

## Concise report

# The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis

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## Abstract

**Objective.** Interstitial lung diseases (ILDs) complicated with PM or DM are frequently aggressive and refractory to treatment. Recently some reports have suggested the potential benefit of tacrolimus for severe ILD complicated with PM/DM. However, little evidence has yet shown the efficacy of tacrolimus in these settings. The aim of this study was to evaluate the efficacy of tacrolimus as a treatment for PM-/DM-related ILD.

**Methods.** This retrospective study comprised 49 previously untreated patients diagnosed as PM-/DM-related ILD admitted to Hokkaido University Hospital from January 2000 to July 2013. These patients were treated with tacrolimus plus conventional therapy or only with conventional therapy (prednisolone, i.v. CYC and/or ciclosporin). The primary endpoint was defined as the time to relapse or death of respiratory cause or a serious adverse event. The secondary endpoint was defined as the time from the initiation of immunosuppressive treatment to relapse or death of respiratory cause. Endpoints were compared by adjusted Cox regression model by using inverse probability of treatment weighting in order to reduce the impact of these selection biases and potential confounding factors.

**Results.** After adjustment, the tacrolimus group ( $n=25$ ) had significantly longer event-free survival as compared with the conventional therapy group ( $n=24$ ). The weighted hazard ratio (HR) was 0.32 (95% CI 0.14, 0.75,  $P=0.008$ ). In addition, the tacrolimus group had significantly longer disease-free survival as compared with the conventional therapy group. The weighted HR was 0.25 (95% CI 0.10, 0.66,  $P=0.005$ ).

**Conclusion.** The addition of tacrolimus to conventional therapy significantly improved the prognosis of patients with PM-/DM-related ILD.

**Key words:** lung diseases, interstitial, tacrolimus, dermatomyositis, polymyositis.

## Introduction

PM and DM are systemic autoimmune diseases that affect skeletal muscle as well as organs such as the lung, heart

and joints [1]. Among such organ involvement, pulmonary complications represented by interstitial lung disease (ILD) are found in ~50% of PM/DM patients [2] and are recognized as common causes of mortality and morbidity in this disease [2, 3]. ILD in patients with clinically amyopathic DM (CADM) includes acute, progressive and severe forms that are pathologically referred to as diffuse alveolar damage [4, 5], being resistant and refractory to treatment.

Although high-dose corticosteroid treatment is the first choice for PM-/DM-related ILD, the choice of a secondary immunosuppressive agent is a matter of controversy. CYC is one of the most commonly selected treatments

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for ILD in systemic autoimmune diseases, including PM/DM [6]. However, neither randomized, multicentre nor placebo-controlled trials have been conducted so far.

Recently the effectiveness of tacrolimus in PM-/DM-related ILD, especially refractory or severe forms of this disease, has been shown in several case reports and retrospective studies [7, 8]. Tacrolimus has an immunosuppressive mode of action similar to ciclosporin, but binds to different intracellular receptors [9]. However, *in vitro*, tacrolimus has up to ~100-fold stronger inhibitory effect on T cell proliferation and cytokine production than ciclosporin [10]. In the area of transplantation, several randomized controlled trials have confirmed the superior clinical efficacy and safety of tacrolimus compared with ciclosporin. Tacrolimus has been shown to improve the graft survival of kidney [11] and liver [12] and to decrease the severity of acute graft-vs-host disease in bone marrow transplantation [13] compared with ciclosporin. Therefore we hypothesized that tacrolimus is more effective than ciclosporin for the treatment of severe autoimmune conditions, including PM-/DM-related ILD.

In the analysis of observational studies, the propensity score is used as an analytical method that estimates the efficacy of intervention by considering the covariates predicting the selection of a certain therapy [14]. In the present study we aimed to evaluate the efficacy of tacrolimus treatment for PM-/DM-related ILD using adjustment by inverse probability of treatment weighting (IPTW) methods in order to minimize bias in the assessment of retrospectively collected data.

## Patients and methods

### Study design

The present retrospective, observational clinical study was conducted in a single centre to see if PM-/DM-related ILD patients treated with tacrolimus have a better prognosis compared with those treated with a conventional regimen. The study was approved by the ethics committee of Hokkaido University Hospital (permission number 012-0048).

The medical records of consecutive untreated PM-/DM-related ILD patients admitted to Hokkaido University Hospital from January 2000 to July 2013 were reviewed retrospectively. The diagnosis was based on Bohan and Peter's criteria [1] in PM/DM and Sontheimer's criteria [15] in CADM. Inclusion body myositis, malignancy-associated or overlapping cases were excluded.

All patients were treated with high doses of prednisolone (0.8–1.0 mg/kg/day). In severe cases, *i.v.* methylprednisolone pulse therapy (1000 mg/day for 3 days) and/or another immunosuppressive agent such as ciclosporin (2–3 mg/kg/day), *i.v.* CYC (500 mg/m<sup>2</sup>/month) or tacrolimus were combined according to the decision of the treating physicians. In all cases treated with *i.v.* CYC, this agent was administered within 1 month from the initiation of immunosuppressive treatment. Tacrolimus was started orally at a dose of 1–3 mg/day, followed by adjustment to trough levels of 5–20 ng/ml.

We divided the patients into two groups based on the treatment protocol including or excluding tacrolimus. The conventional therapy group was defined as the patients treated with corticosteroids alone or in combination with other immunosuppressive agents except tacrolimus. The tacrolimus group was defined as the patients treated with tacrolimus as induction therapy within 28 days from the start of treatment.

### Laboratory and physical findings

Serum lactate dehydrogenase (LDH), creatine kinase (CK) and Krebs von den Lungen-6 (KL-6), one of the markers of lung fibrosis, were determined. Manual muscle testing (MMT) was assessed for the following 18 muscles: the flexor and extensor muscles of the neck, the bilateral side of the deltoid, biceps brachii, brachioradialis, triceps brachii, iliopsoas, gluteus maximus, quadriceps femoris and hamstring. Each muscle was scored on a scale of 0–5 and the total score was evaluated as previously reported [16].

### Evaluation of ILD

All patients underwent high-resolution CT (HRCT) for diagnosis of ILD. Radiographic abnormalities consistent with ILD were determined by radiologists as follows: nodules, irregular linear opacities, ground glass opacities (GGOs), honeycombing and traction bronchiectases.

The following parameters concerning pulmonary function were evaluated by spirometry: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV<sub>1</sub>), the FEV<sub>1</sub>/FVC ratio and the diffusing capacity for carbon monoxide (DL<sub>CO</sub>).

### Endpoints

The primary endpoint was defined as the time from the initiation of immunosuppressive treatment to relapse or death of respiratory cause or serious adverse event (SAE). Secondary endpoint was defined as time from the initiation of immunosuppressive treatment to relapse or death of respiratory cause. Relapse was defined as fulfilling all attributes as follows: (i) worsening of symptoms or hypoxia, (ii) radiological progression of ILD assessed by both radiologists and rheumatologists and (iii) the need for treatment with an increased dose of steroids (>0.5 mg/kg/day) or with other immunosuppressive agents. SAEs were defined as death or hospitalization for any cause.

In the tacrolimus group, patients were censored at the time tacrolimus was discontinued. In the conventional group, patients were censored at the time tacrolimus administration was started. Patients without events were censored in August 2013.

### Statistical analysis

All clinical data were compared between the tacrolimus group and the conventional therapy group. In independent samples, either a chi-squared test or Fisher's exact test was used for binary data and either a *t*-test or the Mann–Whitney *U*-test was used for continuous data.

Survival curves were constructed by Kaplan–Meier methods and hazard ratios (HRs) and 95% CIs were estimated by Cox proportional hazard regression analysis. Primary and secondary endpoints were compared between the both groups by the adjusted Cox regression model using IPTW [17].

The propensity score is the probability of treatment assignment (tacrolimus use) conditional on measured baseline variables. We selected predictive variables for tacrolimus use from several possible confounders (age, sex, disease duration, DM, amyopathic manifestation, anti-Jo-1 antibody, oxygen administration, acute progression within 60 days, serum KL-6 levels, FVC, CYC use, GGO and extensive ILD), which shows the highest likelihood score statistic in all possible logistic regression models. After variable selection, the propensity score was calculated for each patient using a logistic regression model including age, sex, disease duration, DM, anti-Jo-1 antibody, serum KL-6 levels, FVC, CYC use and GGO.

The probability that a patient had his or her own observed treatment was calculated using the propensity score. We used the inverse of the probability as a weight in the IPTW analysis [14]. The weight for a patient receiving tacrolimus was the inverse of the propensity score value, and the weight for each patient not receiving tacrolimus was the inverse of 1 minus the propensity score. In the weighted sample, the Kaplan–Meier curve was depicted and the adjusted HR and a robust 95% CI were estimated in a Cox regression model.

All *P*-values are two-tailed and those <0.05 were considered statistically significant. Data were analysed with SAS version 9.2 (SAS Institute, Cary, NC, USA) and SPSS version 19.0.0 software (SPSS Japan, Tokyo, Japan).

## Results

### Baseline characteristics

A total of 49 patients (17 PM and 32 DM) were enrolled in this study. The median observation period was 25.7 months [interquartile range (IQR) 12.0–46.5]. Steroid pulse therapy, ciclosporin and i.v. CYC were given to 28, 7 and 11 patients, respectively.

Table 1 shows the demographic and baseline clinical features of the tacrolimus group and the conventional therapy group. Ciclosporin was given more in the conventional group and CYC was given more in the tacrolimus group.

### Outcomes

In the tacrolimus group and the conventional therapy group, 5 (20.8%) and 5 (20.0%) patients relapsed, 1 (4.2%) and 5 (20.0%) died of a respiratory cause and 1 (4.2%) and 2 (8.0%) developed other SAEs, respectively. All relapses were from a respiratory cause. Distributions of SAEs were one patient with hepatic cirrhosis in the tacrolimus group and two with malignancy in the conventional therapy group.

Muscular lesions evaluated by MMT and serum CK levels and respiratory lesions evaluated by FVC and

DL<sub>CO</sub> were improved after 1 year of treatment, but no significant difference was found between the two groups (see supplementary Table S1, available at *Rheumatology* Online).

### Safety

Non-SAEs were observed in 3 (12.0%) and 2 (14.3%) patients in the tacrolimus group and the conventional therapy group, respectively. One cytomegalovirus infection and two herpes zoster infections were noted in the tacrolimus group. All these cases resolved with antiviral treatments. Two cases of renal dysfunction were noted in the conventional therapy group.

### IPTW analysis

The survival curves of both groups were adjusted by using IPTW methods. After adjustment, the tacrolimus group had significantly longer event-free survival compared with the conventional therapy group (Fig. 1A). The weighted HR was 0.32 (95% CI 0.14, 0.75, *P*=0.008). In addition, the tacrolimus group had significantly longer disease-free survival compared with the conventional therapy group (Fig. 1B). The weighted HR was 0.25 (95% CI 0.10, 0.66, *P*=0.005).

## Discussion

To the best of our knowledge, this retrospective study is the first report statistically demonstrating that the addition of tacrolimus significantly improves the event-free and disease-free survival of patients with PM-/DM-related ILD compared with conventional therapy. Because PM-/DM-related ILD is a life-threatening condition, it is difficult to conduct randomized clinical trials. Therefore it is meaningful that we have shown the efficacy of tacrolimus as an additional treatment of PM-/DM-related ILD using systematic statistical methods.

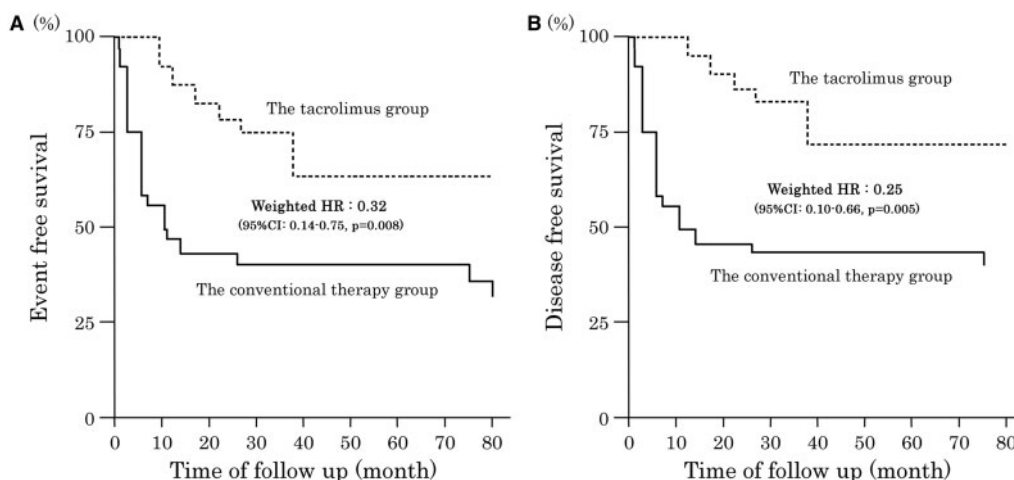
Corticosteroids are empirically used as first-line therapy for PM-/DM-related ILD. However, >50% of patients were resistant to corticosteroid monotherapy, ~20% of patients experienced ILD deterioration and the mortality rate of these refractory patients was ~50% [2]. Additional immunosuppressive agents are often necessary in these unfavourable cases. Although various combination therapies have been attempted recently, no consensus treatment has yet been established. Effective treatment protocols are awaited in the near future for severe/refractory ILD.

T cells are an essential treatment target for PM-/DM-related ILD. Increased lymphocytes in bronchoalveolar lavage fluid (BALF) have been observed in cases of PM-/DM-related ILD, with a low ratio of CD4<sup>+</sup>/CD8<sup>+</sup> lymphocytes [18]. Moreover, CD25<sup>+</sup>/CD8<sup>+</sup> T cells in BALF are significantly increased in corticosteroid-resistant PM-/DM-related ILD patients as compared with corticosteroid-sensitive patients [19]. These facts indicate that activated pulmonary T cells play an important role in the development of corticosteroid-resistant PM-/DM-related ILD. Thus these activated pulmonary T cells in

**TABLE 1** Clinical features of the tacrolimus group and the conventional therapy group

	Tacrolimus ( <i>n</i> = 25)	No tacrolimus ( <i>n</i> = 24)	<i>P</i> -value
<b>Clinical features</b>			
Male/female, <i>n</i> (%)	9 (9)/16 (64)	8 (33)/16 (67)	0.917
Age at onset, mean (s.d.), years	49.3 (15.8)	54.9 (12.8)	0.409
Duration to treatment from onset, median (IQR), months	2.6 (1.1–3.9)	1.0 (0–3.5)	0.409
PM/DM, <i>n</i> (%)	10 (40)/15 (60)	7 (29)/17 (71)	0.152
CADM, <i>n</i> (%)	6 (24)	2 (8)	0.273
Smoking history, <i>n</i> (%)	12 (48)	9 (38)	0.650
Anti Jo-1 antibody, <i>n</i> (%)	4 (16)	8 (33)	0.281
Acute onset (within 2 months), <i>n</i> (%)	9 (36)	10 (42)	0.909
<b>Laboratory findings</b>			
KL-6, median (IQR), U/ml	994 (670–1637)	662 (354–963)	0.031*
LDH, median (IQR), IU/l	515 (321–756)	502 (370–803)	0.897
CK, median (IQR), IU/l	950 (194–2448)	695 (127–2028)	0.569
FVC, mean (s.d.), %	77.9 (25.5)	85.8 (42.4)	0.091
FEV <sub>1</sub> /FVC, mean (s.d.), %	84.8 (23.6)	86.2 (42.0)	0.435
DL <sub>CO</sub> , mean (s.d.), %	53.2 (27.8)	64.7 (33.9)	0.063
<b>HRCT findings</b>			
Ground glass opacity, <i>n</i> (%)	23 (92)	17 (71)	0.123
Linear shadow, <i>n</i> (%)	17 (68)	16 (67)	0.837
Traction bronchiectasis, <i>n</i> (%)	13 (52)	10 (42)	0.291
Consolidation, <i>n</i> (%)	10 (40)	6 (25)	0.415
Honeycomb, <i>n</i> (%)	2 (8)	4 (17)	0.625
Nodule, <i>n</i> (%)	2 (8)	2 (8)	0.632
>50% lesion of total lung, <i>n</i> (%)	6 (24)	6 (25)	0.802
<b>Therapy</b>			
High-dose steroids (>0.5 mg/kg), <i>n</i> (%)	25 (100)	24 (100)	—
Steroid pulse, <i>n</i> (%)	18 (72)	10 (42)	0.063
Ciclosporin, <i>n</i> (%)	0 (0)	7 (29)	0.012*
CYC, <i>n</i> (%)	9 (36)	2 (8)	0.048*

Continuous values are the mean (s.d.) if normally distributed or the median (25 percentile–75 percentile) if not. Binary values are number (%) unless otherwise indicated. CADM: clinically amyopathic DM; KL-6: Krebs von den Lungen-6; IQR: interquartile range; LDH: lactate dehydrogenase; CK: creatine kinase; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; DL<sub>CO</sub>: diffusing capacity of carbon monoxide; HRCT: high-resolution CT. \**P*-values <0.05. *P*-values were calculated for comparison between the tacrolimus group and the conventional therapy group using either the chi-squared test or Fisher's exact test for binary data and either the *t*-test or Mann-Whitney *U*-test for continuous data.

**Fig. 1** Adjusted survival curves of the tacrolimus group and the conventional therapy group

(A) Adjusted event-free survival curves. The tacrolimus group had significantly longer event-free survival compared with the conventional therapy group. (B) Adjusted disease-free survival curves. The tacrolimus group had significantly longer disease-free survival compared with conventional therapy group.

patients with PM-/DM-related ILD would be ideal treatment targets.

Although CYC is the treatment of choice for PM-/DM-related ILD, severe patients are often resistant to a single immunosuppressive agent, including CYC [20]. In this study, concomitant use of CYC was more frequent in the tacrolimus group. The better prognosis of the tacrolimus group might be due in part to the effect of concomitant use of CYC.

Our results must be interpreted with caution because of the following limitations. First, this is a retrospective study from a single institution with a relatively small sample size. Second, treatments except tacrolimus were not homogeneous, i.e. initial corticosteroid doses or tapering protocols were determined and practised by the treating physician, and combinations of other immunosuppressive agents such as CYC varied. Therefore, the efficacy of tacrolimus should be confirmed by larger scale, prospective and, if possible, randomized controlled studies. We enrolled consecutive populations who received treatments as initial induction therapy targeting PM-/DM-related ILD and accounted for variations in patients by performing propensity analysis using the IPTW method. We believe this study is convincing in that tacrolimus improved the prognosis of these patients and has an acceptable safety profile, and we encourage physicians to choose tacrolimus as an additional treatment for patients with severe and difficult conditions.

#### Rheumatology key messages

- Addition of tacrolimus improved the event-free and disease-free survival of patients with PM-/DM-related interstitial lung disease.
- Tacrolimus is one of the important treatment options for PM-/DM-related interstitial lung disease.

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## Supplementary data

Supplementary data are available at *Rheumatology* Online.

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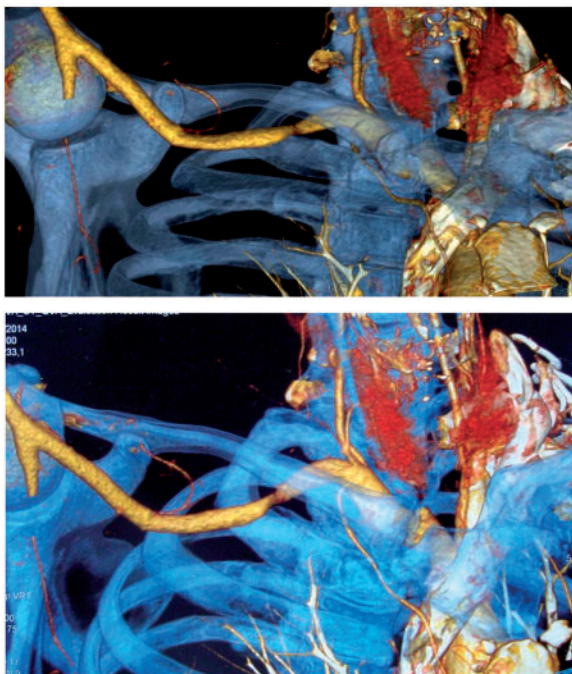
## Clinical vignette

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### Arterial thoracic outlet syndrome

A 32-year-old man, without previous medical history, presented with a 2 month history of severe RP involving his right hand, which was exacerbated when he practised his profession of house painter. On examination, his right

**Fig. 1** CT with 3-dimensional reconstruction: compression of the right subclavian artery in dynamic studies without arterial wall damage at rest



hand was normal; the right wrist pulse decreased with Wright's hyperabduction test. General physical examination was otherwise normal. Autoantibody screening tests (RF, ANA) were negative. Nailfold videocapillaroscopy proved normal. Arterial and venous Duplex ultrasonography of the upper limbs were also normal. CT with 3-dimensional reconstruction showed compression of the right subclavian artery in dynamic studies without arterial wall damage at rest (Fig. 1A and B). The diagnosis of arterial thoracic outlet syndrome (TOS) was made. The patient underwent resection of his right first rib via the supraclavicular approach. He did well and was discharged from the hospital with no complication.

Arterial TOS is a rare cause of shoulder pain and RP due to compression of the subclavian artery within the thoracic outlet. It is the least common form of TOS, accounting for <1% of overall TOS cases. However, arterial TOS is potentially dangerous, as it may lead to acute onset of upper limb ischaemia and intimal damage/aneurysmal degeneration of the subclavian artery related to chronic compression. Knowledge of arterial TOS is crucial, resulting in both prompt diagnosis and management.

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