Intensive induction therapy combining tofacitinib, rituximab and plasma exchange in severe anti-melanoma differentiation-associated protein-5 antibody-positive dermatomyositis

T. Shirai, T. Machiyama, H. Sato, T. Ishii, H. Fujii

Department of Rheumatology, Tohoku University Hospital, Sendai, Miyagi, Japan.

Abstract

Objective

Anti-melanoma differentiation-associated protein-5 (MDA5) autoantibodies (Abs) are associated with rapidly progressive interstitial lung disease (RP-ILD) in dermatomyositis (DM). Because the addition of plasma exchange (PE) and rituximab (RTX) to triple therapy is inadequate in severe cases, we treat such cases with intensive induction therapy (IIT) combining all these options with tofacitinib (TOF). In this study, we investigated the poor prognostic factors and the efficacy and safety of IIT.

Methods

Thirty-three patients diagnosed with anti-MDA5 Ab-positive DM in our institution between 2014 and 2021 were included. The clinical characteristics of poor prognosis were retrospectively analysed using principal component analysis (PCA), and the outcomes of IIT were analysed in terms of survival, assessed using the Kaplan-Meier test, and adverse events.

Results

Although triple therapy with RTX, PE, or intravenous immunoglobulin was administered before the introduction of IIT, eight of 12 RP-ILD cases with a ferritin level >400 ng/mL (mean, 2,342) died within a median of 2.5 months. PCA revealed distinct clusters for prognosis, and age and serum ferritin were leading predictors of the prognosis. IIT, consisting of combinations of triple therapy with higher doses of methylprednisolone, PE, RTX, and TOF, was applied to eight patients (mean ferritin, 3,558). Although two patients died even with these regimens, a significant improvement in survival was documented. Several IIT-related adverse events were observed, including viral and fungal infections and cytopenia.

Conclusion

IIT significantly improved the survival of patients with severe anti-MDA5 Ab-positive RP-ILD. Although infections are noted, their benefits outweigh the risks in younger patients with high serum ferritin levels.

Key words

dermatomyositis, MDA5, plasma exchange, rituximab, tofacitinib

Tsuyoshi Shirai, MD, PhD
Tomoaki Machiyama, MD, PhD
Hiroko Sato, MD, PhD
Tomonori Ishii, MD, PhD
Hiroshi Fujii, MD, PhD

Please address correspondence to:
Tsuyoshi Shirai
Department of Rheumatology,
Tohoku University Hospital,
1-1 Seiryo-machi, Aoba-ku, Sendai,
Miyagi 980-8574, Japan.
E-mail: tsuyoshirajp@med.tohoku.ac.jp

ORCiD iD: 0000-0002-6295-3494

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Introduction

Rapidly progressive interstitial lung disease (RP-ILD) associated with anti-melanoma differentiation-associated protein 5 (MDA5) autoantibody (Ab)-positive dermatomyositis (DM) is a life-threatening autoimmune condition. The clinical course is rapid, leading to death within three months of symptom onset. Although triple therapy consisting of corticosteroids, cyclophosphamide, and tacrolimus has been considered as standard therapy (1) and additional treatments including plasma exchange (PE) (2) and rituximab (RTX) (3) have been reported, the survival rate of patients with poor prognostic factors is poor even on application of these treatments. Recently, there has been increasing evidence on the efficacy of tofacitinib (TOF) in refractory DM (4-6). We treated anti-MDA5 Ab-positive RP-ILD with multiple poor prognostic factors with intensive induction therapy (IIT) which combined triple therapy, PE, RTX, and TOF (7; 8). Although several studies have reported the efficacy of the addition of PE, RTX, or TOF to triple therapy in anti-MDA5 Ab-positive RP-ILD, data presenting a combination of all these available options are lacking. In this study, we investigated the therapeutic efficacy and safety of IIT in patients with anti-MDA5 Ab-positive RP-ILD and multiple poor prognostic factors.

Materials and methods

Patients

This study included 33 consecutive patients with anti-MDA5 Ab-positive DM who were treated in our department between 2014 and 2021. All patients were positive for anti-MDA5 Ab, and their diagnoses were based on the criteria of Bohan and Peter (9) or Sontheimer for clinically amyopathic DM (10). RP-ILD was defined as the presence of progressive dyspnoea, hypoxaemia, and interstitial lesions on chest radiography or computed tomography (CT) within a few months of the onset of respiratory symptoms (2). Figure 1A shows the outline of patients included in this study. 17 patients were treated during 2014-2018, and nine patients survived (group 1) and eight patients died (group 2). 16 patients were treated during 2019-2021, in which eight patients who were considered fatal received IIT (group 3) and eight patients did not receive IIT (group 4).

Treatment regimen of patients

Until 2018, patients with progressive disease had been initially treated with triple therapy (steroid pulse followed by 1-1.5mg/kg/day of prednisolone (PSL), intravenous cyclophosphamide (IVCY), and tacrolimus) and other interventions including PE, intravenous immunoglobulin (IVIG), and/or RTX at the attending physician's discretion. In 2019, the use of TOF was initiated, and patients who were considered at risk for a lethal course, which were determined by the discussion in our department while considering the clinical characteristics for poor prognosis, were treated with IIT. The regimen of IIT is as follows: corticosteroid, a. 1 g of methylprednisolone, tapering to 1 mg/kg by half every three to seven days b. dexamethasone palmitate 2.5 mg/day until the dose of corticosteroid became equivalent to 1mg/kg of PSL; immunosuppressants, a. IVCY 500-750 mg every two weeks according to the white blood cell counts, b. tacrolimus targeting trough level of 10–12 ng/mL, c. RTX 500 mg/w, d. TOF 10 mg/day; and PE, three days per week according to the condition, and one volume of plasma per session was removed and replaced with fresh frozen plasma. In IIT group, TOF and PE were initiated simultaneously with steroid pulse. RTX was also simultaneously administered except for two patients in whom RTX was administered within a few weeks when worsening ILD was confirmed.

Study design

Medical records were retrospectively assessed for the following information: sex, age, duration until treatment (months), which indicates the duration required to get treatment for ILD after developing initial symptoms, laboratory data including serum ferritin, the number of affected lung lobes among six lobes on CT, SpO_2, oxygen use, treatments, outcomes including death

for any reasons, and adverse events. MCK model was calculated as previously published(11). The clinical data were collected up to 36 months after the development of initial symptoms of anti-MDA5 Ab-positive DM. The clinical characteristics of poor prognosis were retrospectively analysed, and the outcomes of IIT were analysed in terms of survival and adverse events. The study protocol complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (reference number: 2021-1-917). Written informed consent was not required owing to the retrospective observational nature of the study. Written informed consent in off-label use of TOF, dexamethasone palmitate, and PE was obtained from patients.

Statistical analysis

All statistical analyses except for cluster analysis were performed using GraphPad Prism 9 (GraphPad, San Diego, CA, USA) software. Principal component analysis (PCA) was used to analyse multivariate parameters (12). The Mann-Whitney U-test or t-test was used for continuous data, and the chi-squared or Fisher's exact test was used for binary data. The cumulative survival rate was calculated using the Kaplan-Meier test. The log-rank test was also used to compare survival. Cluster analysis was performed using JMP software (JMP Pro 16, SAS Institute, Cary, NC, USA). Statistical significance was set at $p<0.05$.

Table I. Clinical characteristics of patients with anti-MDA5 antibody-positive dermatomyositis before and after the introduction of IIT.

	2014-2018 n=17	2019–2021 n=16	*p*-value
Male	3 (17.6%)	3 (18.8%)	0.93
Age	50.4 ± 17.8	53.8 ± 14.5	0.63
Duration till treatment from initial symptoms (months)	3.3 ± 2.6	2.2 ± 2.0	0.17
Serum ferritin (ng/mL)	1221 ± 1761	1528 ± 2222	0.66
ILD	17 (100%)	16 (100%)	1.0
RP-ILD	12 (70.6%)	13 (81.3%)	0.48
Lung lesion	2.8 ± 1.4	3.5 ± 1.6	0.18
SpO_2	95.3 ± 2.8	94.1 ± 3.9	0.23
Oxygen use	3 (17.6%)	5 (31.3%)	0.36
MCK score			0.28
0	8 (47.1%)	7 (43.8%)	
1	8 (47.1%)	5 (31.3%)	
2	1 (5.9%)	4 (25%)	
Irreversible respiratory dysfunction	8 (47.1%)	2 (12.5%)	0.03
Pre-existing structural lung disease	1 (5.9%)	2 (12.5%)	0.51
Dysphagia	3 (17.6%)	4 (25%)	0.61
Smoking history	3 (17.6%)	3 (18.8%)	0.93
Positive ventilation on admission	0 (0%)	0 (0%)	1.0
Triple therapy	14 (82.4%)	16 (100%)	0.09
RTX	7 (41.1%)	8 (50%)	0.61
PE	6 (35.3%)	9 (56.3%)	0.23
IVIG	4 (23.5%)	1 (6.3%)	0.17
TOF	0 (0%)	13 (81.3%)	0.0001
Death	8 (47.1%)	2 (12.5%)	0.03

IIT: intensive induction therapy; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; PE: plasma exchange; RP-ILD: rapidly progressive-interstitial lung disease; RTX: rituximab; TOF: tofacitinib.
Lung lesion indicates the number of the affected lung lobes. The Mann-Whitney U-test or t-test was used for continuous data, and the Fisher's exact test was used for binary data.

Results

Survival rates before introduction of IIT

The clinical characteristics of patients during 2014-2018 and 2019-2021 were shown in Table I. Seventeen patients were treated before the introduction of TOF, and survival rate was 53% (Table I, Fig. 1B). Although all patients who died were treated with triple therapy with or without the additional use of RTX, PE, or IVIG, eight out of 12 RP-ILD cases with a ferritin level >400 ng/mL (range, 402.5–5,831; mean, 2,342 ± 2,069) died within a median of 2.5 months after the development of clinical symptoms (Table II, G1:G2; Fig. 1C). Furthermore, all patients with ferritin level >1.000 ng/mL died within 2.5 months. Meanwhile, all patients with ferritin levels of <400 ng/mL survived. Higher serum ferritin levels were observed in older patients (Fig. 1D); therefore, death was observed in patients older than 45 years in our cohort (Fig. 1E). Although PE and RTX were administered to some patients from the beginning of treatment, early death could not be prevented compared with triple therapy alone, as shown in Figure 1F. IVIG was attempted as an escalation therapy in four patients, and its efficacy was not apparent.

Predictive factors for lethal course before introduction of IIT

All male patients and patients requiring oxygen became lethal in our cohort until 2018, and older age, shorter duration until treatment, higher levels of serum ferritin, more involvement of lung lesions, and lower SpO_2 were significantly different between the alive and dead patients (Table II). Importantly, distinct clusters differentiating dead and alive were formed by such clinical parameters (Fig. 2A). To visualise the contribution of the influencing factors, PCA was performed using multiple factors, including clinical and laboratory data (Fig. 2B, C). Live patients were closely clustered (Fig. 2B), which was characterised by maintained levels of serum albumin, blood cell counts, SpO_2, and longer duration until treatment (Fig. 2C). In contrast, two clusters were observed in patients who died. One was characterised by higher levels of serum ferritin and other deviation enzymes and comprised men. The other was characterised by older age, lung involvement, Krebs von den lungen-6 (KL-6), and elevated C-reactive protein (CRP) levels. The receiver-operating characteristic (ROC) curve predicting death was evaluated, and a high area under the curve (AUC)

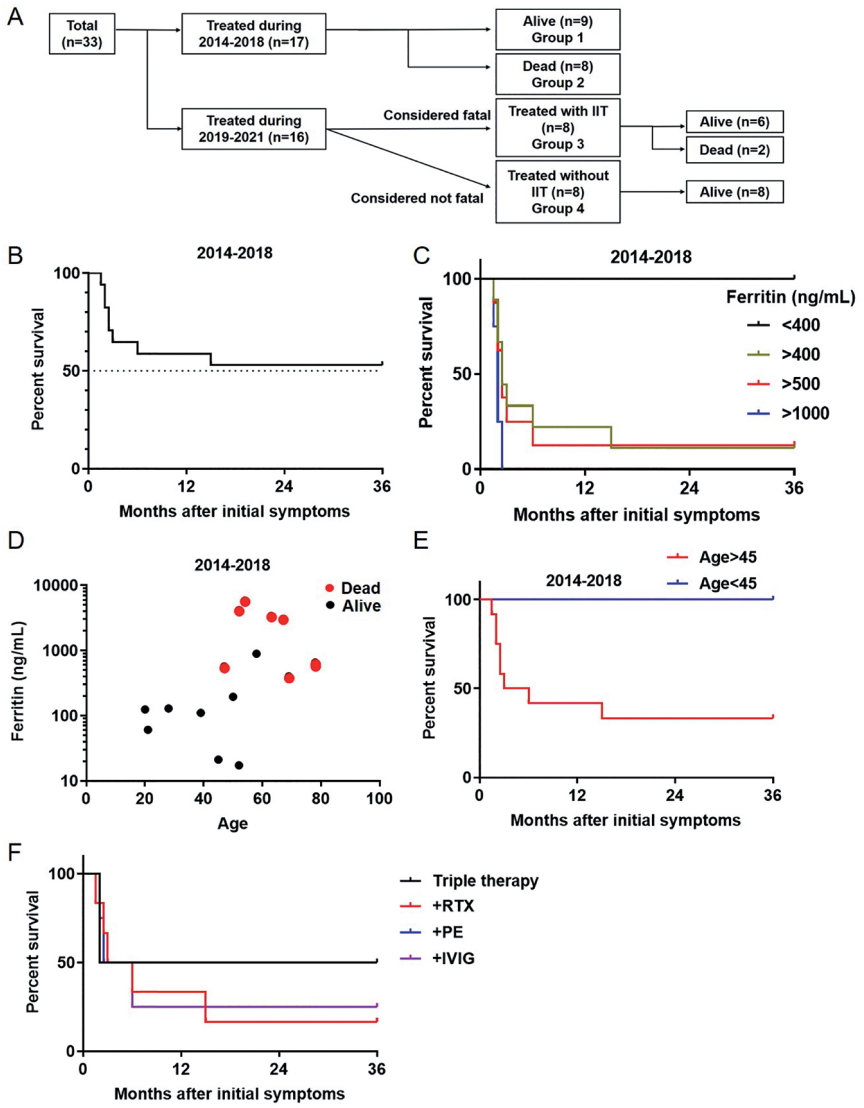

Fig. 1. Survival of patients before introduction of intensive induction therapy.
A. Outline of patients included in this study. **B**. Survival curve of patients with anti-melanoma differentiation-associated protein-5 autoantibody-positive dermatomyositis before intensive induction therapy. **C**. Survival curves according to the corresponding levels of serum ferritin. <400: n=8; >400: n=9; >500: n=8; and >1000: n=4. **D**. Serum ferritin levels and age in each patient. Black indicates alive patients, and red indicates dead patients. **E**. Survival curves according to age. <45: n=6 and >45: n=11. **F.** Survival curves in patients treated with triple therapy alone (n=2), addition of either rituximab (n=7), plasma exchange (n=6), or intravenous immunoglobulin (n=4).

of serum ferritin (cut-off, 487 ng/mL; AUC, 0.94), age (cut-off, 51; AUC, 0.92), and prediction value by PCA component (AUC, 0.99) were shown (Fig- 2D-F). Most patients partially responded to treatment during steroid pulse therapy, and mild improvements in general symptoms, cutaneous lesions, and laboratory data were observed. However, these mild improvements were followed by exacerbation of lung lesions, and in such situations, the addition of multiple treatments was not successful.

Survival rates after introduction of IIT

Because the addition of RTX and PE to triple therapy was insufficient to save severe RP-ILD in anti-MDA5 Ab-positive DM, prevention of the initial exacerbation of ILD was considered important. Based on these observations, de-escalation therapy was considered desirable, and TOF was used because some reports suggested its effectiveness in anti-MDA5 Ab-positive DM (4-6). However, the effectiveness of PE and RTX has also been reported, and the exclusion of these treatments was difficult. Therefore, IIT consisted of the following: triple therapy with decreasing the dose of methylprednisolone by half from 1 g to 1 mg/kg in three to five days, liposteroid to suppress macrophage activity, and TOF, PE, and RTX during the initial induction phase. IIT was applied in eight patients (ferritin levels: range, 412.2–7,095 ng/mL; mean, 3,558±3,152 ng/mL) with multiple poor prognostic factors including serum ferritin levels, age, and prediction by PCA (Fig. 3A). Most of patients with serum ferritin level >500 ng/mL were treated with IIT without one patient whose age and serum ferritin level were 81 and 563.9 ng/mL, respectively. Baseline clinical characteristics were similar between patients who died during 2014-2018 and patients treated with IIT (Table II, G2:G3). After introduction of IIT (2019-2021), significant improvement of survival was observed in total population compared with historical control (Fig. 3B). Early death within 2.5 months was avoided except for one patient, and the survival rate of patients with high levels of serum ferritin was also significantly improved compared to that of historical control (Fig. 3C). Death at two and eight months in the IIT group was due to the exacerbation of ILD. Initial RTX administration was avoided in two patients because of the high intensity of immunosuppression; exacerbation of ILD was observed in a few weeks in both patients, which prompted the use of RTX. Among these two patients, one patient survived and another patient died at eight months. The clinical characteristics of patients who died during IIT are summarised in Table III. Both patients who died manifested rapid progression of ILD on admission, and a different approach is still needed in such situations. Gono *et al*. built a MCK model based on anti-MDA5 Ab, levels of CRP, and KL-6 for predicting prognosis (11). Risk score was defined as 0-2 according to the presence of CRP ≥0.8 mg/dL and KL-6 ≥1,000 U/mL. Survival curves according to the MCK model is shown in Figure 3D, showing the tendency for the improvement of survival in each group.

Table II. Clinical characteristics of patients in each group.

	2014–2018		2019–2021		*p*-value		
	Group 1 Alive (n=9)	Group 2 Dead (n=8)	Group 3 IIT+ (n=8)	Group 4 IIT- (n=8)	G1:G2	G2:G3	G3:G4
Male	0 (0%)	3 (37.5%)	3 (37.5%)	0 (0%)	0.082	1.0	0.2
Age	38.7 ± 13.7	63.5 ± 11.7	51.8 ± 9.1	55.8 ± 18.9	0.0018	0.05	0.59
Duration till treatment from initial symptoms (months)	5.0 ± 2.7	1.6 ± 1.1	1.5 ± 1.4	2.8 ± 2.4	0.0057	0.57	0.082
Serum ferritin (ng/mL)	225 ± 288 (17.3–891.7)	2342 ± 2069 (402.5–5831)	2760 ± 2661 (412.2–7095)	296 ± 163 (63.8–563.9)	0.0019	0.65	0.0006
ILD	9 (100%)	8 (100%)	8 (100%)	8 (100%)	1.0	1.0	1.0
RP-ILD	4 (44.4%)	8 (100%)	8 (100%)	5 (62.5%)	0.03	1.0	0.2
Lung lesion	2.1 ± 0.3	3.6 ± 1.7	4.5 ± 1.7	2.6 ± 0.7	0.023	0.49	0.046
SpO_2	96.8 ± 0.8	93.6 ± 3.3	92.1 ± 3.8	96.0 ± 3.0	0.032	0.55	0.021
Oxygen use	0 (0%)	3 (37.5%)	5 (62.5%)	0 (0%)	0.082	0.62	0.026
MCK score					0.45	0.23	0.04
0	4 (44.4%)	4 (50%)	1 (12.5%)	6 (75%)			
1	5 (55.6%)	3 (37.5%)	4 (50%)	1 (12.5%)			
2	0 (0%)	1 (12.5%)	3 (37.5%)	1 (12.5%)			
Irreversible respiratory dysfunction	0 (0%)	8 (100%)	2 (25%)	0 (0%)	0.0001	0.002	0.24
Pre-existing structural lung disease	0 (0%)	1 (12.5%)	2 (25%)	0 (0%)	0.27	0.52	0.45
Dysphagia	0 (0%)	3 (37.5%)	3 (37.5%)	1 (12.5%)	0.21	1.0	0.57
Smoking history	1 (11.1%)	2 (25%)	2 (25%)	1 (12.5%)	0.58	1.0	1.0
Positive ventilation on admission	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0	1.0	1.0
Triple therapy	6 (66.6%)	8 (100%)	8 (100%)	8 (100%)	0.21	1.0	1.0
RTX	2 (22.2%)	5 (62.5%)	8 (100%)	0 (0%)	0.15	0.2	0.0002
PE	1 (11.1%)	5 (62.5%)	8 (100%)	1 (12.5%)	0.049	0.2	0.0014
IVIG	1 (11.1%)	3 (37.5%)	1 (12.5%)	0 (0%)	0.29	0.57	1.0
TOF	0 (0%)	0 (0%)	8 (100%)	5 (62.5%)	1.0	0.0002	0.20
Death	0 (0%)	8 (100%)	2 (25%)	0 (0%)	<0.0001	0.007	0.47

IIT: intensive induction therapy; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; PE: plasma exchange; RP-ILD: rapidly progressive-interstitial lung disease; RTX: rituximab; TOF: tofacitinib.
Lung lesion indicates the number of the affected lung lobes. The Mann-Whitney U-test or t-test was used for continuous data, and the Fisher's exact test was used for binary data.

Predictive factors for lethal course

We performed PCA in patients in this study, except in those who survived with the use of TOF (Fig. 4A, B). The results were similar but became clearer compared with Figure 2B and C. Alive patients were characterised by maintained levels of serum albumin, blood cell counts, and SpO_2, and dead patients were characterised by higher levels of serum ferritin and other deviation enzymes, or higher age, lung involvement, and CRP levels. The ROC curve predicting death was evaluated, and a high AUC of PC1 (AUC, 0.98) and PC1 + PC2 (AUC, 0.99) was observed (Fig. 2C and D). Among multiple factors, serum ferritin was the best indicator of death (cut-off, 412; AUC, 0.97).

Adverse events in IIT

Several adverse events were observed in the IIT group (Table IV). The most common event was reactivation of cytomegalovirus (75%), while herpes zoster was reported in one case which was not during the induction phase. Haemorrhagic cystitis was observed in one patient, in whom the BK virus and adenovirus were detected. Fungal infections of the lungs were also documented. Three cases were Aspergillus infections, and one patient was diagnosed with Nocardia infection. These infections were successfully controlled by supportive care together with antiviral or antifungal drugs. Sustained leukocytopenia and thrombocytopenia were observed in three patients. Granulocyte-colony stimulating factor was administered, and cytopenia improved within weeks. Although schistocytes were detected in two patients and complications of thrombotic microangiopathy (TMA) were considered, no significant clinical and laboratory manifestations were observed. However, this led to tacrolimus discontinuation. One patient who died after eight months was proven to have pulmonary alveolar proteinosis (PAP) on autopsy, although it coexisted with severe pulmonary fibrosis and the cause of death was considered to be ILD.

Discussion

The survival rate of patients with anti-MDA5 Ab-positive DM differs among studies, possibly due to the heterogeneity of the disease and the different situations of institutions reporting outcomes. Nakashima *et al*. reported the efficacy of triple therapy in 14 patients with a survival rate of 75% (13). So *et al*. recently reported 116 patients, of whom 100 (86.2%) had ILD, 47 (40.5%) had RP-ILD, and 44 (37.9%) patients died (14). Therefore, the prognosis of anti-MDA5 Ab-positive RP-ILD differs among studies and remains poor.

On the other hand, some studies, including ours, presented older age as a poor prognostic factor (8); conversely, younger patients presenting with minor lung involvement might not necessarily require intensive immunosuppression (15). Anti-MDA5 Ab can be positive in patients previously diagnosed

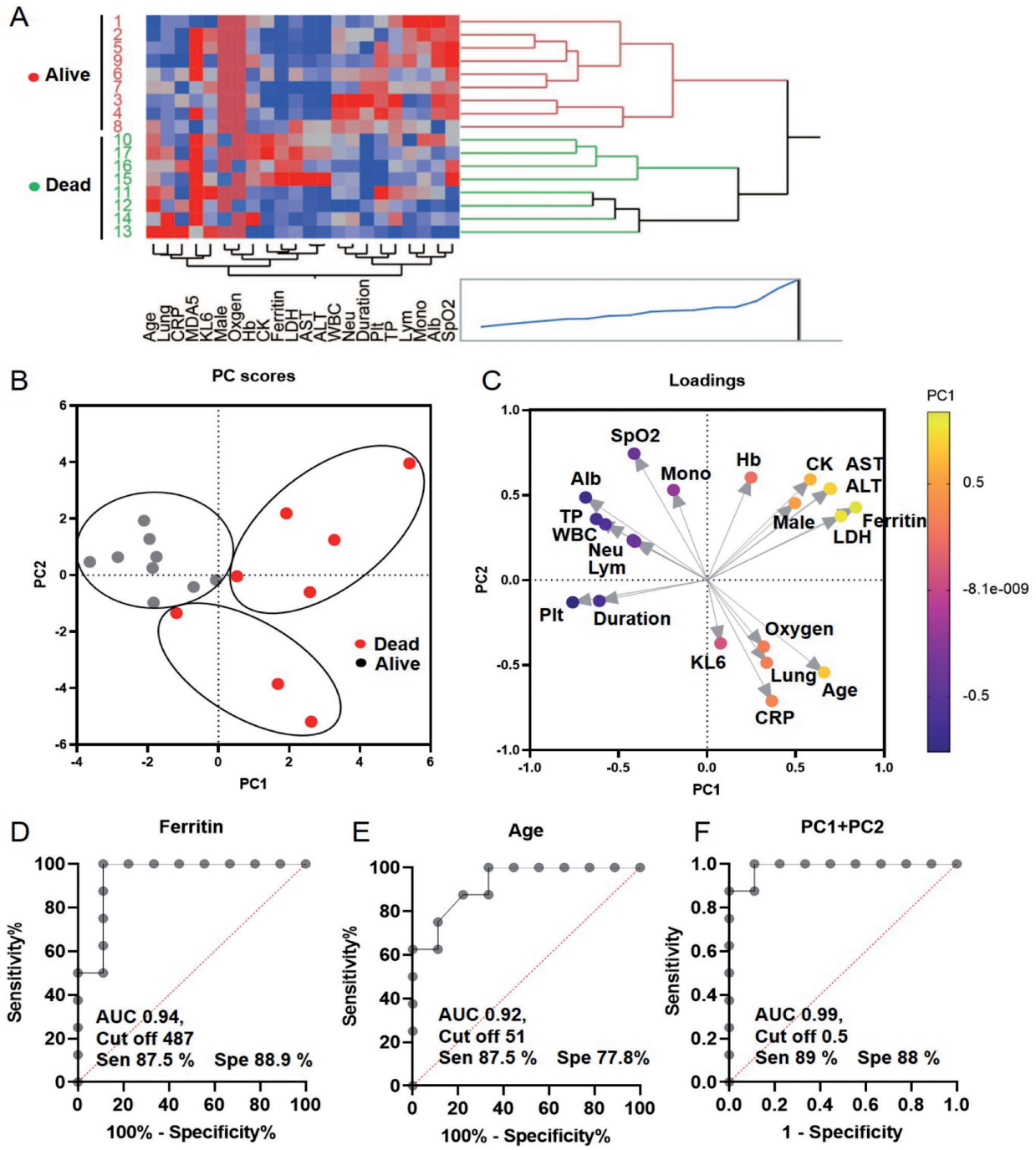

Fig. 2. Principal component analysis of patients before the introduction of intensive induction therapy.
A: Cluster analysis of patients treated during 2014-2018 based on the clinical parameters. Red indicates alive patients and green indicates dead patients.
B-**C**: Principal component analysis (PCA) of 17 patients with anti-MDA5 Ab-positive dermatomyositis before the introduction of intensive induction therapy. **B**: Plots of each patient according to the PC scores. Red indicates dead patients and black indicates alive patients. **C**: The contribution of each loading to the PC is shown.
D-**F**: ROC analysis for death by serum ferritin level (**D**), age (**E**), and prediction by PCA (**F**).
Anti-MDA5-Ab: anti-melanoma differentiation-associated protein-5 autoantibodies; ROC: receiver operating characteristic.

with clinically amyopathic DM with minimal lung involvement, who had been treated with topical medications. Because of the increasing availability of detection methods for anti-MDA5 Ab, diagnosis of such mild cases would also be increasing; therefore, over-treatment should be avoided in such patients.

Several other factors have been reported as poor prognostic factors. Serum ferritin level was the most predictive factor in this study, as reported by Gono *et al*. (16). Interestingly, PCA revealed that one of the clusters of lethal cases was characterised by high serum ferritin levels and elevated deviation enzymes. This suggests an aberrantly activated cytokine network in this population, and male patients seemed to be susceptible. The association of

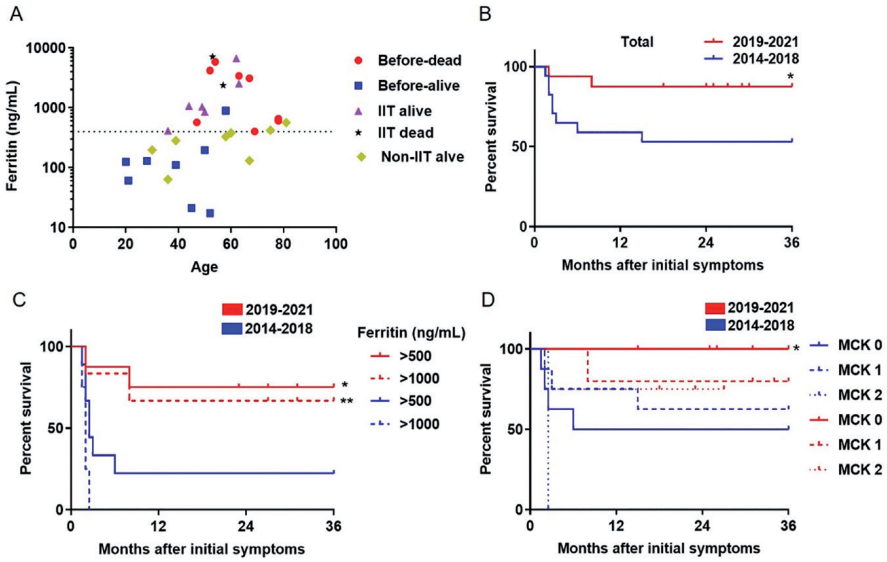

Fig. 3. Improved survival of patients after introducing intensive induction therapy.
A: Serum ferritin levels and age in all patients in this study were plotted. Dot line indicates ferritin levels of 400 ng/mL. **B**: Survival curves comparing total patients treated during 2014-2018 (blue) and 2019-2021 (red). **C**: Survival curves before 2018 (blue) and after 2019 (red) according to serum ferritin. red>500, n=8; red>1000, n=6; blue>500, n=8; and blue>1000, n=4. **D**: Survival curves before 2018 (blue) and after 2019 (red) according to MCK value. blue MCK0: n=8; blue MCK1: n=8; blue MCK2: n=1; red MCK0: n=7; red MCK1: n=5; red MCK2: n=4.
Before-dead: dead patients before introducing IIT; before-alive: alive patients before introducing IIT; IIT alive: alive patients treated with IIT; IIT dead: dead patients treated with IIT; non-IIT alive: alive patients in whom IIT was not performed.
CNi: calcineurin inhibitor; CS: corticosteroid; IVCY: intravenous cyclophosphamide; IVIG: intravenous immunoglobulin; PE: plasma exchange; RTX: rituximab; TOF: tofacitinib.
**p*<0.05; ***p*<0.01.

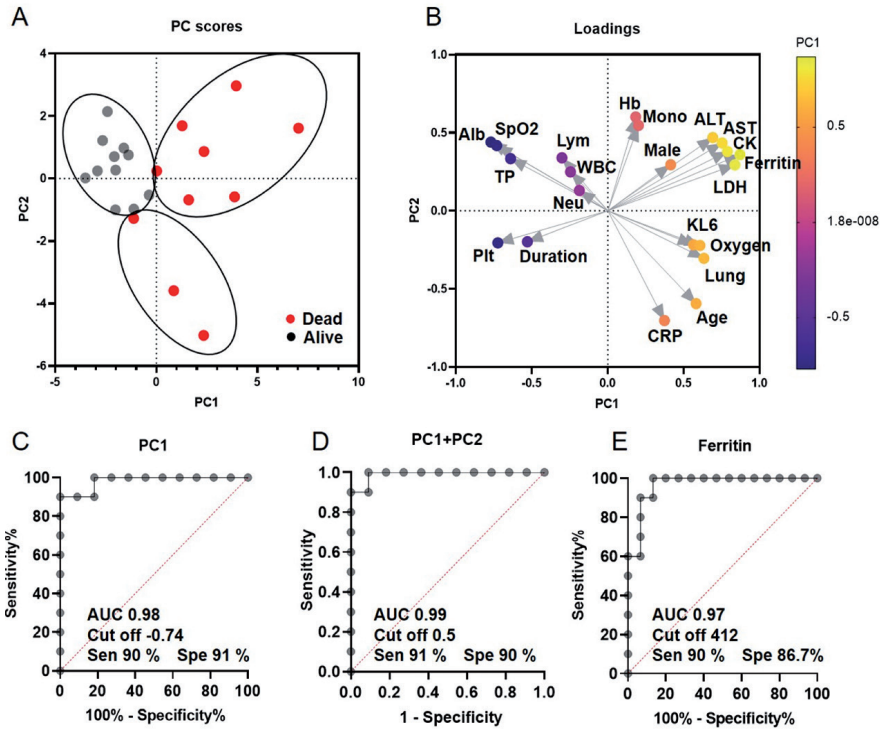

Fig. 4. Principal component analysis of patients without the use of tofacitinib.
A-**B**: Principal component analysis (PCA) of patients in this study except for those who survived with the use of TOF. **A**: Plots of each patient according to the PC scores. Red indicates dead patients and black indicates alive patients. **B**: The contribution of each loading to the PC is shown.
C-**E**: ROC analysis for death by PC1 (**C**), prediction by PCA (**D**), and serum ferritin (**E**).

anti-Ro52 autoantibodies was shown (17). Recently, three different phenotypes were reported using eight variables: age, disease course, myasthenia, arthritis, CRP, CK, anti-Ro52, and anti-MDA5 antibody titres; however, serum ferritin level, which would be the most significant predictive factor, was not included (18). Additionally, two distinct immune cell signatures have been reported (19). PR-ILD is associated with enriched activated $CD8^+$ T cells with decreased $CD56^{dim}$ NK cells.

In addition to such heterogeneity of disease, our hospital is a referral centre in the northeast area of Japan that treats patients with severe autoimmune diseases, including DM. The mean serum ferritin level of patients who died in this study was 2342 ng/mL, which was much higher than that reported in other studies, indicating a more severe disease in this study (2, 20). Therefore, this study suggests that the treatment outcome of anti-MDA5 Ab-positive RP-ILD in such referral hospitals is still poor, even if triple therapy combined with PE, RTX, and IVIG was applied. The median duration to referral and death in this study were 1.6 and 2.5 months, respectively; therefore, lethal cases died within four weeks after admission. The disease activity of most of these cases became uncontrollable within two to three weeks after admission, and the addition of other treatment options on exacerbation was not usually successful, as shown in this study. A systematic review of RTX in anti-MDA5 Ab-positive DM showed an efficacy of 71.43% in the literature (3). Their study included patients who were successfully treated with IIT (7, 8). Moreover, reporting bias should be considered when analysing case reports. The efficacy of RTX was 28.6% (2/7) in patients before introducing IIT in this study, which needed the change in treatment strategy. Shirakashi *et al.* reported the efficacy of PE (2), in which eight refractory patients received PE and five survived. The efficacy of PE in our study before introducing IIT was one survival in six patients, and the difference from our result might be due to the activity status of the disease between studies; the mean serum ferritin

Table III. Clinical characteristics of dead patients under intensive induction therapy.

	Intensive induction therapy		*p*
	Alive (n=6)	Dead (n=2)	
Male	2 (33.3%)	1 (50%)	1
Age	50.1 ± 10.4	55 ± 2.8	0.64
Duration till treatment (M)	1.7 ± 1.6	1	1
Ferritin (ng/mL)	2103 ± 2368 (412–6711)	4731 ± 3344 (2366–7095)	0.29
Lung lesion	4.0 ± 1.7	6.0 ± 0.0	0.35
SpO_2	93.7 ± 2.4	87.5 ± 3.5	0.11
Oxygen use	3 (50%)	2 (100%)	0.46
Triple therapy	6 (100%)	2 (100%)	1
RTX	6 (100%)	2 (100%)	1
PE	6 (100%)	2 (100%)	1
IVIG	0 (0%)	1 (50%)	1
TOF	6 (100%)	2 (100%)	1

IVIG: intravenous immunoglobulin; PE: plasma exchange; RTX: rituximab; TOF: tofacitinib.

Table IV. Adverse events in this study.

	2014-2018 Alive (n=9)	2014-2018 Dead (n=8)	2019-2021 IIT+ (n=8)	2019-2021 IIT- (n=8)
Infection				
Viral				
Cytomegalovirus	2 (22.2%)	2 (25%)	6 (75%)	1 (12.5%)
Varicella zoster	0 (0%)	0 (0%)	1 (12.5%)	1 (12.5%)
BK virus	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)
Adenovirus cystitis	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)
Fugal				
Aspergillus	0 (0%)	0 (0%)	3 (37.5%)	1 (12.5%)
Cryptococcus	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)
Nocardia	0 (0%)	0 (0%)	1 (12.5%)	1 (12.5%)
Pneumocystis	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)
Cytopenia	0 (0%)	2 (25%)	3 (37.5%)	1 (12.5%)
Thrombotic microangiopathy	0 (0%)	0 (0%)	2 (25%)	0 (0%)
Alveolar proteinosis	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)
Death due to respiratory failure	0 (0%)	8 (100%)	2 (25 %)	0 (0%)

level was 488.1 ng/mL in their progressive population. Similarly, IVIG was ineffective. We also attempted de-escalation therapy combining PE and RTX with triple therapy from the beginning, which could not save the lives of most patients in our hospital; therefore, we sought another interventional approach. As a Janus kinase (JAK) inhibitor, ruxolitinib, a selective inhibitor of JAK1 and JAK2, was first reported in patients with DM complicated by post-polycythaemia vera myelofibrosis (21). The efficacy of TOF, a JAK1/3 inhibitor, in DM was first reported by Kurtzman *et al*. in refractory cutaneous DM (22). Thereafter, several case reports have shown its efficacy in systemic manifestations of DM (23). Kurasawa *et al*. first reported the efficacy of TOF in anti-MDA5 Ab-positive refractory ILD, in which TOF was added to patients who failed to respond to triple therapy (4-6). A single-centre, open-label clinical study performed in China reported a significantly higher complete survival at six months (20). Suppression of interferon signalling, which plays an important role in DM by TOF might be critical (24), but TOF also inhibits multiple cytokines. Recently, IL-15 was reported to be higher in anti-MDA5 Ab-positive RP-ILD (25). JAK1/3 is involved in the production of IL-15, and TOF has been shown to have an approximately two-fold stronger inhibitory activity against IL-15 than other JAK inhibitors (26). Therefore, inhibition of JAK1/3 may be preferable for anti-MDA5 Ab-positive RP-ILD. Recent literature review regarding the efficacy of TOF reported that survival rates were 100% in the first induction therapy cases with a median follow-up of six months and 75% in the refractory or relapsing cases (27). On the other hand, publication bias should be considered, and as shown in this study, the addition of TOF to triple therapy in the first induction therapy did not completely overcome anti-MDA5 Ab-positive severe RP-ILD. However, significant improvement in survival was observed after introducing TOF in this study, providing the evidence for its usefulness. Another difference in regimen was the dosing of corticosteroid, which could reduce the exacerbation of ILD during induction therapy. Total dose of corticosteroid equivalent to PSL in the initial two weeks was approximately 4.5 g and 7.4 g, in 2014-2018 and in 2019-2021, respectively. Among the eight patients treated with IIT in this study, RTX was not used initially in two patients. However, exacerbation of the lung lesion was noticed, and RTX was administered simultaneously in the induction therapy in this study. Because of the large number of drugs used in IIT, it is desirable to disuse unnecessary drugs; however, it is difficult to determine which drugs are unnecessary at this stage. Further, it should be recognised that the most severe case was refractory to these intensive regimens.

Such intensive regimens require careful attention to avoid adverse events, including infections. In particular, viral infections were frequent, as has been observed in previous studies. Re-activation of cytomegalovirus was the most frequent but was successfully controlled by ganciclovir. Therefore, pre-emptive and prophylactic ganciclovir therapies are ideal. Although TOF is known to increase the risk of herpes zoster (28), none of the patients developed herpes zoster during the induction phase. Fungal infections, including Aspergillus, require more attention because the lungs are frequent sites for fungal infections. In addition, drug interactions are frequent between tacrolimus and antifungal drugs. Prolonged cytopenia was observed in three patients. Although cytomegalovirus infection and medications, including ganciclovir and IVCY, could be the cause of cytopenia, other reasons were also considered. Cytopenia following the use of RTX has been recognised (29),

and supportive therapy, including granulocyte colony-stimulating factor, is required. TMA was also documented in three patients, although they were mild and presented with schistocytes without apparent laboratory abnormalities related to haemolysis. The complication of TMA in anti-MDA5 Ab-positive DM has occasionally been described in active patients (30), and the use of tacrolimus was discontinued in our cases. PAP is also rarely complicated in DM (31) and was seen in one patient in this study on autopsy. Although dysfunction of alveolar macrophages would have led to secondary PAP, the cause of death was considered to be exacerbation of ILD; therefore, intensive treatment was required in such patients.

As shown in this study, serum ferritin levels tended to be higher in older patients. However, the intensity of immunosuppression of IIT would be extremely high for elderly patients. As shown in Figure 3A, IIT was not performed in patients beyond their late 60s. Because the addition of RTX seemed to significantly affect the immunosuppressive status of patients, additional treatment with PE or TOF to conventional triple therapy was applied in such patients.

The limitations of this study include the small number of patients and retrospective design. The application of IIT was determined by the clinical discussion considering poor prognostic factors, and strict inclusion criteria was not predetermined. The influence of additional immunosuppression before the introduction of IIT on the outcome cannot be ruled out, although intensified treatments would not have negatively affected the poor outcome because progression of ILD was the cause of death in these patients. Moreover, the tapering rate of corticosteroids is not uniform, which could have an impact on patient survival.

In conclusion, a significant improvement in survival was observed with the introduction of IIT in patients with severe anti-MDA5 Ab-positive RP-ILD. IIT would be a treatment option for patients in their 30s to 60s with multiple prognostic factors, particularly those with very high serum ferritin levels. On the other hand, there are patients who are refractory even to these intensive regimens, and further therapeutic approaches and elucidation of pathological mechanisms are required.

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References

1. 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: 488-98. https://doi.org/10.1002/art.41105
2. SHIRAKASHI M, NAKASHIMA R, TSUJI H *et al*.: Efficacy of plasma exchange in anti-MDA5-positive dermatomyositis with interstitial lung disease under combined immunosuppressive treatment. *Rheumatology* 2020; 59: 3284-92. https://doi.org/10.1093/rheumatology/keaa123
3. HE C, LI W, XIE Q, YIN G: Rituximab in the treatment of interstitial lung diseases related to anti-melanoma differentiation-associated gene 5 dermatomyositis: A systematic review. *Front Immunol,* 2021; 12: 820163. https://doi.org/10.3389/fimmu.2021.820163
4. 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: 2114-9. https://doi.org/10.1093/rheumatology/key188
5. WENDEL S, VENHOFF N, FRYE BC *et al*.: Successful treatment of extensive calcifications and acute pulmonary involvement in dermatomyositis with the janus-kinase inhibitor tofacitinib - A report of two cases. *J Autoimmun* 2019; 100: 131-6. https://doi.org/10.1016/j.jaut.2019.03.003
6. KATO M, IKEDA K, KAGEYAMA T *et al*.: Successful treatment for refractory interstitial lung disease and pneumomediastinum with multidisciplinary therapy including tofacitinib in a patient with anti-MDA5 antibody-positive dermatomyositis. *J Clin Rheumatol* 2021; 27: S574-7. https://doi.org/10.1097/RHU.0000000000000984
7. AKIYAMA C, SHIRAI T, SATO H *et al*.: Association of various myositis-specific autoantibodies with dermatomyositis and polymyositis triggered by pregnancy. *Rheumatol Int* 2022; 42: 1271-80. https://doi.org/10.1007/s00296-021-04851-1
8. MACHIYAMA T, SHIRAI T, FUJITA Y *et al*.: Successful concomitant therapy with tofacitinib for anti- melanoma differentiation associated gene 5 antibody-positive rapidly progressive interstitial lung disease with poor prognostic factors: A case report and literature review. *Medicine: Case Reports and Study Protocols*, 2021; 2: e0026. https://doi.org/10.1097/md9.0000000000000026
9. BOHAN A, PETER JB: Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975; 292: 403-7. https://doi.org/10.1056/NEJM197502202920807
10. SONTHEIMER RD: Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? *J Am Acad Dermatol* 2002; 46: 626-36. https://doi.org/10.1067/mjd.2002.120621
11. 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: 677-86. https://doi.org/10.1002/art.41566
12. LEVER J, KRZYWINSKI M, ATMAN N: Points of significance Principal component analysis. *Nature Methods* 2017; 14: 641-2. https://doi.org/10.1038/nmeth.4346
13. NAKASHIMA R, HOSONO Y, MIMORI T: Clinical significance and new detection system of autoantibodies in myositis with interstitial lung disease. *Lupus* 2016; 25: 925-33. https://doi.org/10.1177/0961203316651748
14. SO J, SO H, WONG VT *et al*.: Predictors of rapidly progressive- interstitial lung disease and mortality in patients with autoantibodies against melanoma differentiation-associated protein 5 dermatomyositis. *Rheumatology* 2022; 61: 4437-44. https://doi.org/10.1093/rheumatology/keac094
15. YANG Q, LYU K, LI J *et al*.: Anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis exhibit three clinical phenotypes with different prognoses. *Clin Exp Rheumatol* 2022; 40: 304-8. https://doi.org/10.55563/clinexprheumatol/df2oc3
16. GONO T, KAWAGUCHI Y, SATOH T *et al*.: Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. *Rheumatology* 2010; 49: 1713-9. https://doi.org/10.1093/rheumatology/keq149
17. CAVAGNA L, MELONI F, MEYER A *et al*.: Clinical spectrum time course in non-Asian patients positive for anti-MDA5 antibodies. *Clin Exp Rheumatol* 2022; 40: 274-83. https://doi.org/10.55563/clinexprheumatol/di1083
18. XU L, YOU H, WANG L *et al*.: Identification of three different phenotypes in anti-MDA5 antibody-positive dermatomyositis patients: implications for rapidly progressive interstitial lung disease prediction. *Arthritis Rheumatol* 2022. https://doi.org/10.1002/art.42308
19. YE Y, ZHANG X, LI T *et al*.: Two distinct immune cell signatures predict the clinical outcomes in patients with amyopathic dermatomyositis with interstitial lung disease. *Arthritis Rheumatol* 2022; 74: 1822-32. https://doi.org/10.1002/art.42264
20. CHEN Z, WANG X, YE S: Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. *N Engl J Med* 2019; 381: 291-3. https://doi.org/10.1056/NEJMc1900045
21. HORNUNG T, JANZEN V, HEIDGEN FJ *et al*.:

Remission of recalcitrant dermatomyositis treated with ruxolitinib. *N Engl J Med* 2014; 371: 2537-8. https://doi.org/10.1056/NEJMc1412997
22. KURTZMAN DJ, WRIGHT NA, LIN J *et al*.: Tofacitinib citrate for refractory cutaneous dermatomyositis: an alternative treatment. *JAMA Dermatol* 2016; 152: 944-5. https://doi.org/10.1001/jamadermatol.2016.0866
23. PAIK JJ, CHRISTOPHER-STINE L: A case of refractory dermatomyositis responsive to tofacitinib. *Semin Arthritis Rheum* 2017; 46: e19. https://doi.org/10.1016/j.semarthrit.2016.08.009
24. KAO L, CHUNG L, FIORENTINO DF: Pathogenesis of dermatomyositis: role of cytokines and interferon. *Curr Rheumatol Rep* 2011; 13: 225-32. https://doi.org/10.1007/s11926-011-0166-x
25. SHIMIZU T, KOGA T, FURUKAWA K *et al*.: IL-15 is a biomarker involved in the development of rapidly progressive interstitial lung disease complicated with polymyositis/dermatomyositis. *J Intern Med* 2021; 289: 206-20. https://doi.org/10.1111/joim.13154
26. TRAVES PG, MURRAY B, CAMPIGOTTO F *et al*.: JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib. *Ann Rheum Dis* 2021; 80: 865-75. https://doi.org/10.1136/annrheumdis-2020-219012
27. 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: 231-7. https://doi.org/10.1080/14397595.2021.1906505
28. CURTIS JR, XIE F, YANG S *et al*.: Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. *Arthritis Care Res* 2019; 71: 1249-54. https://doi.org/10.1002/acr.23769
29. SHAH S, KAVADICHANDA CG, BELANI P *et al*.: Early onset neutropenia and thrombocytopenia following rituximab in lupus nephritis. *Int J Rheum Dis* 2019; 22: 946-50. https://doi.org/10.1111/1756-185X.13365
30. YAMAMOTO S, NAGASHIMA T, AKIYAMA Y *et al*.: Fatal thrombotic microangiopathy and posterior reversible encephalopathy syndrome in a patient with anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis. *Intern Med* 2021; 60: 3329-33. https://doi.org/10.2169/internalmedicine.7309-21
31. IMURA Y, YUKAWA N, HANDA T *et al*.: Two cases of autoimmune and secondary pulmonary alveolar proteinosis during immunosuppressive therapy in dermatomyositis with interstitial lung disease. *Mod Rheumatol* 2018; 28: 724-9. https://doi.org/10.3109/14397595.2016.1153443