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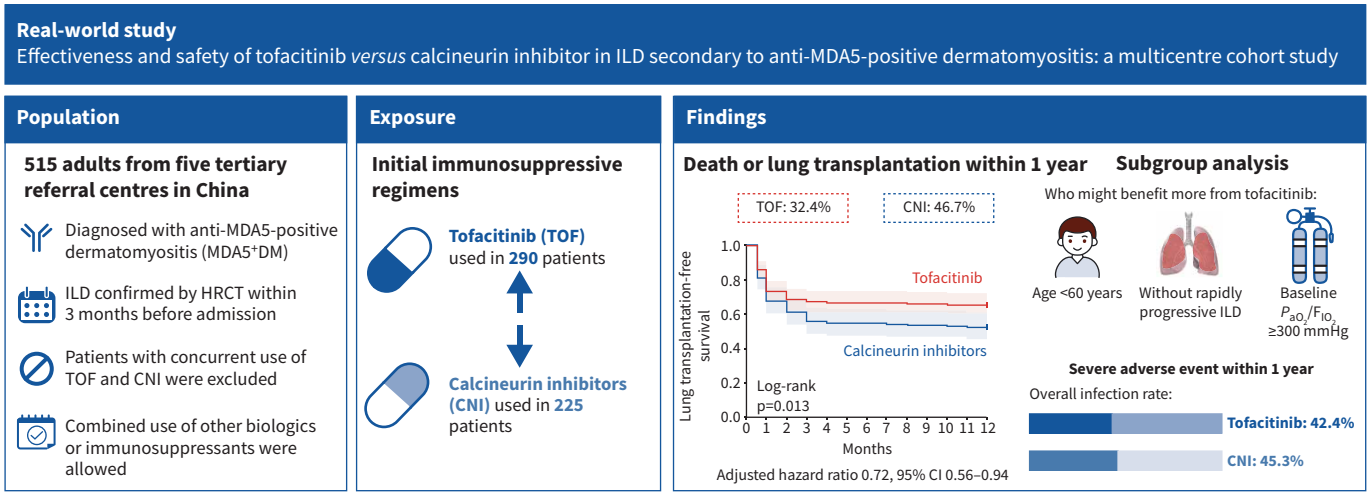

GRAPHICAL ABSTRACT Overview of the study. ILD: interstitial lung disease; MDA5: melanoma differentiation-associated gene 5; HRCT: high-resolution computed tomography; TOF: tofacitinib; CNI: calcineurin inhibitors; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; IPTW: inverse probability of treatment weighting.

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Shareable abstract (@ERSpublications)
In this large multicentre retrospective cohort study (n=515) adjusted by IPTW, tofacitinib was found to significantly reduce the 1-year mortality risk of newly diagnosed anti-MDA5$^+$ dermatomyositis-ILD by 28% compared to calcineurin inhibitors https://bit.ly/40Mzsb6

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Abstract

Objective To compare the effectiveness and safety of tofacitinib *versus* calcineurin inhibitor (CNI) as initial immunosuppressive regimen for anti-melanoma differentiation-associated gene 5-positive dermatomyositis with interstitial lung disease (MDA5$^+$DM-ILD).

Methods Adult Chinese patients with newly diagnosed MDA5$^+$DM-ILD (ILD course <3 months) from five tertiary referral centres between April 2014 and January 2023 were included in this retrospective cohort study. The primary effectiveness end-point was lung transplantation-free survival within 1 year. Propensity score-based inverse probability of treatment weighting (IPTW) was applied for adjustment in this real-world study.

Results In the eligible cohort, a total of 94 (32.4%) and 105 (46.7%) patients died or underwent lung transplantation within 1 year in the tofacitinib group (n=290) and the CNI group (n=225), respectively. After adjustment by IPTW, patients' lung transplantation-free survival rate within 1 year was significantly higher in the tofacitinib group compared to the CNI group (log-rank p=0.013). Multivariable Cox analysis performed in the IPTW dataset revealed that the hazard ratio of tofacitinib *versus* CNI for 1-year survival was 0.72 (95% CI 0.56–0.94; p=0.013). The adjusted difference of survival rate was 9.3% (95% CI 2.8–15.8%). Alternative analytic strategies yielded consistent results in sensitivity analyses. Patients aged <60 years, without rapidly progressive ILD, or with baseline arterial oxygen tension/inspiratory oxygen fraction ⩾300 mmHg might benefit more from tofacitinib. Opportunistic infection was the major treatment-related serious adverse event, with generally comparable incidence (42.4% *versus* 45.3%).

Conclusion In this large multicentre cohort study, tofacitinib showed significantly more benefits for 1-year lung transplantation-free survival than calcineurin inhibitors in MDA5$^+$DM-ILD.

Introduction

Dermatomyositis with anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a distinct autoimmune disease, which is characterised by impressively high mortality due to frequent association

with rapidly progressive interstitial lung disease (RPILD) [1–3]. The current management of this intractable disease is challenging and largely empirical rather than evidence-based [4]. Only few small-sized prospective open-labelled studies have been conducted due to the rarity and complexity of the disease. Appropriate immunosuppressive regimen is still a major unmet clinical need.

An upfront triple-combination therapy combining a calcineurin inhibitor (CNI), *i.e.* tacrolimus, with high-dose glucocorticoids (GC) and intravenous cyclophosphamide was evaluated by Japanese colleagues in a multicentre prospective study, which could improve the 6-month survival of anti-MDA5-positive dermatomyositis with interstitial lung disease (MDA5$^+$DM-ILD) compared to historical step-up treatment, *i.e.* high-dose GC and stepwise addition of immunosuppressant [5]. However, contradictory results from the same group in a large-scale real-world cohort study failed to show survival benefits of initial triple-combination therapy over regimens consisting of GC with or without a single immunosuppressant [6].

Recently, the overactivation of interferon (IFN) pathways has been strongly linked to the pathogenesis of MDA5$^+$DM, supported by analyses from peripheral blood, skin, lung tissues and murine models [7–14]. In view of this, tofacitinib, a potent inhibitor of JAK-STAT signalling and the IFN pathway, became an appealing treatment option for MDA5$^+$DM-ILD [15]. In a previous single-centre proof-of-concept trial, we demonstrated that tofacitinib combined with GC could significantly improve the 6-month survival of early-stage MDA5$^+$DM-ILD, *i.e.* with baseline forced vital capacity (FVC) ⩾50% predicted, compared to matched historical controls treated with conventional immunosuppressants [16]. A few case series also reported favourable treatment response using tofacitinib in both new-onset and refractory MDA5$^+$DM [17–22]. However, the strength of these studies was primarily limited by small sample size and lack of adequately matched controls.

Both JAK inhibitors and CNI have been conditionally recommended as first-line treatment options for DM-ILD in newly published American College of Rheumatology/American College of Chest Physicians treatment guidelines for ILD in patients with systemic autoimmune rheumatic diseases [23]. However, the certainty of evidence was quite low due to lack of high-quality, large-scale data, particularly for the comparison of JAK inhibitors and CNI. Therefore, we conducted a multicentre retrospective cohort study to compare the effectiveness and safety of tofacitinib and CNI (*i.e.* tacrolimus or cyclosporin) as the initial immunosuppressive regimen for newly diagnosed MDA5$^+$DM-ILD. Propensity score-based inverse probability of treatment weighting (IPTW) was applied to adjust confounders and to reduce potential selection bias, aiming to emulate randomised controlled trials in the real-world setting.

Patients and methods

Study cohort

Patients from five Chinese tertiary referral centres were enrolled. Patients eligible for this study fulfilled the following criteria: age ⩾18 years; initially met the criteria for dermatomyositis defined by Bohan and Peter [24, 25] or clinically amyopathic dermatomyositis proposed by Sontheimer [26], thereafter retrospectively confirmed by the 239th European Neuromuscular Centre (ENMC) criteria for dermatomyositis [27], with positive anti-MDA5 antibody identified at diagnosis by commercial line-blotting assay with EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) (Euroimmun, Lubeck, Germany) [28, 29]; diagnosis of ILD by pulmonary high-resolution computed tomography (HRCT), within 3-month interval between ILD diagnosis and hospital admission (baseline). Patients were excluded if they had coexisting severe infection at baseline or had an underlying malignancy within 3 years. The study protocol was approved by the ethics committee of the leading centre, Renji Hospital (LY2023-284-C).

Data collection and clinical outcome

Patients' demographic information, clinical characteristics, laboratory tests, pulmonary function tests at baseline (the time of hospital admission) and treatment data (including regimens prior to baseline, at baseline and during follow-up) were collected retrospectively.

The initial immunosuppressive regimens after admission were evaluated, which were generally selected by the treating physicians based on their experiences and patients' wishes. There was no restriction of accessibility for any agent including tofacitinib, CNIs and other frequently used immunosuppressants/biologics in all study centres. Patients who were treated with both tofacitinib and CNI, or neither of them, were subsequently excluded, leaving those treated with tofacitinib (TOF group) and CNI (CNI group) for the primary analysis. Patients treated with other JAK inhibitors, *e.g.* baricitinib, upadacitinib, were also excluded. Combined use of other immunosuppressant or biologics was allowed and assessed as a confounder.

The primary effectiveness end-point was defined as lung transplantation-free survival within 1 year since baseline. Accordingly, 1-year mortality mentioned in this study refers to the composite outcome of all-cause death and lung transplantation within 1 year. Secondary observational end-points included FVC (% predicted), oxygen requirement, GC dose at 1 year and percentage of changing initial regimen during follow-up among survivors. Treatment-related serious adverse events (SAEs) within 1 year, with a special interest in infections, judged by the investigators, were also recorded.

Definition of variables

Diagnosis of ILD was established upon the first pulmonary HRCT which revealed ground-glass opacities, consolidations, reticulations and/or honeycombing, with the exclusion of infection, heart failure and drug-induced interstitial changes [30].

The definition of RPILD was based on a previous study, with minor modifications [31]. Briefly, RPILD was defined as the presence of each of the following three conditions within 3 months since the onset of respiratory symptoms: 1) progressive worsening of dyspnoea; 2) pulmonary HRCT revealed acute alveolar exudative lesions (*i.e.* ground-glass opacities, consolidations); 3) hypoxaemia (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) <300 mmHg based on arterial blood gas analysis) or severe restrictive ventilation dysfunction (FVC <50% pred or unable to perform pulmonary function tests).

Severe infection was defined as a pathogen-confirmed infection with treatment priority outweighed underlying disease judged by the treating physician, *e.g.* bloodstream infection, severe invasive fungal infection, *etc.*

Statistical analysis

Categorical variables were summarised as numbers and percentages, and subsequently compared using the Chi-squared test and Fisher's exact test, as appropriate. Continuous variables were summarised as medians and interquartile ranges (IQR), with Mann–Whitney U-test used to assess the difference between groups when the assumptions of normality of t-tests were not met. The optimal cut-off values for significant continuous variables were determined by the "survminer" R package.

In the primary analysis, dummy variable was applied to address missing data. Then we used propensity score-based IPTW to construct a weighted cohort of patients who were treated with different study drugs, but with similar disease characteristics. To calculate the inverse probability of treatment weights, we estimated each patient's propensity to receive immunosuppressive regimens using a logistic-regression model including 15 confounding variables for survival, which were selected based on previous studies and clinical significance [32–38]. Patients who received tofacitinib were assigned a weight of 1/(propensity score) and those who received CNI were assigned a weight of 1/(1−propensity score). Weights were stabilised and trimmed at the 0.25th and 99.75th percentiles to reduce the variability of estimates. Balance among covariates were assessed by standard mean difference (SMD) and a difference of $\leqslant$0.1 was considered to be a well-balanced result. Adjusted generalised standard error inflation factor was calculated to test the multicollinearity for covariates.

Kaplan–Meier curves were plotted and log-rank test results were reported to compare the lung transplantation-free survival within 1 year between the tofacitinib and CNI groups based on the IPTW dataset. The hazard ratio (HR) for survival between treatment groups after IPTW adjustment was estimated using multivariable Cox proportional-hazards models including the same covariates as in the propensity score model, with time of enrolment as a stratification variable. Generalised linear models were fitted to estimate covariate-adjusted risk differences with 95% confidence interval.

We performed several sensitivity analyses to assess the robustness of our findings. Multivariable Cox analyses were performed in the raw dataset with no adjustment for missing data and with dummy variable adjustment for missing data, respectively. Multiple imputation was also used to validate whether the use of dummy variable for missing data introduced bias in the IPTW dataset. The IPTW-adjusted Kaplan–Meier survival curves according to time of enrolment (dichotomised by 1 January 2020) were also plotted, to assess whether temporal changes in standards of care would influence patients' outcomes.

In the exploratory subgroup analysis stratified by several prognosis factors, we estimated the HRs associated with treatment groups using univariable Cox proportional-hazards models after adjustment by IPTW. p-values for interaction were calculated to evaluate whether treatment effect differs on the survival within subgroups.

All aforementioned statistical analyses were performed using R, version 4.3.0 (R Foundation, Vienna, Austria). Significance was defined as two-sided p-value <0.05.

Results

Between April 2014 and January 2023, a total of 830 patients were diagnosed as MDA5^{+}DM-ILD in the multicentre cohort. Of those, 119 patients with ILD course >3 months on admission were excluded; 22 patients were lost to follow-up; eight patients were excluded due to coexisting severe infection on admission; and nine patients were excluded owing to malignancy within 3 years. Thus, 672 patients were included for therapeutic analysis. According to initial immunosuppressive regimens after admission, 61 patients treated with both tofacitinib and CNI, and 96 patients treated with neither of them were excluded. Finally, 290 patients treated with tofacitinib and 225 patients treated with CNI were included in the primary analysis (figure 1).

Cohort description

In the eligible cohort (n=515), patients were female-predominant (66.0%) with a median age of 53 years (18–77) years on admission. The median course of ILD on admission was 1 (1–2) months. Of those, 280 (54.4%) patients fulfilled the criteria of RPILD; 72 (14.0%) patients complicated with spontaneous pneumomediastinum and/or pneumothorax. Cumulatively, 199 (38.6%) patients died or underwent lung transplantation within 1 year. Two patients underwent lung transplantation in each treatment group, respectively. Respiratory failure due to dermatomyositis progression (89.9%) was the dominant cause of death, followed by uncontrolled infection. Specific causes of death are shown in supplementary table S1.

Confounding covariates for multivariable analysis

The following baseline characteristics and treatment factors were determined as confounding covariates for multivariable analysis: age, male sex, RPILD, FVC % predicted, P_{aO_2}/F_{IO_2}, spontaneous pneumomediastinum and/or pneumothorax, serum ferritin, lactate dehydrogenase (LDH), peripheral lymphocyte count, CRP elevation, maximum methylprednisolone dosage, combined immunosuppressant or biologics, all previously reported as prognostic factors and also confirmed in our cohort (supplementary table S2). Two other parameters, *i.e.* course of ILD and prior exposure to immunosuppressants or biologics before admission, were also selected as confounding variables for clinical consideration. Time of enrolment (dichotomised by 1 January 2020) was additionally included as a stratification variable.

The optimal cut-off values for significant continuous covariates were determined by the "survminer" R package as follows: 54.7% for FVC % predicted (rounding to 50%), 315 mmHg for P_{aO_2}/F_{IO_2} (rounding to 300 mmHg), 1038.8 ng·mL^{-1} for serum ferritin (rounding to 1000 ng·mL^{-1}), 421 U·L^{-1} for LDH

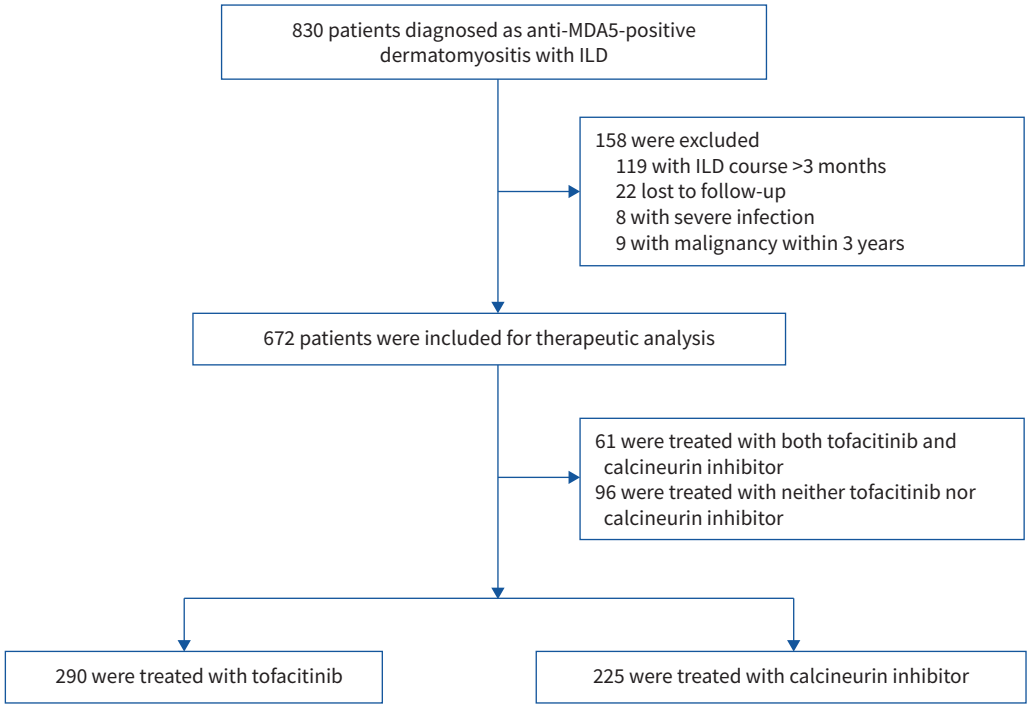

FIGURE 1 Study cohort. MDA5: melanoma differentiation-associated gene 5; ILD: interstitial lung disease.

(rounding to 400 $U \cdot L^{-1}$), 0.66×10^9 cells$\cdot L^{-1}$ for peripheral lymphocyte count (rounding to 0.8×10^9 cells$\cdot L^{-1}$) (supplementary figure S1).

Patients' characteristics before and after propensity score-based IPTW

Table 1 shows patients' characteristics between two treatment groups before adjustment. A total of 30 (5.8%) patients had any missing data. Detailed information on missing data is provided in supplementary figure S2. There were discrepancies in the following baseline characteristics between the tofacitinib group and the CNI group based on univariable comparisons: percentages of enrolment after 1 January 2020 (55.5% *versus* 32.9%), P_{aO_2}/F_{IO_2} <300 mmHg (34.5% *versus* 40.0%), serum ferritin >1000 ng$\cdot$mL^{-1} (51.4% *versus* 53.8%), lymphocyte count $<0.8 \times 10^9$ cells$\cdot L^{-1}$ (61.4% *versus* 50.7%), C-reactive protein elevation (25.2% *versus* 49.8%), maximum methylprednisolone dosage >80 mg$\cdot$day^{-1} (44.5% *versus* 54.7%), combined immunosuppressant therapy (30.3% *versus* 46.2%), and prior exposure to immunosuppressants or biologics (35.9% *versus* 21.8%). Next, propensity score-based IPTW was conducted, and the adjusted patients' characteristics are shown in table 1. All the aforementioned confounding covariates were well balanced, with SMD <0.1 (supplementary figure S3). There was no significant multicollinearity among these covariates, as shown in supplementary table S3. In addition, other treatment data at baseline and during follow-up are provided in supplementary table S4. Of note, five (1.7%) and three (1.3%) patients received extracorporeal membrane oxygenation in the tofacitinib and CNI groups, respectively.

Primary survival analysis

In the unadjusted raw dataset, 94 (32.4%) and 105 (46.7%) patients died or underwent lung transplantation within 1 year in the tofacitinib group (n=290) and the CNI group (n=225), respectively. The Kaplan–Meier curves for the crude survival analysis are provided in supplementary figure S4.

After adjustment by IPTW, patients' lung transplantation-free survival rate within 1 year was significantly higher in the tofacitinib group compared to the CNI group (log-rank p=0.013) (figure 2). The adjusted difference of survival rate was 9.3% (95% CI 2.8–15.8%) between treatment groups in the IPTW dataset. In the multivariable Cox analysis, the HR of tofacitinib for survival was 0.72 (95% CI 0.56–0.94; p=0.013, compared to CNI) adjusted by the aforementioned confounding covariates (table 2).

Sensitivity analysis

In sensitivity analyses, all-cause mortality remained lower in the tofacitinib group than in the CNI group. Alternative analytic strategies yielded consistent results, including multivariable Cox regression in the raw dataset (HR 0.72, 95% CI 0.53–0.99), in the raw dataset with dummy variable adjustment for missing data (HR 0.72, 95% CI 0.53–0.99) and in the IPTW dataset with multiple imputation adjustment for missing data (HR 0.69, 95% CI 0.54–0.89), as shown in supplementary table S5.

In addition, the IPTW-adjusted Kaplan–Meier survival curves according to time of enrolment are displayed in supplementary figure S5. Among patients enrolled before 2020, the adjusted 1-year mortality was lower in the tofacitinib group (38.8%) than the CNI group (49.6%). Among patients enrolled after 2020, the adjusted 1-year mortality was also lower in the tofacitinib group (28.3%) than the CNI group (44.6%). The overall log-rank p-value was 0.027.

Subgroup analysis

In the exploratory subgroup analysis stratified by baseline prognostic factors (figure 3), based on p-values for interaction, patients aged <60 years might be associated with a lower mortality when treated with tofacitinib (HR 0.52, 95% CI 0.35–0.78). Patients without RPILD probably benefit more from tofacitinib than CNI (HR 0.16, 95% CI 0.04–0.59). Patients with baseline $P_{aO_2}/F_{IO_2} \geqslant 300$ mmHg might also benefit more from tofacitinib (HR 0.37, 95% CI 0.21–0.65). Patients without combined immunosuppressants or biologics might be associated with a lower mortality when treated with tofacitinib (HR 0.37, 95% CI 0.22–0.61).

Follow-up data at 1 year among survivors

Pulmonary function tests and treatment data at 1 year among survivors in both treatment groups, particularly reasons for changing initial regimen during follow-up, are summarised in supplementary table S6.

The FVC (% predicted) values significantly improved from baseline to 1-year end-point among survivors in both treatment groups (paired p<0.001). Furthermore, numerically fewer survivors still needed nasal cannula oxygen at 1 year in the tofacitinib group (1.5% *versus* 11.2%). The dosage of prednisone had been tapered to median 7.5 (IQR 5.0–10.0) mg and 10.0 (5.0–12.5) mg per day at 1 year, respectively. In addition, numerically fewer patients in the tofacitinib group (8.2%) changed the initial regimen due to inadequate efficacy or adverse event than those in the CNI group (15.8%).

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TABLE 1 Baseline characteristics and treatment data in the tofacitinib and calcineurin inhibitor groups before and after inverse probability of treatment weighting (IPTW)

	Before IPTW			After IPTW			
	Tofacitinib group	Calcineurin inhibitor group	p-value	Tofacitinib group[#]	Calcineurin inhibitor group	p-value	SMD[¶]
Participants	290	225		292	221		
Enrolment after 2020	161 (55.5)	74 (32.9)	<0.001	131 (44.9)	96 (43.4)	0.767	0.032
Age years	52.0 (44.0–58.0)	53.0 (47.0–59.0)	0.078	53.0 (44.5–59.0)	53.0 (47.0–59.0)	0.508	0.091
Male	102 (35.2)	73 (32.4)	0.579	97 (33.2)	77 (34.8)	0.782	0.029
Course of ILD months	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.862	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.616	0.087
RPILD	152 (52.4)	128 (56.9)	0.356	158 (54.1)	129 (58.4)	0.455	0.080
FVC	66.8 (47.5–81.2)	66.7 (55.1–80.1)	0.383	66.7 (47.0–80.7)	67.0 (55.4–80.8)	0.274	
⩾50% predicted	173 (59.7)	127 (56.4)	0.520	171 (58.6)	123 (55.7)	0.627	0.052
<50% predicted or unable to perform PFTs	117 (40.3)	98 (43.6)		121 (41.4)	98 (44.3)		
P_{aO_2}/F_{IO_2} mmHg	348.5 (259.5–410.0)	314.0 (250.2–383.2)	0.026	340.6 (251.6–408.7)	324.0 (244.4–386.0)	0.300	
⩾300	188 (64.8)	124 (55.1)	0.003	174 (59.6)	128 (58.0)	0.847	0.067
<300	100 (34.5)	90 (40.0)		108 (37.0)	87 (39.4)		
Unknown[+]	2 (0.7)	11 (4.9)		10 (3.4)	6 (2.7)		
Pneumomediastinum and/or pneumothorax	41 (14.1)	31 (13.8)	0.999	39 (13.4)	31 (14.0)	0.845	0.019
Serum ferritin ng·mL^{-1}	1082.1 (438.5–1877.0)	1203.7 (540.9–1928.4)	0.561	1127.6 (443.0–1858.4)	1198.6 (526.6–1859.6)	0.787	
⩽1000	140 (48.3)	89 (39.6)	<0.001	134 (45.9)	93 (42.1)	0.778	0.089
>1000	149 (51.4)	121 (53.8)		151 (51.7)	121 (54.8)		
Unknown[+]	1 (0.3)	15 (6.7)		7 (2.4)	7 (3.2)		
LDH U·L^{-1}	313.0 (246.0–414.2)	310.0 (256.8–404.0)	0.837	315.0 (251.7–419.3)	317.3 (262.6–436.8)	0.447	
⩽400	210 (72.4)	165 (73.3)	0.499	210 (71.9)	154 (69.7)	0.598	0.078
>400	80 (27.6)	59 (26.2)		82 (28.1)	67 (30.3)		
Unknown[+]	0 (0.0)	1 (0.5)		0 (0.0)	1 (0.4)		
Peripheral lymphocyte count ×10^9 cells·L^{-1}	0.7 (0.5–1.0)	0.8 (0.5–1.1)	0.302	0.7 (0.5–1.1)	0.7 (0.5–1.0)	0.231	
Lymphocyte count <0.8×10^9 cells·L^{-1}	178 (61.4)	114 (50.7)	0.019	165 (56.5)	131 (59.3)	0.582	0.058
C-reactive protein mg·L^{-1}	2.9 (2.2–7.3)	8.5 (2.5–18.0)	<0.001	4.0 (2.5–12.3)	5.1 (1.9–14.3)	0.619	
Normal	217 (74.8)	112 (49.8)	<0.001	182 (62.3)	139 (62.9)	0.673	0.064
Elevated	73 (25.2)	112 (49.8)		110 (37.7)	82 (37.1)		
Unknown[+]	0 (0.0)	1 (0.5)		0 (0.0)	1 (0.4)		
Maximum MP dosage >80 mg·day^{-1}	129 (44.5)	123 (54.7)	0.028	136 (46.6)	114 (51.6)	0.353	0.099
Combined immunosuppressant or biologics	88 (30.3)	104 (46.2)	<0.001	108 (37.0)	82 (37.1)	0.971	0.004
Prior exposure to immunosuppressant or biologics before admission	104 (35.9)	49 (21.8)	0.001	85 (29.1)	68 (30.8)	0.757	0.035

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. p-values were calculated using the Mann–Whitney U-test, Chi-squared test or Fisher's exact test. SMD: standard mean difference; ILD: interstitial lung disease; RPILD: rapidly progressive ILD; FVC: forced vital capacity; PFT: pulmonary function test; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; LDH: lactate dehydrogenase; MP: methylprednisolone. [#]: the counts in the weighted cohort may not sum to expected totals owing to rounding; percentages may not total 100 because of rounding; [¶]: calculated to test the balance among covariates in the weighted cohort, with the value <0.1 indicating a good balance; [+]: the following variables had missing values: serum ferritin n=16 (3.1%), P_{aO_2}/F_{IO_2} n=13 (2.5%), LDH n=1 (0.2%), C-reactive protein n=1 (0.2%). 30 (5.8%) patients had any missing data. According to the method of dummy variable, patients with missing data were designated as "unknown".

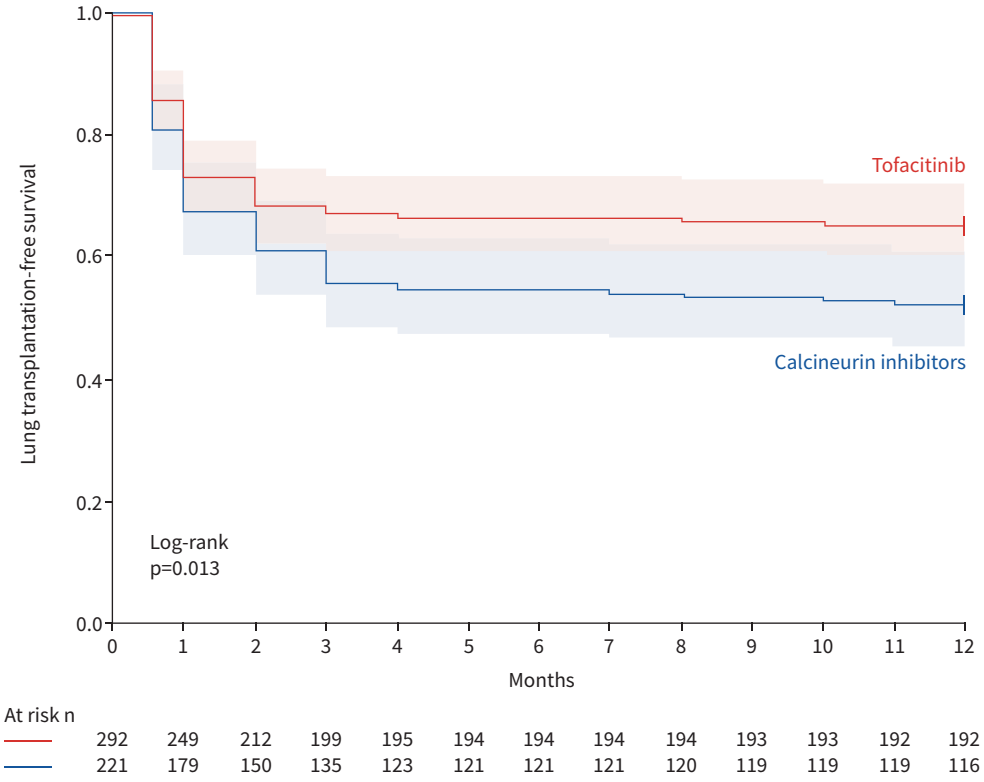

FIGURE 2 Inverse probability of treatment-weighted lung transplantation-free survival curves among anti-melanoma differentiation-associated gene 5-positive dermatomyositis with interstitial lung disease patients treated with tofacitinib or calcineurin inhibitors. Patients treated with tofacitinib had significantly better lung transplantation-free survival than those treated with calcineurin inhibitors (p=0.013 by the log-rank test).

TABLE 2 Association between treatment factor (tofacitinib *versus* calcineurin inhibitors) and the end-point event (all-cause death or lung transplantation within 1 year) determined by multivariable Cox proportional-hazards model conducted in the inverse probability of treatment weighting (IPTW)-adjusted dataset

	Hazard ratio (95% CI)	p-value
Tofacitinib *versus* calcineurin inhibitors	0.72 (0.56–0.94)	0.013
Age	1.03 (1.01–1.04)	<0.001
Male	1.11 (0.83–1.49)	0.475
Course of ILD	0.87 (0.71–1.08)	0.210
RPILD	6.88 (3.51–13.5)	<0.001
FVC <50% predicted or unable to perform PFTs	1.58 (1.08–2.31)	0.018
P_{aO_2}/F_{IO_2} <300 mmHg	1.40 (1.00–1.96)	0.053
Pneumomediastinum and/or pneumothorax	0.93 (0.66–1.32)	0.695
Serum ferritin >1000 ng·mL^{-1}	1.12 (0.80–1.55)	0.517
LDH >400 U·L^{-1}	2.07 (1.56–2.74)	<0.001
Lymphocyte count <0.8×10^9 cells·L^{-1}	1.52 (1.07–2.16)	0.018
C-reactive protein elevation	0.93 (0.70–1.23)	0.612
Maximum MP dosage >80 mg·day^{-1}	1.65 (1.11–2.45)	0.013
Combined immunosuppressants or biologics	0.91 (0.67–1.25)	0.566
Prior exposure to immunosuppressant or biologics before admission	0.93 (0.71–1.23)	0.630

The primary survival analysis was conducted in the IPTW-adjusted dataset with dummy variable adjustment for missing data. Shown are the hazard ratios from the multivariable Cox model, with stratification according to the time of enrolment (dichotomised by 1 January 2020) and additional adjustment for the listed variables. ILD: interstitial lung disease; RPILD: rapidly progressive ILD; FVC: forced vital capacity; PFT: pulmonary function test; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; LDH: lactate dehydrogenase; MP: methylprednisolone.

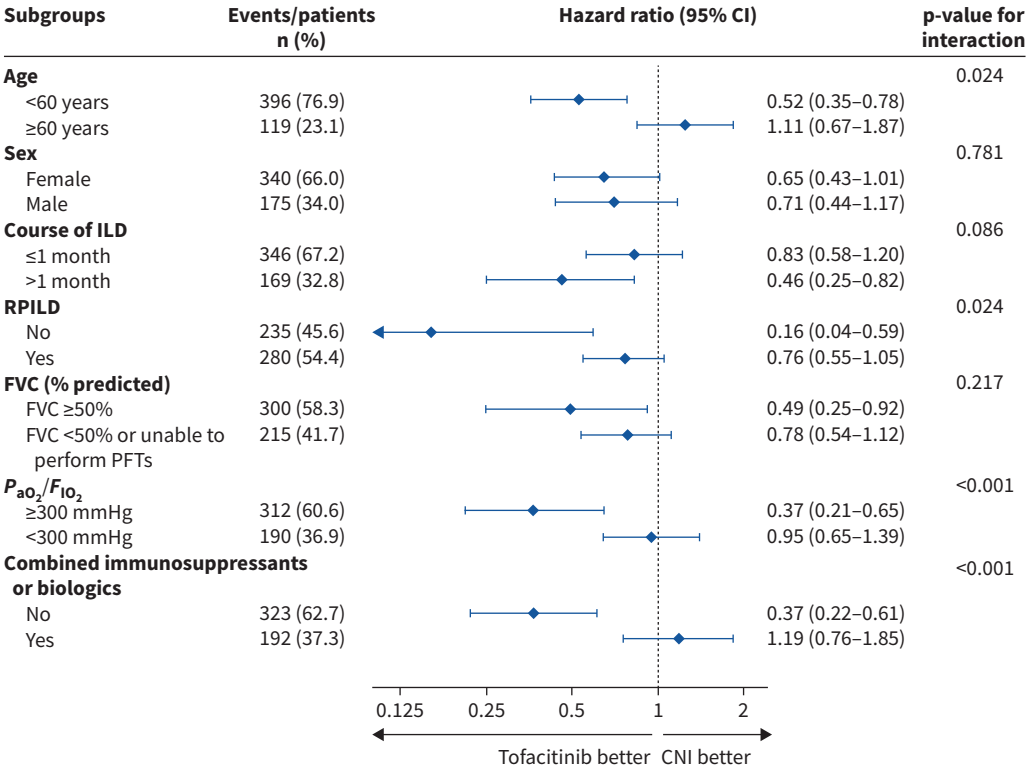

FIGURE 3 Subgroup analyses. Subgroup analyses show the associations between tofacitinib and the end-point event (all-cause death or lung transplantation within 1 year) according to age (<60 years *versus* ⩾60 years), sex (female *versus* male), course of interstitial lung disease (ILD) (⩽1 month *versus* >1 month), rapidly progressive ILD (RPILD) or not, forced vital capacity (FVC) ⩾50% predicted or not, arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) (⩾300 mmHg *versus* <300 mmHg) and combined immunosuppressants or biologics (no *versus* yes). Diamonds represent point estimates for the hazard ratio as compared with calcineurin inhibitors, and horizontal lines indicate the associated 95% confidence intervals. p-values for interaction were calculated to evaluate whether treatment effect differs on the survival within subgroups. PFTs: pulmonary function tests; CNI: calcineurin inhibitors.

Safety

Treatment-related SAEs within 1 year are summarised in table 3. 123 (42.4%) patients in the tofacitinib group and 102 (45.3%) patients in the CNI group had infectious SAEs (p=0.508). Pneumonia was the most frequent infection, more common in the CNI group. Virus infection, particularly Varicella zoster virus (VZV), was more frequently observed in the tofacitinib group. The rates of hospitalised coronavirus disease 2019 were similar. The incidence of fungal infection was also comparable between treatment groups. Deep vein thrombosis occurred in four and two patients in the tofacitinib and CNI groups, respectively. Two and three patients had new-onset malignancy in the tofacitinib and CNI groups, respectively.

Discussion

In this multicentre, retrospective (nonrandomised), real-world study on MDA5$^+$DM-ILD, using propensity score-based IPTW to adjust baseline prognostic factors, tofacitinib was found to significantly reduce the 1-year mortality risk of newly diagnosed (within 3 months) adult MDA5$^+$DM-ILD by 28% compared to CNIs, resulting in an adjusted difference of lung transplantation-free survival rate of 9.3%. Significantly improved pulmonary function and GC-sparing effect as well as high drug-persistence rate at 1-year among survivors further supported the efficacy of tofacitinib. The incidence of treatment-related SAEs was generally comparable between treatment groups.

MDA5, encoded by the IFIH1 gene, involves in the antiviral response by playing a role as a key protein sensor of viral double-stranded RNA and inducing production of type I IFN (IFN-I) and other inflammatory cytokines [39]. Cumulative experimental data have showed that overactivation of IFN-I pathway is highly associated with the pathogenesis of MDA5$^+$DM [14]. IFN-I-stimulated genes (IFI44 and

TABLE 3 Serious adverse events within 1 year

	Tofacitinib group	Calcineurin inhibitor group	p-value
Participants	290	225	
Overall infection, patients	123 (42.4)	102 (45.3)	0.508
Infection site, events			
Pneumonia	84 (29.0)	88 (39.1)	0.015
Skin and soft tissue	30 (10.3)	8 (3.6)	0.003
Bloodstream infection	4 (1.4)	2 (0.9)	0.701
Genitourinary	7 (2.4)	2 (0.9)	0.311
Other	8 (2.8)	10 (4.4)	0.302
Pathogens, events			
Bacteria	51 (17.6)	48 (21.3)	0.284
Tuberculosis	5 (1.7)	2 (0.9)	0.476
Fungi	40 (13.8)	37 (16.4)	0.403
Aspergillus	26 (9.0)	14 (6.2)	0.249
Pneumocystis jirovecii	5 (1.7)	13 (5.8)	0.013
Virus	73 (25.2)	38 (16.9)	0.023
Cytomegalovirus reactivation	39 (13.4)	21 (9.3)	0.149
Varicella zoster virus	29 (10.0)	5 (2.2)	<0.001
Hospitalised COVID-19	11 (3.8)	12 (5.3)	0.401
Hepatitis B virus	1 (0.3)	1 (0.4)	0.999
Deep vein thrombosis, patients	4 (1.4)	2 (0.9)	0.701
New-onset malignancy, patients	2 (0.7)	3 (1.3)	0.658

Data are presented as n (%), unless otherwise stated. Serious adverse events within 1 year judged by the investigators were summarised and compared between treatment groups by the Chi-squared test or Fisher's exact test.

MX1) were found to be significantly higher expressed in peripheral blood mononuclear cells from patients with MDA5$^+$DM. Quantitative IFN-I score was positively correlated with disease activity and mortality in MDA5$^+$DM [7]. Several studies revealed overexpression of IFN-I signature in the skin lesions from patients with MDA5$^+$DM [8–10]. More importantly, single-cell RNA sequencing on lung tissue from patients with refractory MDA5$^+$DM-ILD who underwent lung transplantation illustrated strong activation of IFN-I and fibrosis signalling in affected lungs [12]. In a recently reported murine model of ILD induced by sequential challenges of MDA5 and poly I:C, upregulation of IFN-I signalling was also demonstrated to be essential for the initiation of ILD; while IFN-α receptor-null mice were resistant to develop ILD [13]. All these laboratory evidences vouched the rationale of using a JAK inhibitor, a potent inhibitor of the IFN pathway, to treat MDA5$^+$DM. Indeed, our previous single-arm open-labelled proof-of-concept trial, along with other case series, has provided promising efficacy signals of tofacitinib in patients with MDA5$^+$DM-ILD [16–20].

Unfortunately, randomised controlled trials are difficult to conduct in such a rare and challenging disease. Instead, the multicentre real-world study with propensity score-based IPTW was apparently a viable approach providing evidence to fill the knowledge gap. Discrepancies of baseline characteristics, *i.e.* potential confounders, frequently exist between treatment groups due to lack of randomisation in the observational study. IPTW is a popular method used to address this issue, which aims to create a pseudo-population similar to a randomised trial by re-weighting the individuals so that covariate distributions can be similar between treatment groups. Owing to the large sample size and appropriate data-mining strategy in our study, possible prognostic confounders were exhausted and matched. The superiority of JAK inhibitor-based regimen over CNI-based regimen was thus established. In addition, consistent results from sensitivity analyses using alternative methods to address missing data and different adjustment strategies also demonstrated the robustness of the main findings.

We also performed several exploratory subgroup analyses to search for potential optimal subpopulation for tofacitinib treatment. In brief, younger patients and those without RPILD were more likely to benefit from tofacitinib rather than calcineurin inhibitors. Of note, early-stage patients, *i.e.* those with baseline P_{aO_2}/F_{IO_2} ⩾300 mmHg, might have an even better survival benefit when treated with tofacitinib. The similar efficacy advantage of tofacitinib was also found in the subgroup of patients with baseline FVC ⩾50%, which supported the findings in our previous single-centre study [16]. This result re-emphasises the utmost importance of early diagnosis and timely treatment before the severe deterioration of pulmonary function

in MDA5$^+$DM-ILD [1, 32]. The favourable benefit of tofacitinib over CNI observed in patients without combined immunosuppressant or biologics could also support the primary findings, since the regimen was generally simpler in this subgroup. Of note, this result should be interpreted cautiously since there probably be meaningful treatment-by-indication error in real-world studies. In other words, milder or nonprogressive cases were less likely to be treated with combined therapy in daily practice. In a sense, this result verified the similar findings in subpopulation with less severe disease, *i.e.* baseline P_{aO_2}/F_{IO_2} ⩾300 mmHg, without RPILD.

Not surprisingly, opportunistic infection was the major treatment-related SAE in our study. The incidence of infection was generally comparable between treatment groups. Of note, certain pathogens, *e.g. Aspergillus*, *Pneumocystis jirovecii*, cytomegalovirus and VZV, *etc*. might be prevalent in the background of immune disturbance of the disease *per se*, as well as under the exposure of potent immunosuppression, which is consistent with previous studies [40–42]. Of those, the incidence of VZV was noticeably higher in the tofacitinib group (10%), which is consistent with randomised controlled trial findings in other diseases, *e.g.* rheumatoid arthritis and ulcerative colitis. Prophylactic medications and careful monitoring for opportunistic infections should be considered as a routine in the management of MDA5$^+$DM-ILD [43]. In addition, low incidences of deep vein thrombosis and new-onset malignancy were reported within the first year of study regimens. No novel safety signal concerning tofacitinib treatment was observed. Further studies with long-term follow-up and sufficient safety data are warranted in future.

There are several limitations in our study. First, due to the retrospective study design, missing data is an inevitable issue. In our cohort, only a few patients (5.8%) had missing values for covariates. However, adjustment methods for missing data including dummy variable and multiple imputation might introduce potential bias. We attempted to make up for the deficiency by performing multiple sensitivity analyses. In addition, some potential covariates, *e.g.* serum KL-6, and HRCT score for ILD changes, were unmeasured and unadjusted in our cohort. Second, concomitant medications, *i.e.* combined immunosuppressant or biologics and antifibrotic drugs were diverse and complexed in the real-world setting depending on preference of treating physicians and study centres. This confounding treatment effect had been considered as binary composite variables (combined immunosuppressant or biologics, prior exposure to immunosuppressants or biologics) and subsequently matched by IPTW adjustment. In addition, considering that MDA5$^+$DM-ILD is a life-threatening disease, change of initial regimen in clinical practice is sometimes an inevitable choice for treating physician. Unfortunately, the influence of each individual concomitant medication or sequential therapy could hardly be ideally weighted and adjusted in this study. A prospective randomised controlled trial would be more appropriate to exclude the confounding effect of concomitant medications and sequential therapies. Third, quantitative clinical measures reflecting extrapulmonary dermatomyositis disease activities, *e.g.* rash (Cutaneous Dermatomyositis Disease Area and Severity Index scores), muscle strength (Manual Muscle Testing-8 scores), were not routinely recorded in this real-world cohort. Well-designed prospective studies with pre-defined end-points for extrapulmonary parameters will be helpful to assess the effectiveness for cutaneous and muscular diseases. Fourth, adverse events might not be completely recorded. Furthermore, the prophylaxis rate of trimethoprim-sulfamethoxazole was different between treatment groups (84.8% in the tofacitinib group *versus* 63.1% in the CNI group), which might influence the incidence of *Pneumocystis jirovecii* infection. Finally, since this study was conducted in the Chinese population, whether the findings could be extrapolated to other ethnicities needs to be validated in the future.

In conclusion, this real-world cohort study provides new evidence for treatment of MDA5$^+$DM-ILD. Tofacitinib showed significantly more benefits for 1-year lung transplantation-free survival than CNIs after adjustment by IPTW in this large-scale multicentre cohort.

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Data availability: De-identified participant data will be available on reasonable request to the corresponding author.

Ethics statement: The study protocol was approved by the ethics committee of Renji Hospital (LY2023-284-C). The study was performed in accordance with the Declaration of Helsinki and its amendments. Written informed consent was obtained from each participating patient or designated surrogate.

Author contributions: W. Wu and S. Ye had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: W. Wu and S. Ye.

Acquisition, analysis, or interpretation of data: all authors. Statistical analysis: W. Wu. Drafting of the manuscript: W. Wu and S. Ye. Critical revision of the manuscript for important intellectual content: all authors. All authors approved the final version to be published and had final responsibility for the decision to submit for publication.

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References

1 Wu W, Guo L, Fu Y, *et al.* Interstitial lung disease in anti-MDA5 positive dermatomyositis. *Clin Rev Allergy Immunol* 2021; 60: 293–304.
2 Lu X, Peng Q, Wang G. Anti-MDA5 antibody-positive dermatomyositis: pathogenesis and clinical progress. *Nat Rev Rheumatol* 2024; 20: 48–62.
3 Sato S, Hoshino K, Satoh T, *et al.* RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis Rheum* 2009; 60: 2193–2200.
4 McPherson M, Economidou S, Liampas A, *et al.* Management of MDA-5 antibody positive clinically amyopathic dermatomyositis associated interstitial lung disease: a systematic review. *Semin Arthritis Rheum* 2022; 53: 151959.
5 Tsuji H, Nakashima R, Hosono Y, *et al.* Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Arthritis Rheumatol* 2020; 72: 488–498.
6 Gono T, Masui K, Sato S, *et al.* Mortality risk stratification using cluster analysis in patients with myositis-associated interstitial lung disease receiving initial triple-combination therapy. *Front Med* 2022; 9: 883699.
7 Qian J, Li R, Chen Z, *et al.* Type I interferon score is associated with the severity and poor prognosis in anti-MDA5 antibody-positive dermatomyositis patients. *Front Immunol* 2023; 14: 1151695.
8 Zhang SH, Zhao Y, Xie QB, *et al.* Aberrant activation of the type I interferon system may contribute to the pathogenesis of anti-melanoma differentiation-associated gene 5 dermatomyositis. *Br J Dermatol* 2019; 180: 1090–1098.
9 Ono N, Kai K, Maruyama A, *et al.* The relationship between type 1 IFN and vasculopathy in anti-MDA5 antibody-positive dermatomyositis patients. *Rheumatology* 2019; 58: 786–791.
10 Cassius C, Amode R, Delord M, *et al.* MDA5$^+$ dermatomyositis is associated with stronger skin type I interferon transcriptomic signature with upregulation of IFN-κ transcript. *J Invest Dermatol* 2020; 140: 1276–1279.
11 Allenbach Y, Leroux G, Suárez-Calvet X, *et al.* Dermatomyositis with or without anti-melanoma differentiation-associated gene 5 antibodies: common interferon signature but distinct NOS2 expression. *Am J Pathol* 2016; 186: 691–700.
12 Ye Y, Chen Z, Jiang S, *et al.* Single-cell profiling reveals distinct adaptive immune hallmarks in MDA5$^+$ dermatomyositis with therapeutic implications. *Nat Commun* 2022; 13: 6458.
13 Ichimura Y, Konishi R, Shobo M, *et al.* Autoimmunity against melanoma differentiation-associated gene 5 induces interstitial lung disease mimicking dermatomyositis in mice. *Proc Natl Acad Sci USA* 2024; 121: e2313070121.
14 Hu H, Yang H, Liu Y, *et al.* Pathogenesis of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis: a concise review with an emphasis on type I interferon system. *Front Med* 2022; 8: 833114.
15 Takanashi S, Kaneko Y, Takeuchi T. Tofacitinib in interstitial lung disease complicated with anti-MDA5 antibody-positive dermatomyositis: a literature review. *Mod Rheumatol* 2022; 32: 231–237.
16 Chen Z, Wang X, Ye S. Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. *N Engl J Med* 2019; 381: 291–293.
17 Wang Y, Luo J, Lv X, *et al.* Tofacitinib for new-onset adult patients with anti-melanoma differentiation-associated 5 gene antibody positive dermatomyositis. *Clin Rheumatol* 2023; 42: 1847–1853.
18 Li S, Li S, Wang J, *et al.* Efficacy and safety of tofacitinib in anti-melanoma differentiation–associated 5 gene antibody–positive dermatomyositis. *J Clin Rheumatol* 2023; 29: 281–284.
19 Kurasawa K, Arai S, Namiki Y, *et al.* Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. *Rheumatology* 2018; 57: 2114–2119.

20 Xue Y, Zhang J, Deng J, *et al.* Efficiency of tofacitinib in refractory interstitial lung disease among anti-MDA5 positive juvenile dermatomyositis patients. *Ann Rheum Dis* 2023; 82: 1499–1501.
21 Ida T, Furuta S, Takayama A, *et al.* Efficacy and safety of dose escalation of tofacitinib in refractory anti-MDA5 antibody-positive dermatomyositis. *RMD Open* 2023; 9: e002795.
22 Fan L, Lyu W, Liu H, *et al.* A retrospective analysis of outcome in melanoma differentiation-associated gene 5-related interstitial lung disease treated with tofacitinib or tacrolimus. *J Rheumatol* 2022; 49: 1356–1364.
23 Johnson SR, Bernstein EJ, Bolster MB, *et al.* 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol* 2024; 76: 1182–1200.
24 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344–347.
25 Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975; 292: 403–407.
26 Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? *J Am Acad Dermatol* 2002; 46: 626–636.
27 Mammen AL, Allenbach Y, Stenzel W, *et al.* 239th ENMC International Workshop: classification of dermatomyositis, Amsterdam, the Netherlands, 14–16 December 2018. *Neuromuscul Disord* 2020; 30: 70–92.
28 Montagnese F, Babačić H, Eichhorn P, *et al.* Evaluating the diagnostic utility of new line immunoassays for myositis antibodies in clinical practice: a retrospective study. *J Neurol* 2019; 266: 1358–1366.
29 Espinosa-Ortega F, Holmqvist M, Alexanderson H, *et al.* Comparison of autoantibody specificities tested by a line blot assay and immunoprecipitation-based algorithm in patients with idiopathic inflammatory myopathies. *Ann Rheum Dis* 2019; 78: 858–860.
30 Schaefer-Prokop C, Prokop M, Fleischmann D, *et al.* High-resolution CT of diffuse interstitial lung disease: key findings in common disorders. *Eur Radiol* 2001; 11: 373–392.
31 Moghadam-Kia S, Oddis CV, Sato S, *et al.* Anti-melanoma differentiation-associated gene 5 is associated with rapidly progressive lung disease and poor survival in US patients with amyopathic and myopathic dermatomyositis. *Arthritis Care Res* 2016; 68: 689–694.
32 Wu W, Xu W, Sun W, *et al.* Forced vital capacity predicts the survival of interstitial lung disease in anti-MDA5 positive dermatomyositis: a multi-centre cohort study. *Rheumatology* 2022; 61: 230–239.
33 Gono T, Sato S, Kawaguchi Y, *et al.* Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. *Rheumatology* 2012; 51: 1563–1570.
34 Lian X, Zou J, Guo Q, *et al.* Mortality risk prediction in amyopathic dermatomyositis associated with interstitial lung disease: the FLAIR model. *Chest* 2020; 158: 1535–1545.
35 Gono T, Masui K, Nishina N, *et al.* Risk prediction modeling based on a combination of initial serum biomarker levels in polymyositis/dermatomyositis-associated interstitial lung disease. *Arthritis Rheumatol* 2021; 73: 677–686.
36 Jin Q, Fu L, Yang H, *et al.* Peripheral lymphocyte count defines the clinical phenotypes and prognosis in patients with anti-MDA5-positive dermatomyositis. *J Intern Med* 2023; 293: 494–507.
37 Abe K, Furuta S, Kobayashi Y, *et al.* Prognosis of spontaneous pneumomediastinum occurring in dermatomyositis or polymyositis patients with interstitial lung disease according to antimelanoma differentiation-associated gene 5 antibody status: a retrospective cohort study. *RMD Open* 2023; 9: e002770.
38 He S, Zhou Y, Fan C, *et al.* Differences in sex- and age-associated mortality in patients with anti-MDA5-positive dermatomyositis. *Mod Rheumatol* 2023; 33: 975–981.
39 Dias Junior AG, Sampaio NG, Rehwinkel J. A balancing act: MDA5 in antiviral immunity and autoinflammation. *Trends Microbiol* 2019; 27: 75–85.
40 Chen X, Lin S, Jin Q, *et al.* Prevalence, risk factors, and mortality of invasive pulmonary aspergillosis in patients with anti-MDA5^{+} dermatomyositis: a retrospective study in China. *J Inflamm Res* 2024; 17: 3247–3257.
41 Huang L, Fu Q, Ye Y, *et al.* High incidence and mortality of *Pneumocystis jirovecii* infection in anti-MDA5-antibody-positive dermatomyositis: experience from a single center. *Arthritis Res Ther* 2021; 23: 232.
42 Matsuda KM, Yoshizaki A, Kuzumi A, *et al.* Combined immunosuppressive therapy provides favorable prognosis and increased risk of cytomegalovirus reactivation in anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis. *J Dermatol* 2020; 47: 483–489.
43 Liu L, Zhang Y, Liu S, *et al.* Compounded sulfamethoxazole improved the prognosis of dermatomyositis patients positive with anti-melanoma differentiation-associated gene 5. *Rheumatology* 2023; 62: 3095–3100.