism of low-dose tacrolimus for MG has not been fully clarified, because improvement of MG is not necessarily associated with a reduction in IL-2 production or anti-AChR Abs titers (4, 5). Of our 7 patients, a transient increase in the anti-AChR Abs titer was observed in 3 patients after tacrolimus therapy, though no worsening of myasthenic symptoms was noted. Thus, in addition to its immunosuppressive action, other biological effects, such as enhancing the transport of glucocorticoids to the nucleus and direct action on sarcoplasmic Ca$^{2+}$ release from skeletal muscles, seem to contribute to the improvement of MG (14-16).

Tacrolimus exhibits various dose-dependent adverse effects, thus it is recommended that blood trough levels be maintained between 6 and 10 ng/ml when used as treatment for MG (2, 3, 5, 13). However, no controlled studies have been performed to determine the best range. Without regard to blood trough levels, we administrated 3 mg/day of tacrolimus to our 10 patients, of whom 7 continued the administration for 1.0 to 5.1 years (mean 3.1 years) without serious complications. All 6 of the 7 patients improved from
Figure 2. Changes in clinical variables after tacrolimus administration in Patients 4 and 5. After reducing the dose of prednisolone, a transient increase in anti-ACR Abs and worsening of MG were observed.

as early as the first month of receiving tacrolimus therapy, which made it possible to attempt the tapering of prednisolone. Since there is a report of worsening of MG by a rapid decrease in the dose of prednisolone during tacrolimus treatment (6), we tapered prednisolone by 1 to 5 mg/day at time intervals of 2 to 4 weeks, which successfully led to its discontinuation in 4 patients within an average of 13.2 months, while maintaining the same clinical conditions. A previous study noted that prednisolone was successfully reduced in MG patients from 31.6 to 24.1 mg/day within 4 months of beginning tacrolimus administration (11). Thus, the most important advantage of tacrolimus therapy for MG is the rapid appearance of therapeutic effects, which makes it possible to reduce prednisolone from as early as 1 month after beginning administration.

In our patients, tapering of prednisolone resulted in a worsening of clinical status in 2, who were characterized by a transient increase in anti-AChR Abs during the early phase of tacrolimus therapy and a history of thymoma. It is important to elucidate the relationship between the effects of tacrolimus therapy and thymoma history, as a previous report found that the therapeutic effect of tacrolimus was higher in MG patients with a thymoma as compared to those without (17).

In the present 2 patients, following the discontinuation of prednisolone therapy, tacrolimus was also successfully tapered without a worsening of myasthenic symptoms. A previous report noted the occurrence of myasthenic crisis in an MG patient after abrupt cessation of tacrolimus therapy (12). Thus, the successful tapering of tacrolimus in our patients seems largely ascribable to the extended time interval of 1 year used for that reduction. Additionally, blood trough levels of tacrolimus below the recommended levels (6 to 10 ng/ml) were shown to maintain long-term improvement, supporting previous studies that proposed that, in addition to immunosuppression, other biological actions of tacrolimus contribute to the improvement of MG (14-16).

In conclusion, our results confirm that administration of low-dose tacrolimus is one of the best ways to quickly obtain long-term improvement in steroid-dependent and resistant MG patients. This agent can replace corticosteroids, thus making it possible to reduce or withdraw prednisolone. Tacrolimus may exert its therapeutic effects with very low doses or very low blood trough levels. However, since complete cessation of tacrolimus therapy resulted in the worsening of MG in 73% of 22 MG patients in a previous study.
(18), its tapering should be undertaken carefully.

References