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Letter to the Editor

Ocular myasthenia gravis patients following the administration of tacrolimus and steroids

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1. Introduction

Efficacy and safety of low-dose tacrolimus (3–5 mg/day) in steroid-resistant adult myasthenia gravis (MG) patients have been demonstrated in double-blind studies [1,2]. Tacrolimus promotes muscle strength recovery with lower doses of steroids in adults [1]. However, reports on tacrolimus use in children are scarce [3,4]. Although childhood-onset MG has better steroid reactivity and improved prognosis compared with adult-onset cases [5], some refractory pediatric MG cases are nonresponsive to steroids [6,7].

In this study, we assessed the treatment and prognosis of pediatric ocular MG patients.

2. Methodology

2.1. Patients

This study recruited 9 childhood-onset ocular MG patients treated at Chiba Children's Hospital between 2007 and 2016, including 4 and 5 patients who achieved remission with steroids alone and with steroids and tacrolimus, respectively. All 9 patients were diagnosed with ocular MG (absence of whole body muscle weakness and presence of eyelid ptosis and extraocular muscle paralysis [8], positive results in the edrophonium chloride test, and no attenuation in the repeated stimulation test). All 9 patients were adequately briefed, and treatment was carried out with the parents' consent. This study was approved by the Ethics Committee of Chiba Children's Hospital.

2.2. Analysis

Based on patient medical records, we compared age of symptom onset, start of steroid therapy, number of cases of steroid-only remission, and cases in which remission was achieved with the addition of tacrolimus. For the period between the initiation of steroid therapy and remission, comparisons were made between the 4 patients who achieved remission with steroids alone and the 2 patients who achieved temporary remission but later had a relapse and subsequently received tacrolimus. In addition, a retroactive assessment of progress until remission, the method of dose reduction after remission, the timing of relapse, treatment at relapse, and changes in antibody titers was conducted with respect to the 5 tacrolimus-treated cases. Patients who did not achieve remission through steroid use were considered to be steroid-resistant, and patients where repeated relapses occurred during steroid dose reduction were defined as steroid-dependent. Although there was weight gain, in all cases there were no other serious side effects caused by PSL; neither short stature nor osteoporosis was noticed.

3. Results (Table 1)

3.1. Patient characteristics

Patient age at ocular MG onset ranged 8–30 months (mean: 21.9 months), and all were acetylcholie receptor (AChR) antibody-positive, despite some testing negative during initial diagnosis. The dose of prednisolone (PSL) was as follows: patients 1–3 did not achieve remission receiving 2 mg/kg every other day, patients 4–7 achieved remission receiving 2 mg/kg every other day, and patients 8 and 9 achieved remission receiving 1 mg/kg every other day.

3.2. Comparison between tacrolimus-treated and steroid-only patients

Symptom onset age range in the patients was 8–27 months (mean: 18 months) and 21–30 months (mean: 27 months) in the tacrolimus-treated and the steroid-only group, respectively. No significant differences were observed between the groups with respect to age, but patients in the tacrolimus-treated group tended to be younger. Similarly, anti-AChR antibody titer at symptom onset and the period from onset to the start of steroid therapy did not differ significantly. During the period from the start of steroid therapy to the induction of remission through prednisolone (PSL) use, the time to remission in the 2 steroid-dependent cases that were subsequently treated with tacrolimus was 4–6 months (mean: 5 months), which was longer than that for the 4 steroid-only cases (0.5–2 months; mean: 1.0 month).

Tacrolimus was introduced at 3–5.5 months after symptom onset, and remission was achieved within 0.5–3 months in all cases. The dose of tacrolimus was 0.05–0.2 mg/kg/day, and remission could be induced at a low blood concentration of 1.1–5.2 ng/ml. No side effects, such as

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Table 1
Summary of data of the 9 patients included in this study.

Pt	Onset age (months)	Gender	Anti-AChR antibody titer during initial diagnosis (nmol/l) #1	Period from the start of steroid therapy to remission (months)	Period from symptom onset to tacrolimus treatment (months)	Tacrolimus dose (mg/kg/day)	Period from tacrolimus treatment to remission (months)	Tacrolimus concentration during remission (ng/ml)	Period from symptom onset to relapse after tacrolimus treatment initiation (months)	Treatment at relapse #3		Tacrolimus concentration at relapse (ng/ml) #4	Anti-AchR antibody titer (nmol/l)	
										PSL (mg/kg/evry other day)	Tacrolimus (mg/kg/day)		During remission	During relapse
1	14	F	> 0.2 #1	ND #2	5.5	0.06	2.5	2–2.4	35	S	0.03↓	NT	3.6–4.9	NT
2	20	F	3.3	ND	3.5	0.2	1	2.4–3.1	31	S	→	2.6	2.3–3.1	2.6
3	21	F	4.1	ND	3	0.2	3	2.6–8.7	33	S	S	NT	2.6–8.7	1.1
4	8	M	2.1	6	4.5	0.2	2	2.8–5.2	58	0.5↓	→	4.3	2.8–5.2	1.2–1.4
5	27	F	> 0.2	4	6	0.05	0.5	< 0.01	No relapse					
6	21	F	0.4	2	Patients 6–9 were not administered tacrolimus									
7	26	M	1.1	0.5										
8	30	M	0.3	0.5										
9	30	F	> 0.2	1										

#1 Upon first examination, patients 1, 5, and 9 tested negative against anti-acetylcholine receptor (AChR) antibody, but all patients tested positive later.
#2 ND; no date. Patients 1–3 did not achieve remission through steroid use (steroid resistant).
#3 S; Stopped administration, ↓; reduction, →; no change.
#4 NT; not tested
AChR:acetylcholine receptor antibody, PSL:prednisolone

renal dysfunction or increased susceptibility to infection, due to tacrolimus use were observed.

3.3. Patient course after remission in tacrolimus-treated cases

PSL dose reduction was initiated in all 5 cases. The period from onset to relapse after the introduction of tacrolimus was 31–58 months (mean: 39.25 months). In case 4 only, the third relapse was the first relapse after the introduction of tacrolimus. Both patients who had a relapse during tacrolimus monotherapy (patients 1 and 2) received increased tacrolimus doses, but did not achieve rapid remission and resumed PSL therapy. The concentrations of tacrolimus administered after relapse were within the measurement range during remission. The anti-AchR antibody titer markedly increased only after the third relapse in case 4, but was otherwise within or below the measurement range during remission.

4. Discussion

Childhood-onset ocular MG is considered to resolve with remission in many cases, but it is believed that steroid resistance is relatively high in childhood-onset cases, particularly in patients under 3 years of age [5]. In our study, patients in the tacrolimus group tended to be younger than patients in the steroid-only group. In addition, there was no association with anti-AChR antibody titers; therefore, the anti-AChR antibody titer may be unrelated to this condition.

The period from the start of steroid therapy until remission was significantly shorter in the steroid-only group than in the steroid-dependent group. In the steroid-only group, remission was achieved within 2 months after the start of steroid therapy in all cases, and in steroid-dependent cases, remission took more than 3 months. Accordingly, tacrolimus addition may be considered if remission is not achieved even 3 months after the start of steroid therapy.

Recurrence occurred in four of the five tacrolimus-treated cases. Three cases were after PSL was stopped, and one was after decreasing the dose of PSL. They did not improve even if tacrolimus was increased after relapse. They eventually resumed PSL treatment. Therefore, terminating steroid therapy and administering tacrolimus as a monotherapy is not feasible even when remission is achieved through the addition of tacrolimus.

The limitation of our study is that it involves retrospective analysis. Moreover, the patient pool was small. Therefore, a prospective study in larger cohorts is necessary to validate our observations; however, tacrolimus can be used to induce remission in intractable childhood-onset ocular MG cases not responsive after 3 months of steroid therapy. Even if remission can be achieved through tacrolimus addition, it is necessary to consider the potential difficulty of reducing the dose or completely stopping subsequent PSL administration. Additionally, antibody titers do not often change significantly during relapse; therefore, they are not a useful metric for indicating the dose reduction schedule.

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References

[1] H. Yoshikawa, T. Kiuchi, T. Saida, M. Takamori, Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis, J. Neurol. Neurosurg. Psychiatry 82 (2011) 970–977.
[2] T. Konishi, Y. Yoshiyama, M. Takamori, K. Yagi, E. Mukai, T. Saida, Japanese FK506 MG Study Group, Clinical study of FK506 in patients with myasthenia gravis, Muscle Nerve 28 (2003) 570–574.
[3] T. Mori, K. Mori, M. Suzue, H. Ito, S. Kagami, Effective treatment of a 13-year-old boy with steroid-dependent ocular myasthenia gravis using tacrolimus, Brain and

Development 35 (2013) 445–448.
[4] K. Ishigaki, K. Shishikura, T. Murakami, H. Suzuki, Y. Hirayama, M. Osawa, Benefits of KF506 for refractory eye symptoms in a young child with ocular myasthenia gravis, Brain and Development 31 (2009) 634–637.
[5] P.I. Andrews, A treatment algorithm for autoimmune myasthenia gravis in childhood, Ann. N. Y. Acad. Sci. 841 (1998) 789–802.
[6] C. Liu, M. Gui, Y. Cao, J. Lin, Y. Li, S. Ji, B. Bu, Tacrolimus improves symptoms of children with myasthenia gravis refractory to prednisone, Pediatr. Neurol. 77 (2017) 42–47.
[7] M. Gui, X. Luo, J. Lin, Y. Li, M. Zhang, X. Zhang, M. Yang, W. Wang, B. Bu, Long-term outcome of 424 childhood-onset myasthenia gravis patients, J. Neurol. 262 (2015) 823–830.
[8] A. Jaretzki, R.J. Barohn, R.M. Ernstoff, H.J. Kaminski, J.C. Keesey, A.S. Penn, D.B. Sanders, Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Neurology 55 (2000) 16–23.

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