Effective treatment of a 13-year-old boy with steroid-dependent ocular myasthenia gravis using tacrolimus.

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Abstract

Over the past several years, tacrolimus has attracted attention as a new therapeutic drug for myasthenia gravis (MG), but few reports have considered its use for MG in pediatric patients, and most of these have focused on severe systemic MG. In this case report, we used tacrolimus to successfully treat a 13-year-old boy with ocular MG who had suffered from severe steroid complications, including a failure of thrive and osteoporosis. He first showed symptoms of ocular MG at age 2 years 3 months. At age 13 years, he was receiving PSL (3.75 mg/day), but the symptoms of ocular MG recurred. We increased the dosage of oral PSL up to 30 mg/day, and three courses of mPSL pulse therapy were applied, but these therapies had only limited effect, and his symptoms worsened. Tacrolimus was started at 0.4mg/day (0.011mg/kg/day), and every two weeks the dose was gradually increased by 0.2mg/day. His symptoms of MG began to improve three weeks after the initial administration of tacrolimus. Approximately three months after the start of tacrolimus administration, PSL was discontinued. Currently, at one year and four months after the start of tacrolimus administration, while slight ptosis is observed in the evening, it does not influence his daily life, and his condition remains comparable to that when he stopped taking PSL. No adverse effects of tacrolimus have been recognized. In pediatric patients with steroid-dependent ocular MG without thymectomy, tacrolimus may be a safe and effective alternative to steroid and thymectomy.

Keywords:
tacrolimus; ocular myasthenia; childhood; Steroid-resistant

Introduction

Over the past several years, tacrolimus (Prograf®, Astellas Pharma, Tokyo, Japan) has attracted attention as a new therapeutic drug for myasthenia gravis (MG). This drug specifically inhibits T-cell activation via the disruption of calcineurin signaling and suppresses the antigen-specific proliferation of T cells. In this report, we describe the safety and efficacy of tacrolimus therapy, and the possibility that tacrolimus could be used as an alternative to steroid therapy in pediatric patients with steroid-dependent ocular MG without thymectomy.

Case report (Figure 1)

He first showed symptoms of ocular MG at age 2 years 3 months. 2 courses of methyl prednisone (mPSL) pulse therapy (20 mg/kg/day, 3 days) were applied.

At age 6 years 11 months and again at 7 years 4 months, ptosis recurred in spite of under oral steroid therapy, and 2 and 3 courses of mPSL pulse therapy (20 mg/kg/day, 3 days) were applied, respectively. It was not possible to discontinue PSL because the symptoms of MG recurred when we reduced the dose of PSL. As a side effect of steroid treatment, the patient suffered from a short stature (Figure 2) and osteoporosis.

At age 13 years, he was still receiving PSL (3.75 mg/day), but left-side ptosis recurred and diplopia occurred when he looked to the front and upward. We increased the dosage of oral PSL up to 30 mg/day, but the left-side ptosis and diplopia did not improve. On Day 52, he was admitted to our hospital for mPSL pulse therapy.

On admission, he was 140.8 cm tall (-2.3 SD) and weighed 36.8 kg (-1.2 SD). Mild moon face was observed but central obesity was not marked. No bulbar signs, respiratory failure, or generalized muscle weakness were observed. Left-side ptosis was seen to have a circadian rhythm, in that it worsened in the evening. Diplopia occurred when he looked to the front and upward.

He showed elevated serum AchRAb (1.5nmol/l), but no other blood abnormality was observed. The bone density of his lumbar vertebrae was 48% less than that in boys of the same age. A chest magnetic resonance imaging (MRI) did not show thymoma. Waning was not noted in evoked electromyograms(2-10 Hz) for the orbicularis oculi and hypothenar muscles

After–three courses of mPSL pulse therapy (800 mg/day; 22 mg/kg/day) were applied, his symptoms of left-side ptosis and diplopia persisted, but partially improved (he could gaze upward without ptosis for 30 seconds), so on Day 72, he was discharged from the hospital.

On Day 105, left-side ptosis at rest recurred, and the improvement noted in his diplopia was no longer seen. In light of this inadequacy of steroid therapy and the presence of side effects, we decided to administer tacrolimus.

On Day 147, tacrolimus administration was started at 0.4 mg/day (0.011 mg/kg/day), and the dose was gradually increased every two weeks by 0.2 mg/day. His symptoms of MG, such as ptosis and diplopia, began to improve three weeks after the initial administration of tacrolimus (Day 166, 0.6 mg/day) and his symptoms disappeared completely approximately three months after the initial administration (Day 240、1.4 mg/day). On Day 287, PSL was discontinued.

On Day 370, bilateral ptosis and left-side diplopia recurred, so we increased the dose of tacrolimus to 3.8 mg/kg/day. Currently, at approximately one year and four months after the initiation of tacrolimus administration, slight ptosis is still noted in the evening, but this does not influence his daily life, and he remains off PSL.

No change of the serum AchRAb level was observed. The trough blood concentration of tacrolimus was 6.1 ng/ml (Day 564, tacrolimus 3.8 mg/day). No adverse effects of tacrolimus, such as renal failure, heart failure, a decrease in the lymphocyte count, or glucose intolerance, were recognized.

Discussion

In childhood MG, some cases require steroid for the improvement of symptoms, and can become dependent on steroid. With the long-term use of steroid, various side effects, including a failure to thrive, can be significant problems. Steroid-dependent or -resistant patients require some alternative to steroid.

Thymectomy is performed in many cases of adult MG. Patients of juvenile-onset MG undergoing thymectomy within 12 months of onset had a significantly better remission rate than those who waited over 12 months. [1] In cases in which the onset of MG occurred at less than 11 years of age, it has been reported that thymectomy did not influence the remission of MG symptoms. [2,3] In our case, since he had ocular MG and did not have thymoma by MRI, and since more than 10 years had passed since the onset of MG, we judged that thymectomy would be of very limited benefit.

In adults, the efficacy of the long-term administration of tacrolimus has been evaluated in several studies. [4,5,6] Ponseti et al. reported the results of low-dose tacrolimus (0.1 mg/kg/day, mean trough blood concentration of tacrolimus was 7.8±1.5ng/ml) in 212 MG patients. [4] In this report, 92.9% of the patients showed

positive effects. In 4.9% of the patients, tacrolimus was withdrawn because of major adverse effects.

In pediatric MG, there have been only a few reports on the use of tacrolimus in severe systemic MG [7,8] and ocular MG [9]. (Table) In both types of MG, as in adults, tacrolimus was effective at a low concentration and was not associated with severe side effects. To the best of our knowledge, there has been no previous report on the use of tacrolimus for the treatment of pediatric ocular MG without thymectomy. In our case, as in previous reports in adults and children, the symptoms of MG improved with a low concentration tacrolimus, and without severe side effects. This case suggests that tacrolimus may be useful as a safe and effective drug for the treatment of steroid-dependent pediatric ocular MG without thymectomy.

Due to the limited number of reports on the use of tacrolimus in pediatric MG, the efficacy of tacrolimus in pediatric MG has not yet been established. In pediatric MG, the safety and efficacy of tacrolimus should be examined in a multicenter study.

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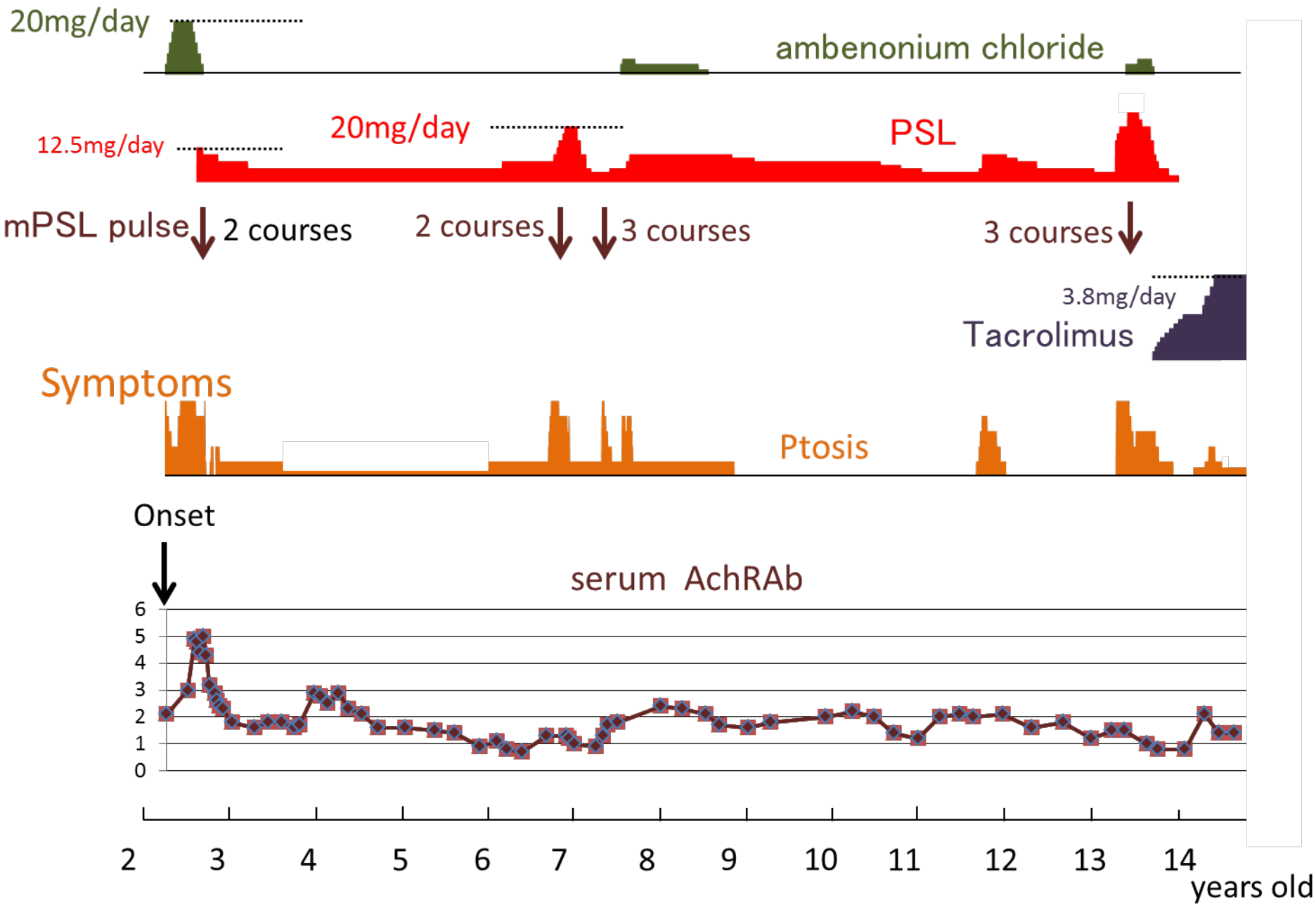
Figure 1 Summary of the patient's course and treatment.

Figure 2 Growth curve
Failure to thrive was noted from the beginning of steroid therapy.

Table Comparison of reports on the use of tacrolimus in pediatric patients.

Fig.1


20mg/day
ambenonium chloride
12.5mg/day
20mg/day
PSL
mPSL pulse
2 courses
2 courses
3 courses
3 courses
3.8mg/day
Tacrolimus
Symptoms
Ptosis
Onset
serum AchRAb
6
5
4
3
2
1
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6
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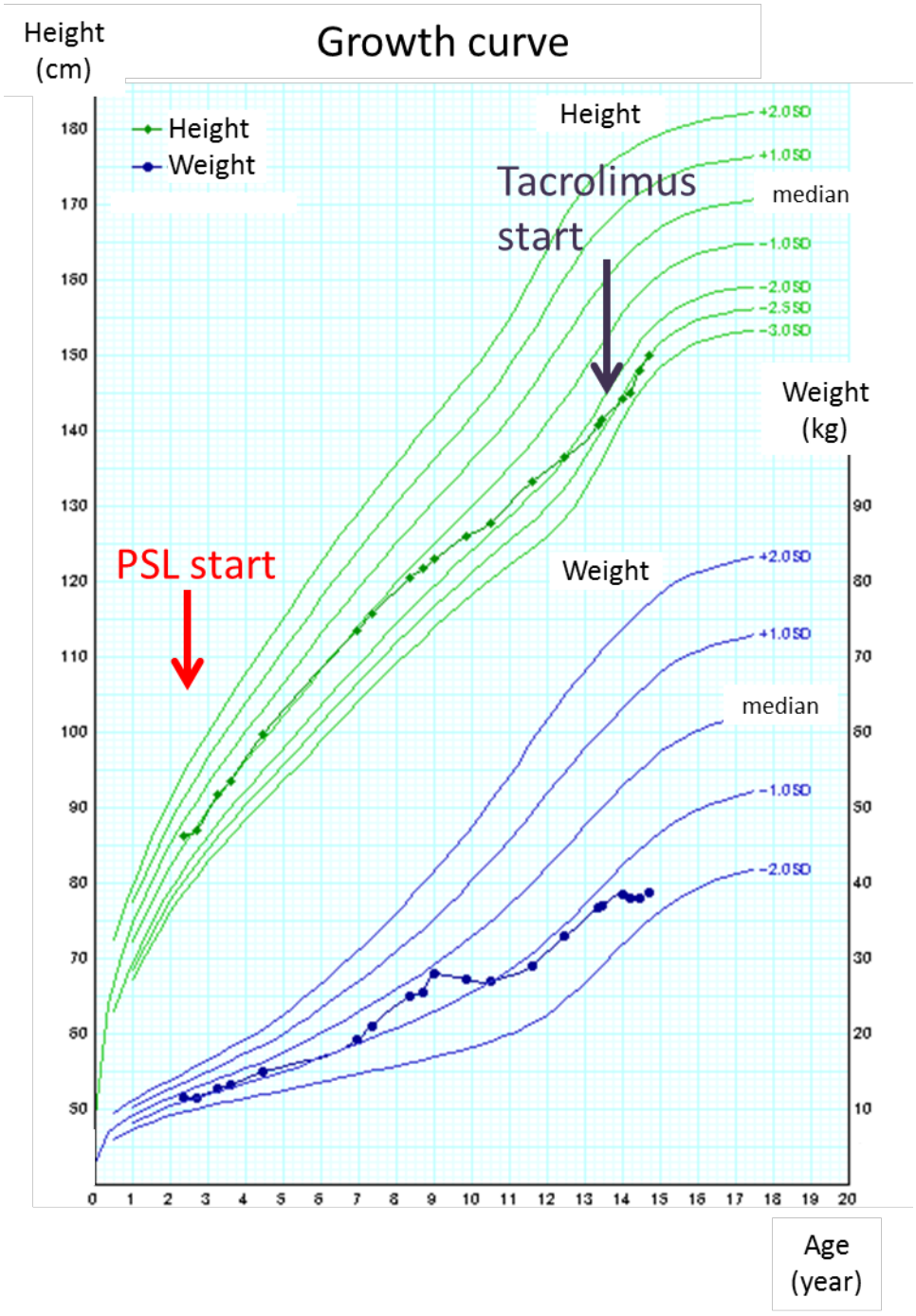
12
13
14
years old

Fig.2


Growth curve
Height (cm)
Height
Weight
Height
+2.0SD
+1.0SD
median
-1.0SD
-2.0SD
-2.5SD
-3.0SD
Tacrolimus start
Weight (kg)
PSL start
Weight
+2.0SD
+1.0SD
median
-1.0SD
-2.0SD
180
170
160
150
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130
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110
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60
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0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (year)

Table　Comparison of reports on the use of tacrolimus in pediatric patients.

Report	case	Type	Age of onset, duration of disease	Therapy before tacrolimus	Initial dose of tacrolimus	Maintenance dose of tacrolimus	concentration	AchRAb (before, final)	Result	Side effect
Kakisaka, et al. [7]	2 years, girl	systemic	2 years, 4 months	Pyridostigmine, PSL, mPSL pulse, IVIG	1mg/day (0.067mg/kg/day)	2mg/day (0.13mg/kg/day)	1.9-5.2 ng/ml	(1.7, 0.6nmol/L)	Remission, dose reduction of PSL	Reduction of lymph cell
Ishigaki, et al. [9]	3 years, girl	ocular	10 months、2 years	Pyridostigmine, PSL, mPSL pulse, Thymectomy	0.5mg/day (0.028mg/kg/day)	2.5mg/day (0.14mg/kg/day)	<3.0-4.3 ng/ml	(3.5, 1.3nmol/L)	Remission, dose reduction of PSL	No
Goto, et al. [8]	7 years, Girl	systemic	7 years, 6 months	Pyridostigmine, PSL, mPSL pulse	1mg/day (0.05mg/kg/day)	3.8mg/day (0.19mg/kg/day)	3.4-4.7 ng/ml	(2.4, 0.6nmol/L)	Remission, dose reduction of PSL	No
Our case	13 years, boy	ocular	2 years and 3 months ,11 years	ambenonium chloride, PSL, mPSL pulse	0.4mg/day (0.011mg/kg/day)	3.8 mg/day (0.10mg/kg/day)	6.1 ng/ml	(1.5, 1.4 nmol/L)	Improving, withdraw of PSL	No

concentration：trough blood concentration（Maintenance dose）