Treatment with prednisolone and tacrolimus versus prednisolone and cyclosporin A for polymyositis/dermatomyositis-associated interstitial lung disease: a randomized, open-label trial

Treatment with prednisolone and tacrolimus versus prednisolone and cyclosporin A for polymyositis/dermatomyositis-associated interstitial lung disease: a randomized, open-label trial

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The authors have nothing to disclose.

Conflict of Interest Statement

The authors of this manuscript declare no conflicts of interest.

Summary at a Glance

This is the first prospective trial to compare the efficacy of two different regimens, prednisolone (PSL) plus tacrolimus and PSL plus cyclosporine A, in patients with PM/DM/CADM-ILD. PSL plus tacrolimus was more likely to be associated with a higher short-term PFS rate compared with PSL plus cyclosporine A.

Abbreviation list

AEs, adverse events;

ARS, anti-aminoacyl tRNA synthetase;

CADM, amyopathic dermatomyositis;

CK, creatine kinase;

CNIs, calcineurin inhibitors;

CsA, cyclosporin A;

DM, dermatomyositis;

GCs, glucocorticoids;

HRCT, high-resolution computed tomography;

ILD, interstitial lung disease;

IVCY, intravenous cyclophosphamide;

IVIG, intravenous immunoglobulins;

MSA, myositis-specific antibody;

MDA5, melanoma differentiation-associated gene 5;

OS, overall survival;

PaO_2, arterial oxygen tension;

PFS, progression-free survival;

PM, polymyositis;

PSL, prednisolone;

SpO_2, oxygen saturation;

TAC, tacrolimus;

Data sharing statements

Will individual participant data be available? Yes.

What data in particular will be shared? Individual participant data that underlie the results reported in this article after deidentification (text, tables and figures).

What other documents will be available? Study protocol.

When will data be available? Beginning 9 months and ending 36 months following article publication.

With whom? Researches who provide a methodologically sound proposal.

For what types of analyses? To achieve aims in the approved proposal.

By what mechanism will data be made available? Proposal may be submitted up to 36 months following article publication.

ABSTRACT

Background and Objective

The efficacy of combination therapy with corticosteroids and calcineurin inhibitors (CNIs), tacrolimus (TAC) and cyclosporin A (CsA), for polymyositis/dermatomyositis-associated interstitial lung diseases (PM/DM-ILD) has been described retrospectively. However, it remains unknown which CNIs treatment regimens, TAC or CsA regimens, are more effective as initial treatments for patients with PM/DM-ILD.

Methods

We conducted a prospective multicenter, open-label, randomized, 52-week phase 2 trial. Patients with PM/DM-ILD were randomly allocated to receive prednisolone (PSL) plus TAC (TAC group) or PSL plus CsA (CsA group). The primary endpoint was progression-free survival (PFS) rate in the intention-to-treat population at 52 weeks. The secondary endpoints were overall survival (OS) rate at 52 weeks, changes in pulmonary function tests from baseline to 52 weeks, and adverse events (AEs).

Results

Fifty-eight patients were randomly assigned to the TAC group (n = 30) and the CsA group (n = 28). The PFS rates at 52 weeks were 87% in the TAC group and 71% in the CsA group (p = 0.16). The OS rates at 52 weeks were 97% in the TAC group and 93% in the CsA group (p = 0.50). The %FVC at 52 weeks in the per protocol populations significantly increased in both groups. None of the patients discontinued the treatment due to AEs.

Conclusions

PSL plus TAC treatment was more likely to be associated with a higher short-term PFS rate compared with PSL plus CsA treatment. Further studies must be conducted to evaluate the long-term efficacy and safety of such treatment.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases characterized by muscular involvement and extramuscular manifestations, including those in the skin and lungs. Polymyositis (PM) and dermatomyositis (DM) are the two major subtypes of IIMs[1], and clinically amyopathic dermatomyositis (CADM) is defined as the presence of a typical skin rash of classic DM with minimal or no features of muscular manifestations[2,3]. Patients with PM, DM, or CADM often present with interstitial lung disease (ILD), which is the most severe extramuscular involvement with high morbidity and mortality[4-7]. Therefore, providing optimal treatments is crucial in the management of patients with PM/DM/CADM-associated ILD (PM/DM/CADM-ILD).

Clinical evidence from nonrandomized observational studies that supports the use of optimal therapies for patients with PM/DM/CADM-ILD is generally limited. Glucocorticoids (GCs) or GCs plus immunosuppressants have been considered as the cornerstone of treatments for PM/DM/CADM-ILD[4,5,7,8]. Cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab have been used in combination with corticosteroid for the treatment of PM/DM/CADM-ILD[8-11], however, most reports are retrospective analyses, and no prospective comparative trials have evaluated the therapeutic efficacy. Recently, several retrospective studies have shown the efficacy of calcineurin inhibitors (CNIs), tacrolimus (TAC), and cyclosporin A (CsA), even in severe forms of PM/DM/CADM-ILD[12-18]. Early intervention with CsA plus GCs has been found to improve the prognosis of DM/CADM-ILD[13,16,19]. The administration of TAC was effective in patients with PM/DM/CADM-ILD, even in those who were resistant to cyclophosphamide or CsA regimens[12,15,18]. These results indicated that treatments with GCs plus CNIs are promising for the management of PM/DM/CADM-ILD; however, it remains unknown which CNIs treatment regimens, TAC or CsA regimens, are more effective for patients with PM/DM/CADM-ILD.

In the present study, we conducted a prospective, multicenter, open-label, randomized trial to compare the efficacy between treatments with prednisolone (PSL) plus TAC and PSL plus CsA in patients with PM/DM/CADM-ILD.

METHODS

Study design and participants

This study was a prospective, stratified-block randomized, phase 2, open-label, parallel group, 52-week trial conducted at 12 medical centers in Japan. The patients aged 18 or older with PM/DM/CADM-ILD were recruited from November 2014 to March 2018. PM and DM were diagnosed according to the Bohan and Peter criteria[1]. CADM was diagnosed according to the presence of characteristic skin rashes of DM, and absence of clinical evidence of muscular disorders along with minimal or no increase in serum creatine kinase (CK) level[6,20,21]. ILD was diagnosed based on the presence of abnormalities on high-resolution computed tomography (HRCT) scan.

This study was performed in accordance with the Declaration of Helsinki and the principles of good clinical practice. All patients provided a written informed consent before participating in the study. The study protocol was approved by the Institutional Review Board of Hamamatsu University School of Medicine (approval number: 14-071) and each participating institution. This study was registered in the UMIN Clinical Trials Registry (UMIN-CTR) system (https://www.umin.ac.jp/ctr/), ID: UMIN000015469.

Full details of the METHODS are available in the online supplement.

Randomization and Masking

Eligible patients were randomly assigned in a 1:1 ratio to receive treatment with either PSL plus TAC (TAC group) or PSL plus CsA (CsA group). Patients were randomly assigned to groups using a computer-generated allocation table stratified by diagnosis of PM, DM or CADM.

Treatments

The patients received treatment with either PSL plus TAC or PSL plus CsA. All patients received oral PSL at an initial dose of 0.6–1 mg/kg/day. Intravenous methylprednisolone pulse therapy (1 g/day for 3 days) was allowed prior to the administration of oral PSL at the discretion of treating physicians. After 4 weeks of initial treatment, PSL was tapered by approximately 10%–20% every 2–4 weeks based on the discretion of the attending physicians. TAC was administered orally at an initial dose of 0.075 mg/kg/day and was adjusted over time to maintain a whole-blood trough level of 5–10 ng/mL. CsA was administered orally at an initial dose of 3 mg/kg/day and was adjusted over time to maintain a whole-blood trough level of 100–150 ng/mL.

Outcomes

The primary outcome was progression-free survival (PFS) rate in the intention-to-treat population at 52 weeks. Disease progression was defined as deterioration of ILD and/or IIM-related disorders (e.g., muscles or skin involvement) that required additional treatments. ILD deterioration was assessed according to the occurrence of two or more of the following during the follow-up period: (1) symptomatic exacerbation (e.g., dyspnea upon exertion), (2) an increase in opacity on chest radiography or chest HRCT scan, and (3) >10% decrease in %FVC or >10 mmHg decrease in PaO_2. The secondary outcome was overall survival (OS) rate in the intention-to-treat population at 52 weeks. Changes in pulmonary function tests (%FVC and %DLCO) from baseline to 52 weeks were evaluated in per protocol populations. Adverse events (AEs) in both treatment groups were assessed based on the Common Terminology Criteria for Adverse Event version 4.0. with slight modifications.

Statistical analysis

We calculated the sample size based on the randomized phase 2 screening trial design[22], with a two-sided α value of 0.20 and a power of 80% to determine the superior treatment group, with consideration of the rarity of the diseases (wherein $p < 0.20$ indicates a positive trial). Using a phase 2 screening design, the α level was set higher than 0.05, and this indicated that if the phase 2 trial is positive (p value < 0.2), such positive result is not usually considered definitive without a phase 3 trial. The sample size was estimated at 25 participants each arm, assuming that the expected difference in the 52-week PFS rate between the two treatment groups is 30%, which was based on the former study about TAC treatment in PM/DM-ILD[15].

We used the chi-square test, Fisher's exact test, the Mann-Whitney U test and the Wilcoxon signed-rank test for statistical analyses. The cumulative PFS and OS rates were assessed using the Kaplan–Meier method. The log-rank test was used to compare the PFS and OS rates between the patient groups. A *p*-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the participants

Sixty patients were screened, and 58 patients were found to be eligible and were randomly assigned to the TAC group (n = 30) and the CsA group (n = 28) (Figure 1). The baseline characteristics of the patients were equally distributed between the treatment groups (Table 1). The %FVC and %DLCO were decreased at baseline in both groups.

PFS and OS

The PFS rate at 52 weeks was relatively higher in the TAC group than in the CsA group (87% vs 71%; p = 0.16) (Figure 2A). The p value of the comparison between the TAC and CsA groups was within the prespecified two-sided α value of 0.20. Four patients in the TAC group had disease progression (n = 2, ILD deterioration; n = 2, deterioration of muscle involvement) during the study period and received additional treatments (e.g., methylprednisolone pulse therapy, increased dose of PSL, intravenous cyclophosphamide [IVCY], mycophenolate mofetil,

and intravenous immunoglobulins [IVIG]). The condition of three patients improved with additional treatments. However, a patient with ILD deterioration died of respiratory failure due to ILD progression. In the CsA group, eight patients had disease progression (n = 6, ILD deterioration; n = 2, deterioration of skin and muscle involvement) and received additional treatments. The condition improved with additional treatments in six of eight patients. Two of the patients died of respiratory failure due to ILD progression. The OS rates at 52 weeks were 97% in the TAC group and 93% in the CsA group (p = 0.50, Figure 2B). All three fatal cases were positive for anti-MDA5 antibody.

The subgroup analyses of PFS rates at 52 weeks based on myositis-specific antibody (MSA) status were performed. In patients who were positive for anti-ARS antibody, the PFS rates were 93% in the TAC group and 93% in the CsA group (Figure S1A). None of the patients who were positive for anti-ARS antibody died during the study period. In patients who were positive for anti-MDA5 antibody, the PFS rates were 63% in the TAC group and 40% in the CsA group (Figure S1B). The OS rates at 52 weeks in patients who were positive for anti-MDA5 antibody were 88% in the TAC group and 80% in the CsA group (Figure S1C).

Other secondary outcomes

In per protocol population analysis, the %FVC significantly increased at 4–52 weeks from baseline in both treatment groups (Figure 3A). The %DLCO gradually improved in both treatment groups (Figure 3B). No differences were observed in the change in %FVC and %DLCO at 52 weeks from baseline between the two groups (Table 2).

Treatments and AEs

The mean initial doses of PSL were similar between both treatment groups (40.2mg/day in TAC group, 43.6mg/day in CsA group), and PSL was gradually tapered during the study period. Intravenous methylprednisolone pulse therapy was provided prior to the administration of oral PSL in seven (23.3%) patients from the TAC group and nine (32.1%) from the CsA group.

Whole-blood TAC trough levels and CsA levels were maintained within the target ranges during the study period. The AEs are listed in Table 3. Infection and renal dysfunction were major AEs in both treatment groups. Most patients with AEs in both treatment groups tolerated the drugs without discontinuation. None of the patients died due to severe AEs.

DISCUSSION

This study first conducted a prospective comparison of the efficacy of two different therapeutic regimens, including GCs plus immunosuppressants, PSL plus TAC, and PSL plus CsA, in patients with PM/DM/CADM-ILD. The present study primarily showed that PSL plus TAC treatment was more likely to be associated with a higher short-term PFS rate compared with PSL plus CsA treatment with tolerable safety profiles.

The present study showed that combination treatment with PSL and TAC may achieve a better PFS rate at 52 weeks (87%) than PSL and CsA (71%). Several cohort studies have retrospectively reported the efficacy of TAC regimen in patients with PM/DM and PM/DM-ILD, even in those who are refractory to conventional treatment[12,15,17,18,23]. Kurita et al. have shown that the addition of TAC to conventional treatment (corticosteroid alone or corticosteroid plus other immunosuppressants except TAC) significantly improved event-free and disease-free survival in patients with PM/DM-ILD[15]. Sharma et al. have assessed a cohort from the USA and reported that the condition of 72% of the patients with myositis-associated ILD who were not successfully treated with conventional therapy improved after receiving TAC[18]. Recently, Takada et al. have performed a single-arm prospective clinical trial to evaluate the efficacy of combination treatment with GCs and TAC in patients with PM/DM-ILD. Results have shown that the treatment regimen may be effective in improving short-term mortality and PFS (88% of the 52-week survival rate and 76.4% of the 52-week PFS rate)[24], and such finding was consistent with that of the current study. In addition, this phase 2 trial suggested that GCs plus TAC treatment may be superior to GCs plus CsA treatment in achieving PFS in patients with PM/DM-

ILD; however, larger controlled studies are needed to provide definitive evidence for the efficacy of treatment with GCs and TAC.

The importance of assessing serum MSA status, particularly anti-MDA5 antibody and anti-ARS antibody, for predicting clinical phenotype and prognosis has recently been recognized in the management of myositis-associated ILD[21,25-31]. Anti-MDA5 antibody was found in about 30% of patients with PM/DM-ILD[28,29], which was associated with a high incidence of the acute form of ILD with a poor prognosis. By contrast, patients with anti-ARS antibody-positive PM/DM-ILD often have a better response to GC treatments and favorable prognosis[28,32,33]. In this prospective study, 18 (31%) of 58 patients were positive for anti-MDA5 antibody and 50% for anti-ARS antibody. The PFS rates were better in the patients with anti-ARS antibody-positive (93% in the TAC group and 93% in the CsA group) than in those with anti-MDA5 antibody-positive (63 % in the TAC group and 40% in the CsA group), indicating that patients with anti-MDA5 antibody-positive were more resistant to initial immunosuppressive therapy, which was consistent with previous retrospective studies[28,34]. To investigate optimal treatments based on MSA status, especially positive/negative for anti-MDA5 antibody, are required in future studies.

The standard treatments for patients with anti-MDA5 antibody-positive DM/CADM-ILD have not been established yet. Recently, Tsuji et al. have conducted a single-arm clinical trial to evaluate the efficacy and safety of the combined immunosuppressive regimen with GCs, TAC, and IVCY in patients with anti-MDA5 antibody-positive DM/CADM-ILD. Moreover, they have shown that the 12-month survival rates improved in the immunosuppressive regimen group (85%) compared to the historical control group treated with conventional step-up treatment (GC, immunosuppressant). In terms of survival rate, the present study showed that the OS rate at 52 weeks in patients positive for anti-MDA5 antibody in the TAC group was 88%, which was nearly identical to that of patients who received the combined immunosuppressive regimen with GCs, TAC, and IVCY[35]. Although the number of participants in this study was relatively small, these findings indicate that the co-administration of GCs and TAC was a promising regimen for patients with anti-MDA5 antibody-positive DM/CADM-ILD. Disease activity and prognostic

factors (e.g., rapidly progressive ILD, low PaO_2 level, and high serum ferritin level)[30,36,37] should be considered to identify better initial therapies for patients with anti-MDA5 antibody-positive DM/CADM-ILD.

Patients with PM/DM/CADM-ILD can exhibit a variety of HRCT patterns and findings, including non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), NSIP with OP[28,38]. In patients with positive for anti-ARS antibody, the NSIP and NSIP with OP patterns are frequently observed[28]. In contrast, the lower consolidation and ground-glass attenuation are often detected in patients with positive for anti-MDA5 antibody, which is one of the predictive factors for poor outcome in PM/DM/CADM-ILD[39]. In this study, HRCT patterns and findings of the enrolled patients were not evaluated; however, these factors could affect the response to treatments and prognosis.

The present study had several limitations. First, the sample size was determined based on the randomized phase 2 screening trial design[22], with a two-sided α value of 0.20 and a power of 80%, considering the rarity of the diseases ($p < 0.20$ indicates a positive trial). Because the level was set higher than 0.05, a positive result is not usually considered definitive without further trials. Second, the subgroup analyses based on MSA status could not be applied with statistical significance because the sample size was relatively small. Since the responses to treatments differed in terms of MSA status, optimal treatments will be validated based on MSA status. Third, duration of ILD and HRCT patterns may be associated with the response of treatments. We categorized onset of ILD into two types, acute/subacute and chronic ILD, but did not evaluate detailed characterization of ILD.

In summary, this prospective phase 2 trial has shown that combination treatment with PSL and TAC may achieve a higher short-term PFS rate than PSL and CsA with tolerable safety profiles in patients with PM/DM-ILD. Larger prospective trials will be needed to validate the efficacy and safety of this regimen. Importantly, therapeutic strategy based on MSA status (e.g. anti-ARS antibody-positive or anti-MDA5 antibody-positive) should be investigated in future studies.

Authorship list

T. F.: conception and design of the work, acquisition , analysis and interpretation of data, and manuscript writing.. Y. K., Y. K., T. A., H. K., Y. S., M. M., H. M., K. Y., N. K., M. T., S. I., H. Y., Y. S., M. K., K. F., N. E.: acquisition and analysis of data. K.M.: acquisition and analysis of data, statistical analysis. H. H, Y. N., N. I.: conception and design of the work, analysis and interpretation of data. T.S.: conception and design of the work, interpretation of data, and manuscript writing. All authors reviewed and approved the manuscript.

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Figure legends

Figure 1. Trial profile

Sixty patients were screened, and 58 were found to be eligible and were randomly assigned to the TAC group (n = 30) and CsA group (n = 28)

Figure 2. Kaplan–Meier curves of the study outcomes used for comparison between the TAC and CsA groups

(A) The progression-free survival rates at 52 weeks were 87% in the TAC group and 71% in the CsA group (p = 0.16). (B) The overall survival rates at 52 weeks were 97% in the TAC group and 93% in the CsA group (p = 0.50)

Figure 3. Changes in pulmonary function test

(A) %FVC significantly increased at 4–52 weeks from baseline in both treatment groups.

(B) %DLCO gradually improved in both treatment groups.

Points and bars show the mean and SD, respectively.

FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; SD, standard deviation

* $p < 0.01$, vs 0 week in the TAC group; † $p < 0.01$, vs 0 week in the CsA group.

Table 1. Baseline characteristics of the patients

	TAC group n = 30	CsA group n = 28	P value
Median age, years	61.6 (11.0)	59.2 (13.0)	0.45
Sex, female	19 (63)	22 (79)	0.25
Smoking history, never	24 (80)	24 (88)	0.73
IIM			0.58
PM	6 (20)	4 (14)	
DM	10 (33)	13 (47)	
CADM	14 (47)	11 (39)	
ILD form			0.18
Acute/subacute	16 (53)	20 (71)	
Chronic	14 (47)	8 (29)	
Clinical features			
Dyspnea on exertion	24 (80)	21 (75)	0.76
Fine crackles	28 (91)	25 (89)	0.67
MSA			
Anti-ARS antibody, positive	15 (50)	14 (50)	1.00
Anti-MDA5 antibody, positive	8 (27)	10 (36)	0.57
Laboratory data			
Ferritin level, ng/mL	476 (806)	255 (265)	0.30
CPK level, IU/L	1283 (2824)	633 (1697)	0.69
Aldolase level, U/L	16.6 (29.8)	18.2 (44.7)	0.66
KL-6 level, U/mL	1265 (917)	1177 (1189)	0.35
SP-D level, ng/mL	200 (230)	249 (290)	0.46
Pulmonary function			
%FVC, %	74.8 (20.4)	76.4 (17.8)	0.59
%DLCO, %	64.1 (21.6)	68.5 (22.4)	0.31
PaO_2, Torr	79.4 (11.7)	77.3 (17.0)	0.50

Data were expressed as mean (SD) or number (percentage).

IIM, idiopathic inflammatory myopathies; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease; MSA, myositis-specific antibodies; ARS, aminoacyl tRNA synthetase; MDA5, melanoma differentiation-associated gene 5; CPK, creatine phosphokinase; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; PaO_2, arterial oxygen tension

Table 2. Mean change in the study outcomes from baseline to 52 weeks

	TAC group n = 26	CsA group n = 20	Statistical analysis
FVC, % of the predicted value	16.9 (12.1)	19.7 (14.5)	0.64
DLCO, % of the predicted value	14.7 (23.3)	9.7 (23.3)	0.39

Data were expressed as mean (SD).

FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; NS, not significant

Table 3. Adverse events during the study period

	TAC group n = 30	CsA group n = 28	p value
Infection	7 (23.3)	3 (10.7)	0.30
Bacterial infection	2	0	
Cytomegalovirus infection	2	3	
Herpes zoster	1	0	
Pulmonary aspergillosis	1	0	
Tuberculosis	1	0	
Renal dysfunction *	4 (13.3)	7 (25.0)	0.16
Liver dysfunction **	2 (6.7)	2 (7.1)	
Hyperglycemia	4 (13.3)	0	
Pneumomediastinum	0	1	
Deep vein thrombosis	0	1	

* Renal dysfunction was defined as greater than 50% increase in creatinine level at any time point in the study from the baseline level.

** Liver dysfunction was defined as an increase in the upper limit of the normal liver enzyme values by threefold.

Figure 1.

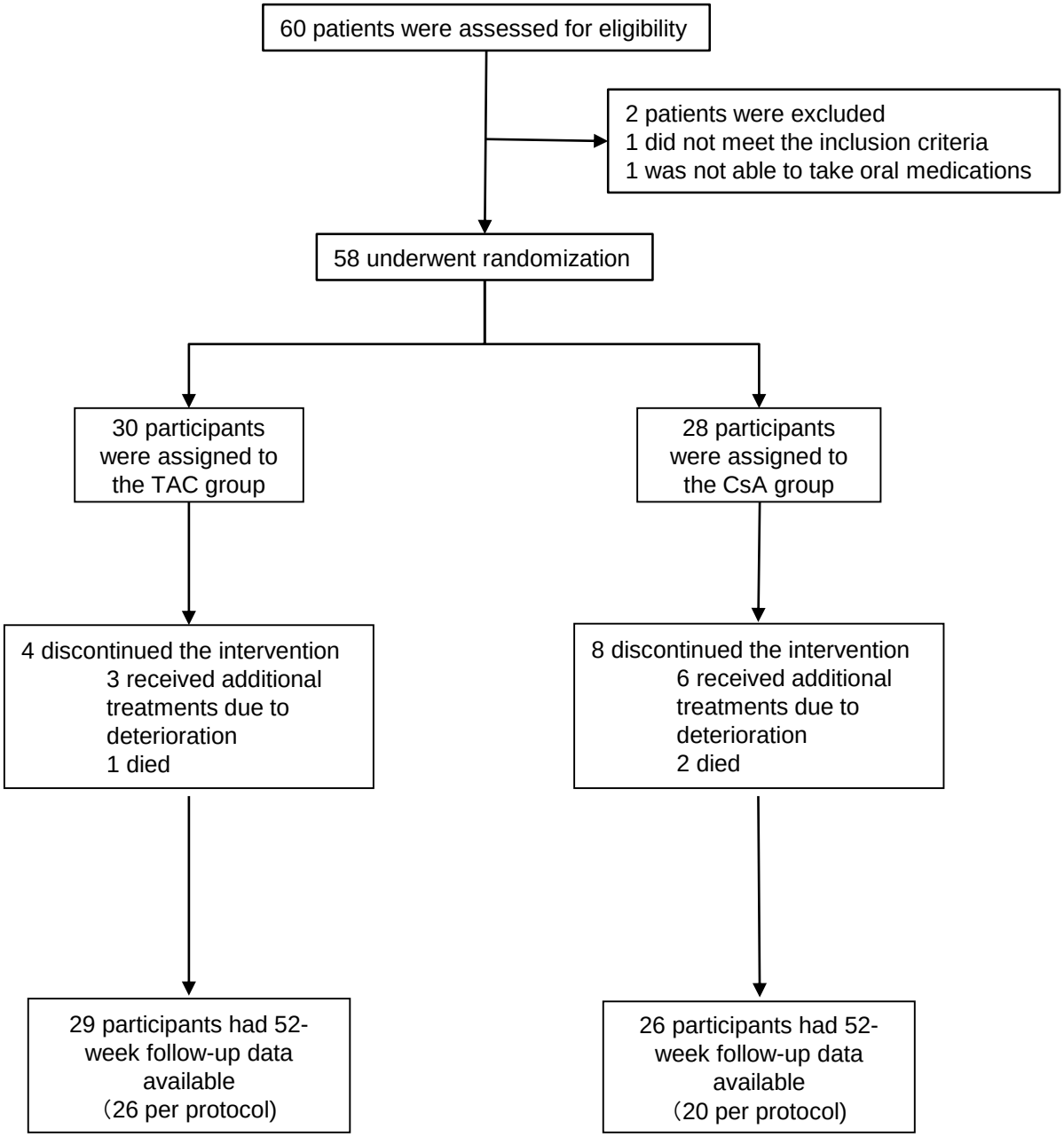
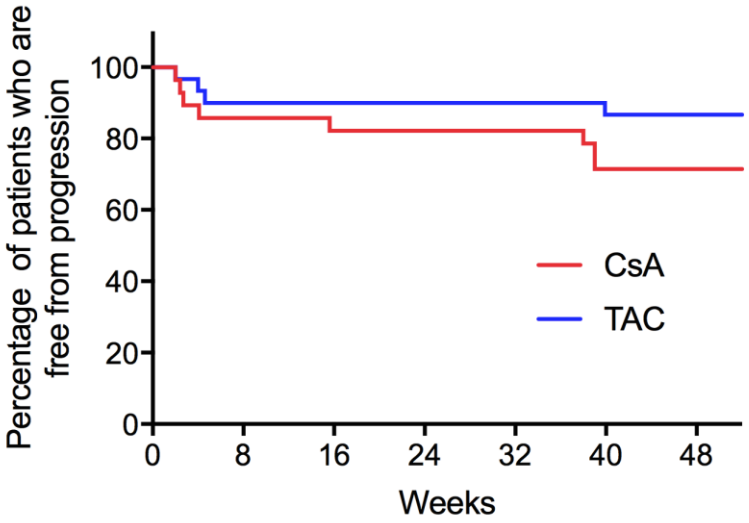

60 patients were assessed for eligibility
2 patients were excluded
1 did not meet the inclusion criteria
1 was not able to take oral medications
58 underwent randomization
30 participants were assigned to the TAC group
28 participants were assigned to the CsA group
4 discontinued the intervention
3 received additional treatments due to deterioration
1 died
8 discontinued the intervention
6 received additional treatments due to deterioration
2 died
29 participants had 52-week follow-up data available
（26 per protocol)
26 participants had 52-week follow-up data available
（20 per protocol)

Figure 2.

A.


Percentage of patients who are free from progression
100
80
60
40
20
0
0
8
16
24
32
40
48
Weeks
CsA
TAC

B.

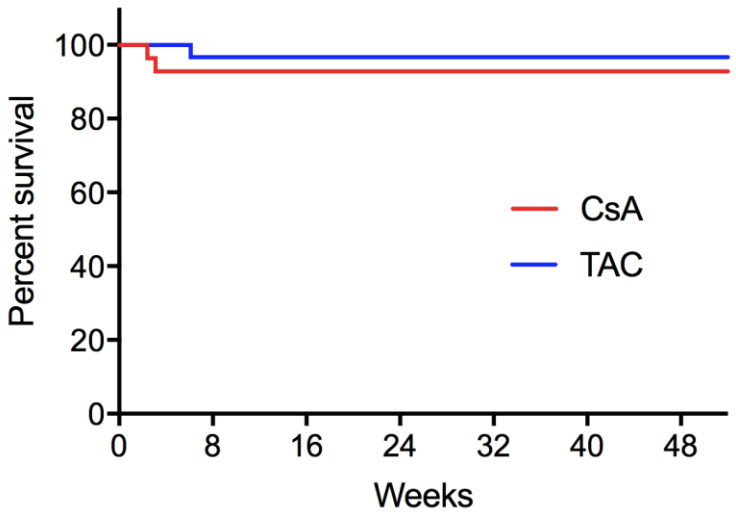
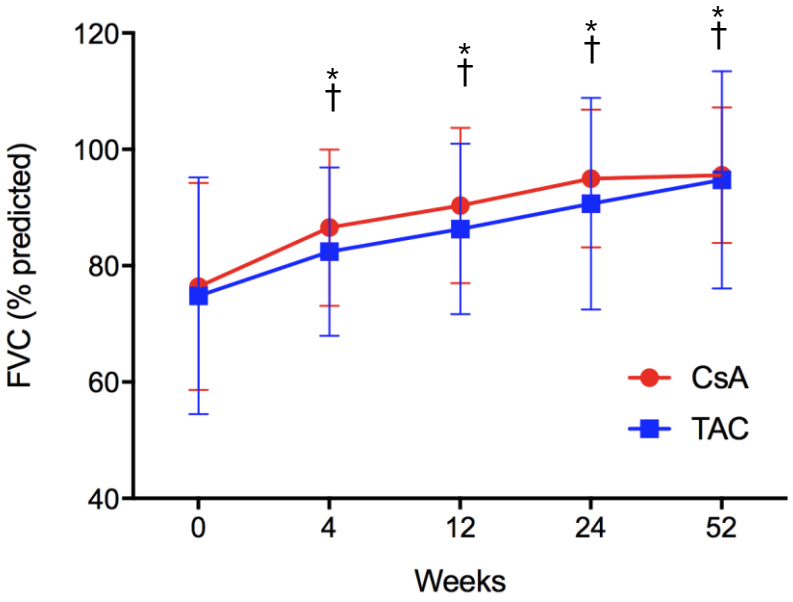
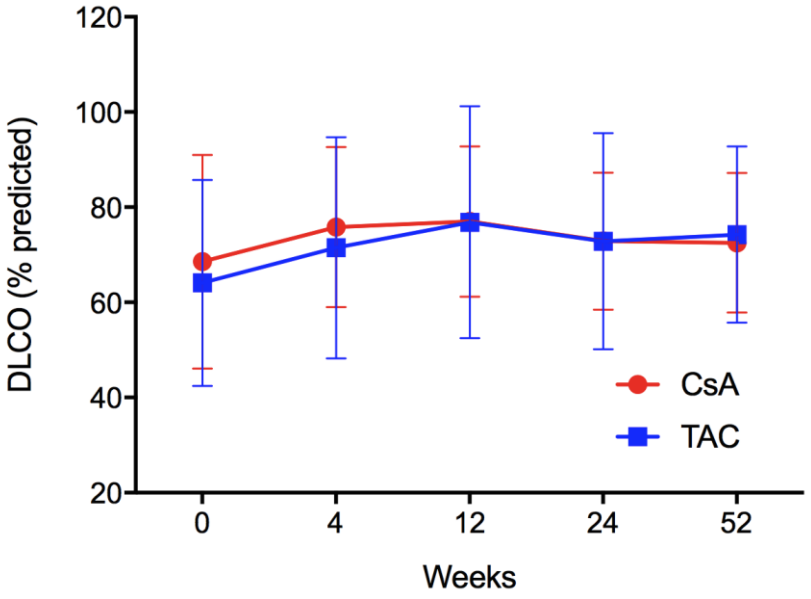

Percent survival
100
80
60
40
20
0
0
8
16
24
32
40
48
Weeks
CsA
TAC

Figure 3.

A.


120
100
80
60
40
FVC (% predicted)
*
†
*
†
*
†
*
†
CsA
TAC
0
4
12
24
52
Weeks

B.


120
100
80
60
40
20
DLCO (% predicted)
CsA
TAC
0
4
12
24
52
Weeks