Original article

Advantage of administering tacrolimus for improving the prognosis in polymyositis and dermatomyositis

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A concise title: Tacrolimus in polymyositis and dermatomyositis

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Abstract

The purpose of this study is to investigate the therapeutic advantage of administering tacrolimus (TAC) in patients with polymyositis (PM) and dermatomyositis (DM). We retrospectively analyzed the clinical outcomes and findings after starting treatment in 66 patients with PM/DM (28 PM and 38 DM). Clinical outcomes were compared between patients whom TAC was concomitantly given with PSL (the concomitant TAC group) and those who was treated with PSL alone. The therapeutic efficacy of TAC was also evaluated by analyzing clinical findings, including serum creatine kinase (CK) levels, muscle strength, and the daily dose of prednisolone (PSL), not only in the concomitant TAC group but also in patients who additionally started TAC after a relapse (the additional TAC group). Patients in the concomitant TAC group significantly indicated lower frequency of relapse and longer survival without relapse than those who treated with PSL alone (P = 0.0001, P = 0.001, respectively). The significant decreases of CK levels were shown one month after starting TAC both in the concomitant TAC group and in the additional TAC group. Moreover, the effects of withdrawing PSL were also significantly indicated in both groups. Concomitant use of TAC with PSL obviously provide a favorable outcome in DM/PM. And furthermore, additional TAC is also useful for improving the prognosis even after a recurrence.

Key words: tacrolimus, polymyositis, dermatomyositis, prednisolone

Introduction

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory disorders principally affecting skeletal muscle and skin. The pathogenesis of PM/DM is implicated in the activation of lymphocytes especially including T cells-mediated immunity through antigen-specific induction and inflammatory cytokines expression, resulting in myotoxicity and microangiopathy [1,2]. These immune-pathogenesis clinically derive myalgia, weakness of extremities, trunk, and throat-laryngeal muscle with and without characteristic skin involvements.

Corticosteroids are conventionally administered as the first-line therapy in DM/PM, but it is usually shown that patients treated with corticosteroid alone have a recurrence during their reducing the dose of corticosteroid [3]. In addition, long-term use of high dose corticosteroid often brings patient the harmful effects such as osteoporosis and infection. Therefore, another immunosuppressant should be additionally required in order to obtain the PSL-sparing efficacy as well as to improve the muscle-skeletal prognosis in PM/DM. We previously demonstrated the efficacy of tacrolimus (TAC) in patients with PM/DM who indicated the difficulty for the reduction of prednisolone (PSL) [4]. Some reports also showed that the administration of TAC is useful in refractory PM/DM [5-8]. TAC is the immunosuppressive agent which directly reduces the activity and growth of T cells and expression of interleukin-2 by inhibiting intracellular activating signaling via calcineurin [9].

In this study, we demonstrated some therapeutic benefits of administering TAC in PM/DM. The clinical outcome in patients initiating the combination therapy of TAC with PSL was compared with that in those having monotherapy with PSL. And furthermore, the usefulness of TAC was also evaluated in patients whom

TAC was additionally administered after a relapse.

Materials and Methods

Patients

We reviewed the clinical records of patients with PM/DM who initiated the treatment in our hospital from July 2003 to October 2015. The diagnosis was determined according to the criteria proposed by Bohan and Peter for PM/DM [10], and that proposed by Gerami et al for clinically amyopathic DM (CADM) [11]. The patients with proven malignancy, infection, and acute interstitial pneumonia in the systemic assessment at admission into our hospital were excluded from this study. After all, 66 patients with PM/DM (28 PM and 38 DM) were enrolled. Among them, the patients who were treated with PSL alone were categorized into the PSL alone group, and those who were concomitantly treated with TAC and PSL were categorized into the concomitant TAC group. For determining the demographic and clinical characteristics between two groups, we detected the information of gender, age, levels of serum creatine kinase (CK), more than 160 titer of anti-nuclear antibody (ANA), anti-Jo-1 antibody positivity, and muscle strength before initiating treatment. The Ethics Committee of Shinshu University School of Medicine approved this study. All patients provided informed consent before starting treatment.

Treatment and management

All patients receive the treatment with PSL at the initial daily dose of 0.5—1 mg/kg. The dose of PSL is gradually reduced every 2 weeks in the hospital and every 4—8 weeks in the outpatient clinic as long as

patients keep symptomatic and laboratory improvement without any exacerbation. TAC is given at the initial daily dose of 2 mg to patients without a crucial problem in the administration of TAC such as renal dysfunction and infection. The blood trough concentration of TAC were controlled between 5 and 10 ng/mL. For monitoring the adverse event ascribable to TAC toxicity, the regular laboratory examinations, including chemistry, hematology and urinalysis, are performed at least once a week in the hospital and once a month in the outpatient clinic. When the severe adverse event, such as intractable hypertension, hyperpotassemia and renal dysfunction, appears despite of adjusting appropriate trough blood concentration, TAC is ceased.

Assessment for evaluating outcome

We extracted the value of serum CK, daily dose of PSL, and muscle strength from the medical records for analyzing the efficacy of treatment. Muscle strength was quantitatively graded in bilateral six muscles, which include deltoid, biceps brachii, triceps brachii, iliopsoas, quadriceps femoris, and hamstrings, by the manual muscle test (MMT). The MMT scale uses the numeral grades 0―5, which are confirmed by the assigned evaluation (0: no contraction, 1: trace or flicker contraction, 2: active movement in full range with gravity eliminated, 3: active movement in full range against gravity, 4: active movement in full range against gravity and resistance, 5: normal). The sum of them was defined as MMT-6 score whose scale range is up to 60. As for skin involvements associated with DM, including Gottron's papule, heliotrope rush and ulcerative eruption, therapeutic efficacy was judged according to visible findings.

We set up the end-point for evaluating the prognosis after the initiation of treatment. The end-point was established when the relapse of PM/DM was shown. The judgment of relapse was determined when the

additional treatment with another immunosuppressant and/or increase of corticosteroid was given ascribable to the following states: 1) persistence of serum CK elevation, and/or 2) worsening of skin involvements associated with DM. In the comparison between the PSL alone and concomitant TAC group, clinical outcomes after initiating treatment were evaluated by survival analysis. Patients who had severe adverse event due to TAC toxicity were classified into dropout in this survival analysis.

Statistical analysis

Chi-square test for independence and the Mann-Whitney U-test were used in statistical analyses of the demographic characteristics and laboratory findings. Survival curves were established by the Kaplan-Meier method, and statistical significance between the PSL alone and the concomitant TAC group was analyzed by the log-rank test. For determining the statistical differences of evaluation items between before and after treatment, the Wilcoxon signed-ranks test was employed. The values in the comparative analysis are shown as mean ± SD. Two-sided *P* values are expressed for each result, and a *P* value < 0.05 was regarded as statistically significant.

Results

Demographic and clinical characteristics

Thirty nine patients were classified into the PSL alone group, in which 16 patients (41%) with PM and 23 with DM (59%) were composed. Twenty seven patients, including 12 with PM (44%) and 15 with DM (56%), were classified into the concomitant TAC group. **Table 1** shows the demographic and clinical findings before

initiating treatment in two groups. The comparison of those between two groups were performed separately in PM and DM. There were not statistically significant differences in the distribution of gender, that of age, serum CK levels, MMT-6 score, positivity of ANA, and anti-Jo-1 antibody.

Outcomes between the PSL alone and concomitant TAC group

We compared the clinical outcomes between two groups. The mean observation periods since the initiation of treatment were 26.9 ± 21.0 months in the PSL alone group and 24.1 ± 19.9 months in the concomitant TAC group ($P = 0.974$). Initial daily dose of PSL was significantly lower in the concomitant TAC group than that in the PSL alone group (mean 39.3 mg vs. 49.0 mg, $P = 0.002$) **(Table 2)**. With regards to the daily dose of PSL per body weight (mg/kg/day) in the concomitant TAC group, lower doses were significantly administered in both PM and DM compared with those in the PSL alone group (mean 0.72 mg/kg vs. 0.97 mg/kg in PM, 0.79 mg/kg vs. 0.93 mg/kg in DM [$P = 0.0006$, $P = 0.016$, respectively]). In the comparison of event-free survival, longer survival was significantly shown in the concomitant TAC group ($P = 0.001$ by log-rank test) **(Figure 1)**. Considering the incidence of relapse in the concomitant TAC group, the frequencies of that were significantly lower in both PM and DM compared with those in the PSL alone group (25% vs. 68% in PM, 13% vs. 65% in DM [$P = 0.027$, $P = 0.002$, respectively]). Of five patients who had a relapse (3 PM, 2 DM) in the concomitant TAC group, 4 patients recovered by the increase of PSL or additional intravenous immunoglobulin (IVIg) with keeping TAC, whereas another with PM had to change TAC to cyclosporine A (CsA) after intensive treatment by methylprednisolone pulse therapy, intravenous cyclophosphamide, and IVIg in order to suppress progressive muscle weakness with serious dysphagia and dysarthria. Mean trough blood

concentration of TAC were not significantly different between patients with and without relapse (5.9 ± 1.6 vs. 5.4 ± 1.8 ng/mL, $P = 0.495$). Severe adverse event due to TAC toxicity appeared in elder 2 patients after their clinical remission. One patient with PM had renal dysfunction, and another with DM had hyperpotassemia. Both patients ceased TAC, however, they had maintained a remission by keeping PSL during their observation period. In the PSL alone group, TAC was additionally given to 18 patients who experienced a relapse (10 PM and 8 DM) at 4.8 ± 7.6 months since initiating PSL. For the next evaluation, we newly categorized them into the additional TAC group. All of them achieved clinical remission after adding TAC without any TAC toxicity, on the other hand, IVIg was given to 2 patients (one PM and one DM) and PSL was increased in one with DM simultaneously when TAC was added to them.

Evaluation of clinical findings after administering TAC

As the next evaluation, we explored how clinical findings changed in patients who had been consecutively treated with TAC. In the concomitant TAC group, MMT-6 score significantly increased 3 months in PM and one month in DM after initiating treatment (53.4 ± 5.1, 59.2 ± 1.7 [$P = 0.018$, $P = 0.005$], respectively) **(Figure 2)**. Moreover, it was judged to be fully recovered at 6 months in all patients with DM. In the additional TAC group, we defined MMT-6 score just before adding TAC as the baseline. Comparing with MMT-6 score before initiating PSL, the baseline was not significantly different in both PM and DM (49.0 ± 6.0 vs. 52.3 ± 7.7 in PM, 52.9 ± 8.4 vs. 49.0 ± 9.7 in DM). Eventually, DM patients indicated significant increase of that one month after adding TAC compared with baseline (54.3 ± 5.1, $P = 0.042$), whereas no statistical significance was shown in PM during observation period (55.8 ± 6.4 at 12 months, $P = 0.101$). However, MMT-6 score in PM

at 3 months after adding TAC was significantly higher than that before initiating PSL (54.8 ± 6.5, $P = 0.024$). Typical skin manifestations in all DM patients were visibly improved one month after initiating treatment in the concomitant TAC group. In the additional TAC group, one DM patient took approximately 6 months after adding TAC for the recovery from worsening of skin symptom; nevertheless remaining patients including 2 CADM indicated their improvement around one month later.

In analyzing the changes of serum CK levels, we excluded those of patients with CADM. In the concomitant TAC group, decrease of those was significantly shown one month after initiating treatment in both PM and DM (415 ± 336, 299 ± 407 IU/L [$P = 0.002$, $P = 0.001$], respectively) **(Figure 3)**. This analysis was also performed in the additional TAC group. Serum CK levels just before adding TAC were significantly lower than those prior to initiating PSL in PM (1183 ± 685 vs. 3375 ± 2112 IU/L, $P = 0.005$), whereas no significant difference was shown in DM (1918 ± 1683 vs. 2835 ± 3813 IU/L, $P = 0.249$). However, serum CK levels significantly decreased one month after adding TAC in comparison with those just before adding TAC in both PM and DM (450 ± 228, 571 ± 992 IU/L, [$P = 0.007$, $P = 0.028$], respectively).

We also analyzed the daily dose of PSL after the initiation of treatment (**Figure 4**). Patients in the concomitant TAC group could significantly reduce the daily dose of PSL one month later in both PM and DM (29.8 ± 7.9 mg, 29.0 ± 2.6 mg, [$P = 0.004$, $P = 0.001$], respectively). In the additional TAC group, we defined the daily dose of PSL at the point of adding TAC as the baseline. The baseline was significantly lower than the initial dose in PM (25.3 ± 12.6 vs. 47.0 ± 9.8 mg, $P = 0.012$), however, significant difference of that was not indicated in DM (41.9 ± 18.9 vs. 51.3 ± 13.8 mg, $P = 0.109$). In comparison with the baseline after adding

TAC, significant efficacy for reducing PSL dose was demonstrated at 8 month in PM (13.2 ± 5.7 mg, P = 0.043), and that was indicated at one month in DM (32.2 ± 11.8 mg, P = 0.042).

Discussion

The present study demonstrated that the combination therapy of TAC with PSL enables to accomplish more favorable outcome than the monotherapy with PSL in PM/DM. As the additional advantage in this therapeutic manner, the required initial dose of PSL was ultimately lower in the concomitant use of TAC, resulting in that the synergistic effect by combining TAC and PSL is more useful than higher dose of PSL alone. Under the concomitant use of TAC, the initial daily dose of PSL at 0.8 mg/kg is sufficient for achieving therapeutic effect in another study [8], and that also approximates to the initial dose in our patients. Consequently, this initial dosage of PSL may be reasonable when TAC is concomitantly initiated in PM/DM. Besides, our study demonstrated that concomitant use of TAC allowed constant withdrawal of PSL as well as reducing a relapse. It is generally thought that long-term and high dose intake of PSL are often the cause of several side effects such as obesity, osteoporosis, vertebral compression fracture, arteriosclerosis and infection. The risk of infection in rheumatoid arthritis, for instance, is dependent on the dose of PSL [12,13]. Therefore, we always seek how to reduce PSL as early as possible with keeping clinical remission. In our analyses, withdrawal efficacies of PSL were significantly performed not only in patients who concomitantly initiated TAC but also those who additionally started TAC after a relapse. Even though it relatively took longer period for patients with PM in the additional TAC group to attain a significant reduction of PSL compared with the baseline, the

daily dose of PSL was ultimately reduced to almost same level as that in the concomitant TAC group (**Figure 4**), suggesting that TAC is also useful in patients who have a relapse. Accordingly, not only TAC contributes to the successful outcomes with PSL-sparing effect as described in the previous reports [14], but also has further advantage as the additional treatment for a recurrence.

In the results of clinical manifestations, significant improvements were also exhibited in the series of patients whom TAC was given. The reduction of serum CK levels was particularly demonstrated one month after administering TAC even in patients who started TAC after a relapse. With regard to skin manifestation associated DM, visible improvements were also shown around one month in the majority of patients. It was described that conventional immunosuppressive agents such as azathioprine take a couple of months for indicating their therapeutic efficacy, whereas CsA can provide a curative effect much earlier [15-17]. CsA also works as the calcineurin inhibitor whose mechanism of intracellular signaling in T cells is similar to that of TAC [9]. On the other hand, TAC has higher pharmacological potent and safety as well as fewer necessity of monitoring the blood trough concentration until adjusting appropriate level than CsA [18,19,4]. Considering these literal and pharmacokinetic background, TAC is a suitable immunosuppressive agent for providing prompt therapeutic effect in PM/DM.

As for the response of TAC, the therapeutic susceptibility may be different between PM and DM. Regarding the MMT-6 score, patients with DM significantly indicated earlier improvement compared with those with PM. PSL-sparing effect was also immediately shown in patients with DM who additionally started TAC after a relapse, although their daily dose of PSL just before starting TAC was not significantly different from initial

that. Accordingly, these results suggested that therapeutic response of TAC is more sensitive to patients with DM, especially such a tendency may be remarkable when TAC is added after a relapse. The immune-pathological background is supposed to discriminate between PM and DM. Cytotoxic T cells directly attack muscle fibers expressing major histocompatibility complex class I antigens in PM, whereas cytokine-producing CD4 positive T cells and B cells invade around endomysial capillaries in DM [2]. Therefore, it may be important for establishing more definite therapeutic strategy to investigate the detail of pharmacokinetic impact of TAC on the immune-pathogenesis in PM/DM, although several experimental reports indicated TAC can suppress both the activity of cytotoxic T cells and cytokine production of CD4 positive cells [20,21].

It has been thought that how to derive the efficacy of TAC with avoiding the toxicity is dependent on the trough blood concentration level, which may be suitable between 5 and 10 ng/mL [7,14,22,23]. Mean trough blood concentration was at appropriate level in our patients, but some of them had a recurrence. The pharmacokinetic variability of TAC attributes to individual physical condition within narrow control range [24], therefore, it is necessary to accumulate more data for determining a definitive trough blood concentration of TAC in PM/DM.

In conclusion, administration of TAC is a beneficial therapy in PM/DM for providing a favorable outcome with the withdrawal effect of PSL not only as the initial treatment but also as the additional one for a relapse. However, we suggest that TAC should be concomitantly administered with PSL as first-line therapy for PM/DM in order to prevent a relapse and harmful effect ascribable to long-term use of high dose PSL.

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Compliance with ethical standards

Conflict of Interest: All authors have no financial or personal conflict of interest in this manuscript.

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Figure legends

Figure 1: Survival curves analyzed by the Kaplan-Meier test and compared by the log-rank test between the concomitant TAC (n = 27) and PSL alone group (n = 39). Event-free survival curve includes patients without relapse nor severe adverse event associated with TAC toxicity.

Figure 2: The changes of MMT-6 score after starting TAC in the concomitant TAC and the additional TAC group. Those were separately evaluated in PM (**A**) and DM (**B**). The baseline is the MMT-6 score before initiating the treatment in the concomitant TAC group, and that just before adding TAC in the additional TAC group. The reference mark indicates the first time point in which the significant increase of score is statistically shown compared with the baseline ($^{※}P < 0.05$; $^{※※}P < 0.005$; Wilcoxon signed-ranks test).

Figure 3: The changes of serum CK level after starting TAC in the concomitant TAC and the additional TAC group. Those were separately evaluated in PM (**A**) and DM (**B**). The baseline is the serum CK level before initiating the treatment in the concomitant TAC group, and that just before adding TAC in the additional TAC group. The reference mark indicates the first time point in which the significant decrease of serum CK level is statistically shown compared with the baseline ($^{※}P < 0.05$; $^{※※}P < 0.005$; Wilcoxon signed-ranks test).

Figure 4: The changes of daily PSL dose after starting TAC in the concomitant TAC and the additional TAC group from baseline. Those were separately evaluated in PM (**A**) and DM (**B**). The baseline is the daily dose of PSL before initiating the treatment in the concomitant TAC group, and that just before adding TAC in the additional TAC group. The reference mark indicates the first time point in which the significant reduction of

daily PSL dose is statistically demonstrated compared with the baseline ($^{※}P < 0.05$; $^{※※}P < 0.005$; Wilcoxon signed-ranks test).

Table 1. Demographic and clinical characteristics between the PSL alone and concomitant TAC group

	PSL alone (n = 39)		Concomitant TAC (n = 27)		*P* value※2	
	PM	DM	PM	DM	PM	DM
	n = 16 (41%)	n = 23 (59%)	n = 12 (44%)	n = 15 (56%)		
Male : female	5 : 11	6 : 17	2 : 10	3 : 12	0.334	0.490
Age, year	55 ± 19	51 ± 19	63 ± 11	49 ± 21	0.275	0.731
CK, IU/L	3228 ± 2343	2326 ± 2977	2844 ± 2137	1777 ± 1910	0.676	0.777
MMT score (≦ 60)	47.6 ± 6.9	53.0 ± 6.0	49.1 ± 5.2	55.6 ± 4.7	0.656	0.103
Antinuclear antibody (%)	4 (25%)	6 (26%)	7 (58%)	5 (33%)	0.081	0.802
Anti-Jo1 antibody (%)	0	1 (4.3%)	0	1 (6.7%)	0.606	0.640

CK, cratine kinase; DM, dermatomyositis; PM, polymyositis; TAC, tacrolimus

※1Seven patients in the PSL alone group and 3 in the concomitant TAC group are classified into clinically amyopathic DM (CADM). There is no significant difference in the distribution of CADM between two groups ($P = 0.373$).

The variable data are shown as mean ± SD (standard deviation).

※2Data between two groups were compared by using Mann-Whitney U-test and Chi square for independent test.

Table 2. Outcomes and treatments between two groups

		PSL alone (n = 39)	Concomitant TAC (n = 27)	*P* value※
Total relapse numbers (%)		26 (67%)	5 (19%)	**0.0001**
	PM (%)	11 (68%)	3 (25%)	**0.027**
	DM (%)	15 (65%)	2 (13%)	**0.002**
Treatment				
Initial dose of PSL, mg/day (mg/kg/day)				
	All patients	49.0 ± 13.0 (0.95 ± 0.20)	39.3 ± 12.3 (0.76 ± 0.19)	**0.002 (< 0.0001)**
	PM	47.2 ± 9.3 (0.97 ± 0.13)	36.3 ± 11.1 (0.72 ± 0.21)	**0.011 (0.0006)**
	DM	50.2 ± 15.2 (0.93 ± 0.23)	41.7 ± 13.0 (0.79 ± 0.18)	0.051 **(0.016)**
Additional treatment after relapse				
	mPSL pulse	2 (8%)	1 (20%)	0.940
	Increasing PSL	4 (15%)	1 (20%)	0.827
	IVIg	8 (31%)	4 (80%)	0.060
	TAC	18 (69%)	§	—
	CsA	6 (23%)	1 (20%)	0.688
	IVCY	0	1 (20%)	0.161

CsA, cycrosporin A; IVCY, intravenous cyclophosphamide; DM, dermatomyositis; IVIg, intravenous immuneglobrine; mPSL, methylprednisolone (1g x 3 consecutive days); PSL, prednisolone; PM, polymyositis; TAC, tacrolimus

The variable data are shown as mean ± SD.

※Data between two groups were compared by using Mann-Whitney U-test and Chi square for independent test.

§Four patients had kept TAC, whereas TAC was changed to CsA after IVCY and IVIg administration in one patient with PM.