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A Retrospective Analysis of Outcome in Melanoma Differentiation–Associated Gene 5–Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus

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ABSTRACT. ***Objective.*** The efficacy of tofacitinib (TOF) in the early diagnosis of melanoma differentiation–associated gene 5 (MDA5)–related interstitial lung disease (ILD) has been described. However, whether TOF exposure is associated with a reduced 1-year mortality rate remains undetermined.

Methods. Patients diagnosed with MDA5-ILD receiving TOF or tacrolimus (TAC) treatment were included. A Cox proportional hazards model, which was adjusted for age, sex, smoking history, anti-MDA5 antibody titers, and concurrent use of other steroid-sparing agents, was performed to compare all-cause mortality and to investigate the risk factors predicting 1-year mortality rates in the 2 treatment groups.

Results. During the study period, 26 patients were treated with TOF and 35 were treated with TAC. The 6-month (38.5% vs 62.9%; $P = 0.03$) and 1-year (44.0% vs 65.7%; $P = 0.03$) mortality rates in the TOF group were significantly lower than those in the TAC group. There were 13 patients diagnosed with rapidly progressive ILD (RP-ILD) in the TOF group and 22 in the TAC group. The majority of deaths occurred in patients with RP-ILD. The 6-month (76.9% vs 95.5%; $P = 0.02$) and 1-year (84.6% vs 100.0%; $P = 0.02$) mortality rates of patients with RP-ILD in the TOF group were also lower than those in the TAC group, respectively. The adjusted model showed that TOF exposure was associated with a lower risk for 1-year mortality (hazard ratio 0.44, 95% CI 0.20-0.96; $P = 0.04$). However, the incidence of adverse events (73.1% vs 74.3%; $P > 0.99$) and medication discontinuation rates (23.1% vs 14.3%; $P = 0.50$) in the TOF and TAC groups were similar, respectively.

Conclusion. Our observational study showed that TOF use might have a potential effect on improving the outcomes of MDA5-ILD. Future clinical trials are needed to assess the long-term efficacy and tolerability of TOF.

Key Indexing Terms: interstitial lung disease, MDA5, survival, tofacitinib

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous spectrum of systemic autoimmune diseases that affect multiple organs other than skeletal muscle.[1,2] Interstitial lung disease (ILD) is the most common and severe extramuscular manifestation contributing significantly to morbidity and mortality in patients with IIM.[3,4] Typically, the adult-onset IIM phenotypes encompass polymyositis (PM), dermatomyositis (DM), amyopathic DM (ADM), and antisynthetase syndrome (ASS). Advancements in the knowledge of myositis-specific autoantibodies have enabled clinicians to better understand patients with IIM with distinctive clinical phenotypes.[5] For instance, patients with ASS have similar clinical presentations, including myositis, ILD, arthritis, mechanic's hands, and Raynaud phenomenon; however, recent studies suggest that there is heterogeneity in clinical features among different patients who are positive for aminoacyl-tRNA synthetase antibodies. Patients who are positive for anti-Jo1 antibodies have more myositis and arthritis, whereas patients who are positive for anti-PL7 or anti-PL12 antibodies have a higher rate of ILD and higher mortality.[6,7] Anti–Mi-2 antibodies are associated with classic DM skin rash, good response to steroid treatment, and good prognosis.[8] In recent years, much attention has been focused on anti-melanoma differentiation–associated gene 5 (MDA5) antibodies for their close association with rapidly progressive ILD (RP-ILD), a life-threatening phenotype that is resistant to conventional therapy.[9-11]

The management of MDA5-related ILD (MDA5-ILD) is a huge challenge. High-dose glucocorticoids (GCs) and

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calcineurin inhibitors (ie, cyclosporine or tacrolimus [TAC]) in combination with cyclophosphamide has been recommended as the first choice to treat MDA5-ILD.[12] Despite aggressive therapy, the short-term mortality of MDA5-ILD was shown to be up to 50%.[13] Tofacitinib (TOF), a Janus kinase inhibitor, has exhibited an excellent response in early-stage anti-MDA5–positive ADM-related ILD (ADM-ILD) in a single-center, open-label clinical study.[14] Prior literature also reported its efficacy as a rescue option for patients with high-risk ADM-ILD refractory to conventional treatment.[13] However, to date, few studies have investigated the effects of TOF on survival in patients with MDA5-ILD. We performed this retrospective study to determine the relationship between TOF exposure and 1-year mortality in MDA5-ILD. Patients with MDA5-ILD who were seen in our center and treated with TOF were recruited. Patients treated with TAC during the study period served as a comparator control group. Moreover, we investigated the risk factors predicting mortality in patients with MDA5-ILD in 2 treatment groups.

METHODS

Subjects. We reviewed the medical records of patients diagnosed with anti-MDA5 autoantibody–positive IIM-ILD at Nanjing University Medical School Affiliated Drum Tower Hospital from October 2017 to December 2020. Patients who received a combination treatment of systemic corticosteroids and TOF or TAC for at least 6 months were identified. Switching from another immunosuppressant to TOF or adding TOF to the initial treatment was allowed if it occurred within 1 month of therapy initiation. Patients who concurrently received TOF and TAC treatment were excluded. Included patients had been diagnosed with ILD in the previous 6 months. IIMs were diagnosed according to the 2017 European Alliance of Associations for Rheumatology/American College of Rheumatology classification criteria.[15] ILD was diagnosed based on a combination of clinical manifestations, physical examination, and high-resolution computed tomography (HRCT) abnormalities according to the current guidelines.[16] RP-ILD was defined as follows: a worsening of respiratory symptoms combined with new emerging radiologic interstitial abnormalities in chest HRCT within 1 month with the exclusion of identified causes, such as acute heart failure or pulmonary embolism in the first 12 months after diagnosis.[17,18] This study was approved on March 28, 2022, by the Ethics Committee of Nanjing University Medical School Affiliated Drum Tower Hospital according to their policy (protocol number: 2022-067-02).

Clinical data. Clinical data, including demographics, laboratory examinations, radiographic findings, and treatments, were extracted from the medical records. Demographic information included age of onset, sex, and smoking history. Laboratory examinations included partial pressure of oxygen in the arterial blood (PaO_2), PaO_2/fraction of inspired oxygen (FiO_2), white blood cell (WBC) counts, neutrophil counts, neutrophil percentage, lymphocyte counts, lymphocyte percentage, red blood cell counts, hemoglobin, platelet counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin, globulin, urea nitrogen, serum creatinine, C-reactive protein (CRP), creatine kinase (CK), CK myocardial band (CK-MB) isoenzyme, ferritin, erythrocyte sedimentation rate (ESR), and D-dimer, among others. Baseline pulmonary function tests (PFTs), if available, were performed, including forced vital capacity (FVC), FVC% predicted, diffusing lung capacity for carbon monoxide (DLCO), and DLCO% predicted.

Myositis-associated antibody profiles were determined for all patients who were positive for anti-MDA5 antibodies. In our center, the following antibodies are routinely measured: anti-MDA5, anti–Mi-2α, anti–Mi-2β, anti-TIF1γ (transcriptional intermediary factor 1-γ), anti-NXP2 (nuclear matrix protein 2), anti-SAE1 (small ubiquitin-like modifier activating enzyme 1), anti-Ku, anti–PM-Scl100, anti–PM-Scl75, anti-SRP (signal recognition particle), anti-Ro52, and antisynthetase antibodies, including anti-Jo1, anti-PL7, anti-PL12, anti-EJ, and anti-OJ. The titers of anti-MDA5 antibodies were detected in immunoblotting and the results were analyzed by LineScan software (Zeiss). Gray values of 6 to 15 represented negative results, values of 16 to 50 represented weak-positive results, values of 51 to100 represented moderate-positive results, and values > 100 represented strong-positive results. Medications were recorded, including systemic corticosteroids and other immunosuppressants, such as cyclophosphamide, hydroxychloroquine, azathioprine, and *Tripterygium wilfordii*, among others.

Chest HRCTs were performed in 59 patients in the supine position at diagnosis; 2 patients underwent chest HRCT at other hospitals within 1 week before admission. All images were reviewed independently by 1 experienced radiologist and 1 pulmonary specialist. Based on the current guidelines,[16,19] HRCT appearances were mainly described as having usual interstitial pneumonia pattern, nonspecific interstitial pneumonia (NSIP) pattern, organizing pneumonia (OP) pattern, and diffuse alveolar damage pattern.

Adverse events (AEs) that occurred after 5 days of TAC or TOF treatment were recorded as therapy-related AEs; these included cytopenia, digestive tract reactions, liver and renal dysfunction, infections, and thrombosis, among others.

Follow-up data. Each patient's vital status was obtained through review of medical records and telephone follow-up. The survival time was calculated from the first HRCT indicating the diagnosis of ILD to all-cause death. Clinical outcomes, including 6-month and 1-year mortality, were recorded. Follow-ups took place until December 2021.

Statistical analysis. Statistical analysis was performed using SPSS (version 22.0; IBM Corp) and Prism (version 8.0; GraphPad Software). All analyses were 2-sided, and the level of significance was set at $P < 0.05$. Qualitative data were presented as numbers and percentages, and quantitative data were presented as means and SDs or medians and IQRs. The normality of the data was assessed by the Shapiro-Wilk test. For comparison of clinical data, the *t* test, chi-square analysis, Fisher exact test, and Mann-Whitney *U* test were conducted as appropriate. The Kaplan-Meier curve with the log-rank test was used to assess differences in survival. In this study, 2 treatment groups were compared using a Cox proportional hazards model adjusted for confounding factors (ie, time-to-event analyses). The following confounding factors were taken into account in comparisons between groups: age of onset, sex, smoking history, anti-MDA5 antibody titers, and concurrent use of other steroid-sparing agents. The Cox proportional hazards model was also performed to assess the risk factors predicting mortality in 2 treatment groups.

RESULTS

Baseline characteristics. Through the review of medical records, we identified 26 patients who received TOF treatment; 35 patients who received initial treatment with TAC during the study period served as the comparator group. The demographic and baseline clinical features are presented in Table 1. No significant differences were observed regarding age, sex, and smoking history. The mean (SD) age in the TAC group was 55.94 (1.72) years, whereas the mean age in the TOF group was 55.42 (2.20) years. In total, 15 (57.7%) patients in the TOF group and 22 (62.9%) patients in the TAC group were female. There were 4 (15.4%) and 7 (20.0%) patients who reported having a history of smoking in the TOF and TAC groups, respectively. No significant differences were observed in the baseline

Table 1. Baseline characteristics and differences between the TOF group and the TAC group.

	TOF Group, n = 26	TAC Group, n = 35	*P*
Age of onset, yrs, mean (SD)	55.42 (2.20)	55.94 (1.72)	0.85
Female sex	15 (57.7)	22 (62.9)	0.79
History of smoking	4 (15.4)	7 (20.0)	> 0.99
CADM	17 (65.4)	26 (74.3)	0.57
RP-ILD	13 (50.0)	22 (62.9)	0.60
Laboratory findings			
PaO_2, mmHg, mean (SD)[a]	77.28 (4.16)	74.28 (3.68)	0.68
PaO_2/FiO_2, mean (SD)[a]	265.77 (19.01)	277.57 (18.49)	0.66
LDH, U/L, mean (SD)[b]	354.85 (20.44)	388.62 (24.81)	0.30
CRP, mg/L, mean (SD)[a,c]	20.89 (5.17)	18.60 (4.65)	0.74
CK, U/L, mean (SD)[d]	70.62 (9.53)	74.88 (11.30)	0.77
ESR, mm/h, mean (SD)[c,e]	44.36 (5.05)	37.53 (4.04)	0.30
Ferritin level, ng/mL, median (IQR)[f,g]	1425.90 (764.00-1650.00)	1305.55 (508.63-1641.38)	0.55
D-dimer, ng/mL, median (IQR)[h]	0.64 (0.43-1.21)	0.96 (0.48-1.60)	0.19
Constitution of anti-MDA5 antibody titers			0.002
Weak-positive	16 (61.5)	9 (25.7)	
Moderate-positive	6 (23.1)	9 (25.7)	
Strong-positive	4 (15.4)	17 (48.6)	
Anti-Ro52 positivity	18 (69.2)	17 (48.6)	0.12
PFTs, mean (SD)			
FVC[i,j]	2.20 (0.35)	1.91 (0.19)	0.48
FVC, % of predicted value[i,j]	60.41 (5.60)	57.16 (4.42)	0.65
DLCO[k,l]	4.65 (0.87)	3.98 (0.49)	0.51
DLCO, % of predicted value[k,l]	59.86 (9.76)	54.55 (6.39)	0.66
HRCT findings[a]			
OP pattern	16 (61.5)	23 (69.7)	0.56
NSIP pattern	2 (7.7)	5 (15.2)	0.45
UIP pattern	0 (0)	1 (3.0)	> 0.99
DAD pattern	2 (7.7)	0 (0)	0.19
DAD/OP overlapping pattern	5 (19.2)	4 (12.1)	0.49
OP/NSIP overlapping pattern	1 (3.8)	0 (0)	0.44
Therapy, mean (SD)			
Initial GC dosage, mg/d	152.88 (19.04)	185.86 (26.05)	0.88
Maintenance dose of GCs, mg/d[m,n]	6.69 (1.49)	5.42 (1.06)	0.50
Duration of GC tapering, months	12.06 (1.74)	15.96 (2.36)	0.20
Concurrent use of other steroid-sparing agents	16 (61.5)	23 (65.7)	0.79
TAC and TOF discontinuation	6 (23.1)	5 (14.3)	0.50
6-month mortality	10 (38.5)	22 (62.9)	0.03
1-year mortality	11 (44.0)	23 (65.7)	0.03

Data are in n (%) unless otherwise indicated. [a] The TAC group had 33 participants. [b] The TAC group had 34 participants. [c] The TOF group had 25 participants. [d] The TAC group had 32 participants. [e] The TAC group had 30 participants. [f] The TOF group had 8 participants. [g] The TAC group had 10 participants. [h] The TAC group had 31 participants. [i] The TOF group had 12 participants. [j] The TAC group had 16 participants. [k] The TOF group had 9 participants. [l] The TAC group had 13 participants. [m] The TOF group had 14 participants. [n] The TAC group had 12 participants. Statistical significance was set at $P < 0.05$. CADM: clinical amyopathic dermatomyositis; CK: creatine kinase; CRP: C-reactive protein; DAD: diffuse alveolar damage; DLCO: diffusing lung capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FiO_2: fraction of inspired oxygen; FVC: forced vital capacity; GC: glucocorticoid; HRCT: high-resolution computed tomography; LDH: lactate dehydrogenase; MDA5: melanoma differentiation–associated gene 5; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PaO_2: partial pressure of oxygen in the arterial blood; PFT: pulmonary function test; Ro52: 52-kDa Ro protein; RP-ILD: rapidly progressive interstitial lung disease; TAC: tacrolimus; TOF: tofacitinib; UIP: usual interstitial pneumonia.

laboratory examinations, including PaO_2/FiO_2, LDH, CRP, CK, ferritin, and ESR, among others. Results from the baseline PFTs, including FVC, FVC% predicted, DLCO, and DLCO% predicted, also showed no differences. In total, 13 (50.0%) patients in the TOF group and 22 (62.9%) patients in the TAC group were diagnosed with RP-ILD. At treatment initiation, the constitution of anti-MDA5 antibody titers differed between the 2 groups, with more patients with weak-positive titers in the TOF group (16/26, 61.5%) than in the TAC group (9/35, 25.7%; $P = 0.002$). The number of patients with moderate- and strong-positive anti-MDA5 antibody titers in the TOF group were 6 (23.1%), and 4 (15.4%), respectively; in the TAC group these values were 9 (25.7%), and 17 (48.6%), respectively. There were 18 (69.2%) patients in the TOF group and 17 (48.6%) patients in the TAC group who were concomitantly positive for anti-Ro52 antibodies ($P = 0.12$). In both groups, the most

common HRCT finding was OP pattern (TOF group: 61.5%; TAC group: 69.7%; $P = 0.56$).

Treatment information. As seen in Table 1, there were no differences in the initial GC doses between the 2 groups ($P = 0.88$). In the TOF group, the initial GC dose was 152.88 (SD 19.04) (range 35-500) mg/d, and in the TAC group, the initial dose was 185.86 (SD 26.05, range 15-500) mg/d. The TOF dose was 5 mg once daily in 2 patients and 5 mg twice daily in 24 patients. The TAC dose was 2 mg to 4 mg administered orally daily. The concurrent use of other steroid-sparing agents showed no significant difference between groups (TOF group: 61.5%; TAC group: 65.7%; $P = 0.79$). The mean maintenance GC dose in the TOF group was 6.69 (SD 1.49) mg daily, and in the TAC group the mean dose was 5.42 (SD 1.06) mg daily ($P = 0.50$). The duration of GC tapering from initial treatment to a maintenance dosage was 12.06 (SD 1.74) months in the TOF group and 15.96 (SD 2.36) months in the TAC group ($P = 0.20$). The medication discontinuation rate as a result of AEs was 23.1% (6/26) in the TOF group and 14.3% (5/35) in the TAC group ($P = 0.50$).

Survival analysis. The mean follow-up time was 11.62 (SD 1.72, range 0.23-48.60) months. There were 23 (65.7%) deaths in TAC group, with a mean survival of 11.52 (SD 2.65, range 0.23-48.60) months, compared with 12 (46.2%) deaths in TOF group, with a mean survival of 11.76 (SD 1.95, range 0.27-28.07) months. As seen in Table 1, the 6-month all-cause mortality rate was 38.5% in the TOF group and 62.9% in the TAC group ($P = 0.03$). The 1-year mortality rate was 44.0% in the TOF group and 65.7% in the TAC group ($P = 0.03$; Figure). After adjustment for age, sex, smoking history, anti-MDA5 antibody titers, and concurrent use of other steroid-sparing agents, the Cox proportional hazards model showed that TOF exposure was associated with a lower risk of 1-year mortality (hazard ratio [HR] 0.44, 95% CI 0.20-0.96; $P = 0.04$).

We compared mortality rates among patients with RP-ILD in both treatment groups (Table 2). There were 22 patients diagnosed with RP-ILD in the TAC group and 13 in the TOF group. Patients with RP-ILD in the TOF group had higher platelet count ($P = 0.04$) and ESR levels ($P = 0.01$) than those

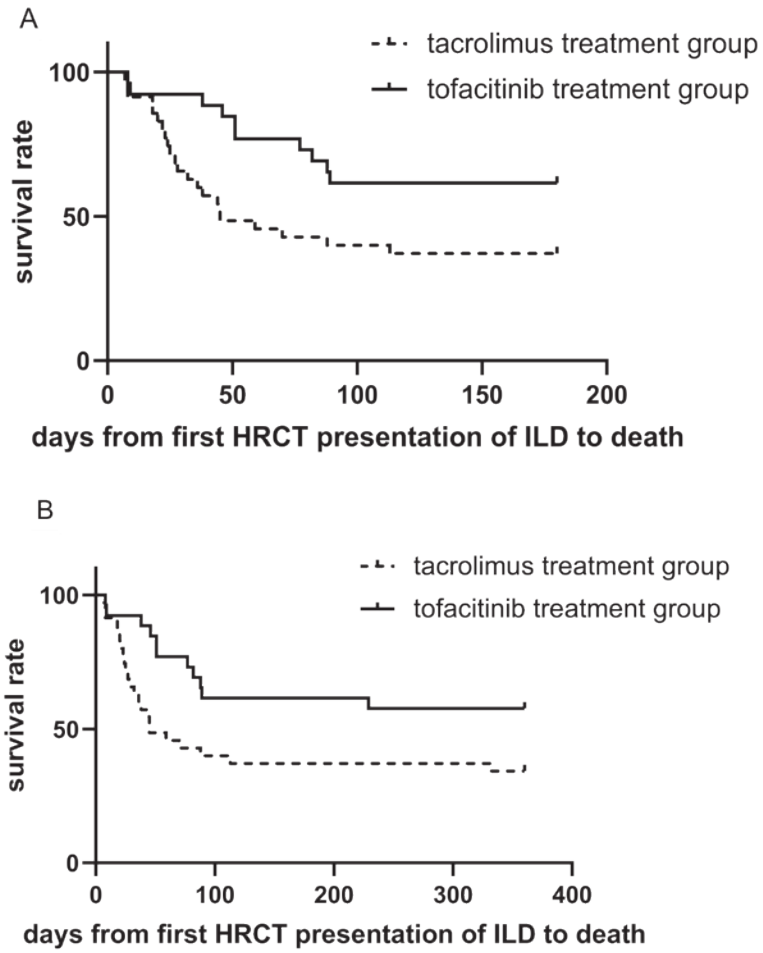

Figure. The 6-month and 1-year survival curves of patients with MDA5-ILD treated with TOF or TAC. (A) The 6-month mortality rate in the TOF group was 38.5% and in the TAC group was 62.9% (log-rank, $P = 0.03$). (B) The 1-year mortality rate in the TOF group was 44.0% and in the TAC group was 65.7% (log-rank, $P = 0.03$). Time is represented in days. HRCT: high-resolution computed tomography; ILD: interstitial lung disease; MDA5: melanoma differentiation–associated gene 5. TAC: tacrolimus; TOF: tofacitinib.

Table 2. Baseline characteristics and differences between the TOF group and the TAC group with RP-ILD.

	Tofacitinib Group, n = 13	Tacrolimus Group, n = 22	*P*
Age of onset, yrs, mean (SD)	59.23 (10.75)	60.05 (9.10)	0.82
Female sex	8 (61.5)	13 (59.1)	> 0.99
History of smoking	2 (25.4)	6 (27.3)	0.68
CADM	8 (61.5)	15 (68.2)	0.73
Laboratory findings			
PaO_2, mm Hg, median (IQR)[a]	64.00 (48.00-101.00)	70.00 (50.00-93.00)	0.94
PaO_2/FiO_2, mean (SD)[a]	202.45 (85.73)	240.13 (96.63)	0.25
PLTs, × 10^9/L, mean (SD)	247.85 (84.61)	185.18 (79.02)	0.04
LDH, U/L, mean (SD)	400.92 (118.49)	416.95 (105.42)	0.69
CRP, m/L, median (IQR)	20.30 (1.60-92.00)	9.65 (2.10-107.90)	0.20
CK, U/L, median (IQR)[b]	57.00 (20.00-169.00)	62.00 (20.00-346.00)	0.99
ESR, mm/h, median (IQR)[c]	64.00 (23.00-95.00)	30.00 (8.00-80.00)	0.01
Ferritin level, ng/mL, median (IQR)[d]	1421.95 (354.00-1650.00)	1464.50 (617.70-1650.00)	0.95
D-dimer, ng/mL, median (IQR)	0.89 (0.25-2.18)	1.29 (0.42-8.15)	0.21
Constitution of anti-MDA5 antibody titers			0.01
Weak-positive	8 (61.5)	6 (27.3)	
Moderate-positive	4 (30.8)	4 (18.2)	
Strong-positive	1 (7.7)	12 (54.6)	
Anti-Ro52 positivity	9 (69.2)	11 (50.0)	0.31
PFTs, mean (SD)			
FVC[e]	1.85 (0.94)	1.99 (0.83)	0.82
FVC, % predicted[e]	52.68 (14.89)	56.73 (20.07)	0.72
DLCO[f]	6.22 (1.51)	3.61 (1.50)	0.18
DLCO, % predicted[f]	80.40 (21.35)	51.60 (20.37)	0.26
HRCT findings			
OP pattern	5 (38.5)	14 (70.0)	0.15
NSIP pattern	1 (7.7)	1 (5.0)	> 0.99
UIP pattern	0 (0)	1 (5.0)	> 0.99
DAD pattern	2 (15.4)	0 (0)	0.15
DAD/OP overlapping pattern	4 (30.8)	4 (20.0)	0.68
OP/NSIP overlapping pattern	1 (7.7)	0 (0)	0.39
Therapy: initial GC dosage, mg/d, median (IQR)	160.00 (40.00-500.00)	160.00 (20.00-500.00)	0.42
Concurrent use of other steroid-sparing agents	8 (61.5)	14 (63.6)	> 0.99
TAC and TOF discontinuation	2 (15.4)	3 (13.6)	> 0.99
6-month mortality	10 (76.9)	21 (95.5)	0.02
1-year mortality	11 (84.6)	22 (100)	0.02

Data are in n (%) unless otherwise indicated. [a] The tacrolimus group had 21 participants. [b] The tacrolimus group had 20 participants. [c] The tacrolimus group had 19 participants. [d] The tofacitinib group had 6 participants and the tacrolimus group had 8 participants. [e] The tofacitinib group had 4 participants and the tacrolimus group had 6 participants. [f] The tofacitinib group had 2 participants and the tacrolimus group had 5 participants. Statistical significance was set at $P < 0.05$. CADM: clinical amyopathic dermatomyositis; CK: creatine kinase; CRP: C-reactive protein; DAD: diffuse alveolar damage; DLCO: diffusing lung capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FiO_2: fraction of inspired oxygen; FVC: forced vital capacity; GC: glucocorticoid; HRCT: high-resolution computed tomography; LDH: lactate dehydrogenase; MDA5: melanoma differentiation–associated gene 5; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PaO_2: partial pressure of oxygen in the arterial blood; PFT: pulmonary function test; PLT: platelet; Ro52: 52-kDa Ro protein; RP-ILD: rapidly progressive interstitial lung disease; TAC: tacrolimus; TOF: tofacitinib; UIP: usual interstitial pneumonia.

in the TAC group. The proportion of patients with weak-positive titers of anti-MDA5 antibodies (8/13, 61.5%) was higher in the TOF group than in the TAC group (6/22, 27.3%; $P = 0.01$). No differences were found in other baseline laboratory examinations, PFTs, initial GC dosages, and concurrent use of other steroid-sparing agents. The 6-month all-cause mortality of patients with RP-ILD in the TOF group (10/13, 76.9%) was significantly reduced compared to that in the TAC group (21/22, 95.5%; $P = 0.02$). The 1-year all-cause mortality of patients with RP-ILD in the TOF group (11/13, 84.6%) was also significantly reduced compared to that in the TAC group (22/22, 100%; $P = 0.02$). After adjusting for confounding factors, the Cox proportional hazards model showed that TOF exposure was associated with a lower risk of 1-year mortality (HR 0.25, 95% CI 0.07-0.91; $P = 0.04$).

Comparison between survivors and nonsurvivors in the 2 treatment groups. We further performed subgroup analysis between survivors and nonsurvivors in the 2 treatment groups (Supplementary Tables S1-2, available from the authors upon request). In the TOF group, the nonsurvivors were older than the survivors ($P = 0.04$). PaO_2/FiO_2 ($P = 0.003$), lymphocyte percentage ($P = 0.04$), and albumin ($P = 0.049$) were significantly lower in the nonsurvivors group than in the survivors group. WBCs

(P = 0.02), neutrophils (P = 0.02), platelets (P = 0.01), CRP level (P = 0.02), and ESR (P = 0.001) were significantly higher in nonsurvivors than in survivors. All of the nonsurvivors had RP-ILD. There were no significant differences in anti-MDA5 antibody titers (P > 0.99) and concurrent use of other steroid-sparing agents (nonsurvivors: 8/12, 66.7%; survivors: 8/14, 57.1%) between the 2 groups (P = 0.70). In the TAC group, compared to survivors, nonsurvivors were older (P = 0.001); had higher neutrophil percentage (P = 0.01), ALT (P = 0.02), AST (P = 0.03), CK-MB (P = 0.006), D-dimer (P = 0.01), and ferritin (P = 0.04) levels at baseline; and had reduced PaO_2 (P = 0.049), PaO_2/FiO_2 (P = 0.001), lymphocyte percentage (P = 0.003), lymphocyte (P = 0.001), albumin (P < 0.001), and globulin (P = 0.04) levels. NSIP was more common in survivors (33.3%) than in nonsurvivors (4.8%; P = 0.047). In total, 95.7% (22/23) of nonsurvivors had RP-ILD. There were no significant differences in anti-MDA5 antibody titers (P = 0.42) and concurrent use of other steroid-sparing agents (nonsurvivors: 15/23, 65.2%; survivors: 8/12, 66.7%; P > 0.99) between the 2 groups.

Among nonsurvivors in the TOF group, the mean survival time was 2.18 (SD 0.57, range 0.27-12.73) months. Univariate analysis showed that the following were predictors of mortality: older age (HR 1.07, 95% CI 1.01-1.04), decreased PaO_2/FiO_2 ratio (HR 0.99, 95% CI 0.98-0.996), increased WBC count (HR 1.28, 95% CI 1.06-1.54), increased neutrophils (HR 1.31, 95% CI 1.07-1.60), decreased lymphocyte percentage (HR 0.89, 95% CI 0.80-0.99), increased CRP level (HR 1.03, 95% CI 1.01-1.05), increased ESR (HR 1.05, 95% CI 1.02-1.07), and presence of RP-ILD (HR 184.49, 95% CI 1.07-31,961.15). Among nonsurvivors in the TAC group, the mean survival time was 1.67 (SD 0.48, range 0.23-11.03) months. Univariate analysis showed that the following were predictors of mortality: older age (HR 1.04, 95% CI 1.01-1.07), decreased PaO_2/FiO_2 ratio (HR 0.99, 95% CI 0.99-0.997), decreased lymphocyte percentage (HR 0.88, 95% CI 0.81-0.95), decreased albumin (HR 0.80, 95% CI 0.71-0.91), increased CK-MB (HR 1.04, 95% CI 1.001-1.08), increased ferritin (HR 1.01, 95% CI 1.001-1.01), and presence of RP-ILD (HR 41.13, 95% CI 5.24-322.56). As a result of the large number of covariates and the small sample size, multivariate analysis could not be performed for both groups (data not shown).

AEs. There was no significant difference in the overall incidence of AEs between the 2 groups (TOF group: 19/26, 73.1% and TAC group: 26/35, 74.3%, P > 0.99). The observed AEs included liver and kidney dysfunction, lymphocytopenia, anemia, diarrhea, reactivation of cytomegalovirus (CMV) and Epstein-Barr virus (EBV), herpes zoster, sepsis, pulmonary fungal infections, pulmonary bacterial infections, intermuscular vein thrombosis, and pulmonary thrombosis. The most common AE was liver damage in both groups (TOF group: 16/26, 61.5% and TAC group: 23/35, 65.7%).

The detailed therapy-related infections are described in Table 3 and Table 4. In the TAC group, evidence of infection was detected in 11 (31.4%) patients. The blood 1,3-β-D glucan test (referred to as the G test; >151.5 pg/mL) was positive in 5 patients (patients 1, 2, 4, 7, and 8). Among these 5 patients, 3 had new emerging HRCT abnormalities and 1 (patient 7) was positive for blood galactomannan antigen (referred to as the GM test; > 0.5). Sputum culture showed *Candida* in 2 patients with abnormal chest images (patients 6 and 9). All 7 of these patients had received antifungal therapy, including fluconazole, voriconazole, and sulfamethoxazole (SMZ), and 3 of them required discontinuation of TAC (patients 2, 4, and 7). In addition, *Pseudomonas aeruginosa* in patient 10 and *Acinetobacter baumannii* in patient 11 had been found in sputum culture accompanied with abnormal chest images; both patients had received broad-spectrum antibiotics treatment, but neither survived. In total, 3 patients were diagnosed with oral *Candida* infection based on oral leukoplakia and *Candida* in sputum culture (patients 2, 4, and 5). In total, 4 patients (patients 5, 6, 7, and 8) were positive for EBV DNA (> 500 IU/mL), and 1 patient had shingles (patient 3).

In the TOF group, evidence of infection was detected in 11 (42.3%) patients. In total, 5 patients were clinically considered to have pulmonary fungal infection (patients 1, 5, 9, 10, and 11). Of these 5 patients, 2 patients had a positive G test or GM test, with evidence of a fungal infection based on tissue biopsy or high-throughput sequencing of bronchoalveolar lavage fluid (patients 1 and 9). Of the 5 patients, 2 had a positive G test or GM test, with new emerging HRCT abnormalities (patients 5 and 11). Patient 10 had a sputum culture of *Aspergillus fumigatus* with abnormal chest images. All 5 patients had received antifungal therapy, including fluconazole, voriconazole, SMZ, caspofungin, posaconazole, and amphotericin B, and 3 of them discontinued TOF treatment (patients 1, 5, and 9). Among them, 1 patient survived and 4 patients died. Additionally, oral *Candida* infection was diagnosed in 2 patients (patients 2 and 7), EBV reactivation occurred in 2 patients (patients 1 and 3), and CMV reactivation—confirmed by detection of CMV DNA in the blood over 500 IU/mL—occurred in 3 patients (patients 1, 4, and 6). In total, 2 patients had herpes zoster (patients 2 and 4). In addition, 1 patient (patient 8) had developed a pulmonary infection, which progressed to severe sepsis, and the patient died despite combined antibacterial therapy with imipenem/cilastatin and vancomycin. The mean duration from treatment initiation to occurrence of infection was 30.50 (SD 7.66, range 5.50-43.50) days in the TOF group and 53.18 (SD 25.57, range 7.00-74.00) days in the TAC group (P = 0.89).

Patients in the TOF group had lymphocytopenia (10/26, 38.5%) to a greater degree than patients in the TAC group (5/35, 14.3%; P = 0.04). In addition, 1 case of renal dysfunction was noted in each group. In total, 2 cases of diarrhea and 1 case of anemia were observed in the TAC group. In addition, 1 case of pulmonary embolism was observed in the TAC group, and 1 case of intermuscular vein thrombosis of both lower extremities was observed in the TOF group. Non-AEs were observed in 7 (26.9%) patients in the TOF group and in 9 (25.7%) patients in the TAC therapy group (data not shown).

DISCUSSION

This observational study showed that the 6-month and 1-year all-cause mortality rates of patients with MDA5-ILD treated with TOF were significantly lower compared to the mortality rates of

Table 3. Therapy-related infections in patients with MDA5-ILD treated with TAC.

Patient, Sex	Age, yrs	Initial GC Dose, mg/d	TAC Dose, mg/d	Other Treatments	Infections	Antiinfective Therapies	TAC Discontinuation	Outcome
Patient 1, male	54	80	2	IVIG	Pulmonary fungal infection[a]	Fluconazole	No	Died
Patient 2, female	60	40	2	—	Oral *Candida* infection[b] and pulmonary fungal infection	SMZ and fluconazole	Yes	Died
Patient 3, female	70	80	2	—	Herpes zoster	—	No	Alive
Patient 4, female	48	160	4	IVIG	Oral *Candida* infection and pulmonary fungal infection	SMZ, caspofungin, and fluconazole	Yes	Died
Patient 5, female	86	20	2	—	Oral *Candida* infection and EBV DNA (+)[c]	Fluconazole	No	Died
Patient 6, male	57	500	2	IVIG	Pulmonary fungal infection and EBV DNA (+)	Caspofungin and ganciclovir	No	Died
Patient 7, female	56	160	3	—	Pulmonary fungal infection and EBV DNA (+)	Voriconazole	Yes	Died
Patient 8, male	49	500	4	IVIG	Pulmonary fungal infection and EBV DNA (+)	SMZ	No	Died
Patient 9, female	54	160	4	IVIG	Pulmonary fungal infection	Fluconazole	No	Died
Patient 10, female	74	160	2	—	Pulmonary bacterial infection (*Pseudomonas aeruginosa*)	Imipenem/ cilastatin	No	Died
Patient 11, female	68	240	4	PE and IVIG	Pulmonary bacterial infection (*Acinetobacter baumannii*)	Imipenem/ cilastatin and linezolid	No	Died

[a] Pulmonary fungal infection was defined as a new high-resolution computed tomography abnormality (ie, new pulmonary nodules) plus an elevated G test or GM test of blood or fungi in sputum culture, with or without histopathological biopsy. [b] Oral *Candida* infection was defined as oral leukoplakia plus *Candida* in sputum culture. [c] EBV DNA positivity referred to the detection of > 500 IU/mL of EBV DNA in the blood. EBV: Epstein-Barr virus; G test: blood 1,3-β-D glucan test; GC: glucocorticoid: GM test: blood galactomannan antigen detection; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; MDA5: melanoma differentiation–associated gene 5; PE: plasma exchange; SMZ: sulfamethoxazole: TAC: tacrolimus.

Table 4. Therapy-related infections in patients with MDA5-ILD treated with TOF.

Patient, Sex	Age, yrs	Initial GC Dose, mg/d	TOF Dose, mg/d	Other Treatments	Infections	Antiinfective Therapies	TOF Discontinuation	Outcome
Patient 1, male	53	160	10	—	Pulmonary fungal infection[a], CMV DNA (+)[b], and EBV DNA (+)[c]	Ganciclovir, caspofungin, voriconazole, posaconazole, and amphotericin B	Yes	Alive
Patient 2, female	67	80	10	—	Oral *Candida* infection[d] and herpes zoster	—	No	Alive
Patient 3, female	45	160	10	—	EBV DNA (+)	Ganciclovir	No	Alive
Patient 4, male	47	40	5	PE and IVIG	CMV DNA (+) and herpes zoster	Ganciclovir	No	Alive
Patient 5, male	41	160	5	IVIG	Pulmonary fungal infection	SMZ	Yes	Died
Patient 6, female	58	80	10	—	CMV DNA (+)	—	No	Alive
Patient 7, male	57	35	10	—	Oral *Candida* infection	Fluconazole	No	Alive
Patient 8, male	46	240	10	PE, IVIG, and pirfenidone	Sepsis[e] (eg, hemolytic *Staphylococcus*)	Imipenem/cilastatin and vancomycin	No	Died
Patient 9, male	65	80	10	IVIG	Pulmonary fungal infection	Voriconazole	Yes	Died
Patient 10, female	68	160	10	IVIG	Pulmonary fungal infection	Voriconazole	No	Died
Patient 11, male	48	240	10	—	Pulmonary fungal infection	Voriconazole	No	Died

[a] Pulmonary fungal infection was defined as a new high-resolution computed tomography abnormality (ie, new pulmonary nodules) plus an elevated G test or GM test of blood or fungi in sputum culture, with or without histopathological biopsy. [b] CMV DNA positivity referred to the detection of > 500 IU/mL of CMV DNA in the blood. [c] EBV DNA positivity referred to the detection of > 500 IU/mL of EBV DNA in the blood. [d] Oral *Candida* infection was defined as an oral leukoplakia plus *Candida* in sputum culture. [e] Sepsis was defined as bacteremia plus clinically systemic infectious manifestation. CMV: cytomegalovirus; EBV: Epstein-Barr virus; G test: blood 1,3-β-D glucan test; GC: glucocorticoid; GM test: blood galactomannan antigen detection; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; MDA5: melanoma differentiation–associated gene 5; PE: plasma exchange; SMZ: sulfamethoxazole; TOF: tofacitinib.

those treated with TAC. The adjusted Cox proportional hazards model showed that TOF exposure was associated with a lower risk of 1-year mortality. This therapeutic effect was maintained in patients with RP-ILD, whereas the incidence of AEs and the medication discontinuation rates were similar. To our knowledge, this study included the largest cohort to date to assess the effects of TOF on survival and AEs in patients with MDA5-ILD.

Anti-MDA5 antibody–positive IIM-ILD is a challenging disease with remarkably high short-term mortality.[10,11] Ochi et al[20] found that TAC was markedly effective in decreasing the serum Krebs von den Lungen-6 level and in radiographic improvement. In a retrospective study, TAC usage was associated with decreased doses of both GCs and other disease-modifying antirheumatic drugs.[21] A multicenter, single-arm, 52-week clinical trial showed that initial treatment with TAC and GCs may improve short-term mortality of patients with PM/DM-ILD, with a 52-week survival rate of 88%.[22] Further, TAC had an up to 100-fold stronger inhibitory effect on T cell proliferation and cytokine production than cyclosporine in a number of in vitro studies.[23] A Japanese study also showed that the addition of TAC could significantly prolong event-free survival in patients with PM/DM-ILD.[24] Recently, in a prospective, multicenter, open-label, randomized, 52-week phase II trial of 58 patients with PM/DM-ILD, 30 patients received GCs plus TAC treatment, and 28 patients received GCs plus cyclosporine treatment. In that study, the final progression-free survival rate at 52 weeks was 87% in the TAC group, which was significantly higher than the survival rate of 71% in the cyclosporine group; in addition, the FVC% predicted increased significantly in both groups.[25]

TOF has been used in several autoimmune diseases,[26] including rheumatoid arthritis,[26] inflammatory bowel disease,[27] psoriasis,[28] and vitiligo,[29] among others. Many studies have reported its role in improving the symptoms of skin, muscles, and joints in patients with DM.[30-32] In a previous clinical trial,[14] all 18 patients with MDA5-ILD receiving a GC combined with TOF had an overwhelming survival advantage compared to patients who received conventional therapy. Further, the ferritin levels, PFT results, and HRCT findings in the TOF group also considerably improved over time, with low-grade AEs. In another study, additional TOF was prescribed to 5 patients with MDA5-ILD who failed to respond to conventional triple therapy: 3 of them survived and 2 died.[13] Consistently, our study showed that TOF was beneficial for 6-month and 1-year survival, even among patients with RP-ILD. More patients with weak-positive anti-MDA5 antibody titers were in the TOF group than in the TAC group, which could partly explain our results. In addition, the small sample sizes in each of the 2 groups did not match, owing to the retrospective nature of the study. Moreover, patients with anti-MDA5 antibodies who were also positive for anti-Ro52 antibodies were found to have more severe clinical phenotypes and worse prognoses compared to those who were only positive for anti-MDA5 antibodies[33]; however, in our study, we found no difference in the frequency of anti-Ro52 antibodies between the 2 treatment groups. Additional well-designed multicenter studies are needed to confirm the efficiency of TOF and to identify the subtype of patients who would best benefit from TOF treatment.

A number of case series have been published reporting the beneficial effects of biological agents and small molecules in MDA5-ILD. Yamaguchi et al[34] reported 1 case with anti-MDA5–positive RP-ILD who failed to respond to conventional immunosuppressive treatment but responded to rituximab. In another study, 4 patients with anti-MDA5–positive RP-ILD received additional rituximab after failing to respond to combination immunosuppressant therapy[35]; all 4 patients survived, with improvements in their respiratory symptoms and lung function. HRCT findings improved in 3 of these patients and remained stable in 1 patient. Plasmapheresis and polymyxin B hemoperfusion may also be used as rescue options to treat refractory cases.[36,37] A study[36] reported that 6 patients who received plasmapheresis had significantly better 1-year survival rates (100%) than those who did not (25%). Plasmapheresis was also performed in patients with active infectious disease who were immunocompromised by intensive immunosuppressive therapy.[36] In our study, 1 RP-ILD survivor in the TOF group underwent 4 plasmapheresis sessions successfully and was discharged. Moreover, veno-venous extracorporeal membrane oxygenation was considered in critical cases to improve the opportunity for lung transplantation.[38,39]

This study had several limitations, including its retrospective nature and indication bias, which might lead to overestimating or underestimating the efficacy of the medication. In addition, few patients had reperformed lung function tests because of the short follow-up time, thereby not allowing us to demonstrate longitudinal physiology changes. Also, the concurrent use of other steroid-sparing agents precluded an evaluation of the specific benefits of TOF or TAC as monotherapy. In spite of these limitations, because a majority of fatalities may occur within 1 year of the onset of ILD and the disease tends to stabilize after 1 year, we assessed the effects of TOF on the 6-month and 1-year all-cause mortality rates of patients with MDA5-ILD.

In conclusion, this observational study showed that TOF use was associated with improvements in 6-month and 1-year survival rates in patients with MDA5-ILD and even in patients with anti-MDA5–positive RP-ILD, while not increasing the risks of AEs. Future well-designed, multicenter, randomized controlled trials are needed to assess the long-term efficacy and tolerability of TOF in MDA5-ILD.

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