Nintedanib could potentially lead to improvements in anti-melanoma differentiation-associated 5 dermatomyositis-associated interstitial lung disease

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Abstract

Objective

To determine the efficacy and safety of nintedanib in patients with anti-melanoma differentiation-associated gene 5 antibody positive dermatomyositis-associated interstitial lung disease (anti-MDA5+ DM-ILD).

Methods

The study was a retrospective cohort design that evaluated patients with anti-MDA5+ DM who either received or did not receive nintedanib. Clinical symptoms, laboratory tests, and survival were compared in the two groups using a propensity score-matched analysis. The primary endpoint was mortality, while adverse events were recorded descriptively.

Results

After propensity score matching, 14 patients who received nintedanib (nintedanib+ group) and matched 56 patients who did not receive nintedanib (nintedanib- group) were enrolled. Compared with the nintedanib- group, the nintedanib+ group had a lower incidence of heliotrope and arthritis, higher lymphocyte counts, lower serum ferritin levels, and greater 12-month survival (all $p<0.005$). Although lung function, HRCT score, and lung VAS were not statistically different between the two groups, the longitudinal study showed significant improvement in HRCT scores ($p=0.028$) and pulmonary VAS ($p=0.019$) in the nintedanib+ group. Adverse events occurred in 28.6% of patients, with the most common adverse event with nintedanib being diarrhoea.

Conclusion

Nintedanib may be effective for improving clinical symptoms, laboratory parameters, lung lesions, and survival in anti-MDA5+ DM. Diarrhoea was the most common adverse event associated with nintedanib, although the drug was well tolerated by most patients.

Key words

dermatomyositis, nintedanib, anti-melanoma differentiation-associated protein 5 antibody, interstitial lung disease

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Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune disorders with a global average prevalence of 4.27-7.89/100,000 people (1). The clinical presentation and disease course of IIM are variable, with myositis-specific antibodies (MSA) appearing to be associated with distinct clinical phenotypes (2). The melanoma differentiation-associated gene 5 (MDA5) product was identified in 2009 as an autoantigen associated with dermatomyositis (DM) when it was shown that the anti-MDA5 antibody correlated with clinically amyopathic DM (CADM), interstitial lung disease (ILD), and especially with rapidly progressive ILD (RP-ILD) (3). Several studies reported that anti-MDA5+ DM patients have a poor response to conventional therapy (such as high-dose glucocorticoids and immunosuppressants), leading to death from respiratory failure within 6 months in 50–60% of patients (4, 5). Therefore, there is an unmet need to search for other potent therapeutic agents to alleviate this lung involvement.

Nintedanib, an indolinone derivative with inhibitory activity against tyrosine kinase inhibitor activity has been shown to have antifibrotic, anti-inflammatory, and vascular remodelling effects (6). The TOMORROW, INPULSIS I and INPULSIS II trials demonstrated the clinical value of nintedanib by showing it was associated with a significant reduction in the deterioration of lung function in idiopathic pulmonary fibrosis (IPF) (7, 8). Of note, the gain in a lower annual rate of decline in forced vital capacity (FVC) following the use of nintedanib in progressive fibrotic ILDs in the INBUILD trial was comparable to that obtained in IPF in the INPULSIS trial. This observation suggested that diseases with fibrotic progressive ILD may benefit from treatment with nintedanib regardless of their underlying aetiology. Recently, a randomised, double-blind, placebo-controlled trial in 576 systemic sclerosis (SSc) patients, the SENSCIS trial, demonstrated the efficacy of nintedanib in SSc-ILD (9). Its utility in IIM-ILD has also been investigated in one prospective open-label study (10), although the findings should be interpreted carefully due to a lack of clinical and imaging data and a small sample size. Moreover, only a small number of studies have focused on the application of nintedanib in anti-MDA5+ DM.

The objective of the present study was, therefore, to evaluate the possible therapeutic effects of nintedanib in a propensity score-matched cohort of patients with anti-MDA5+ DM-ILD. Understanding the therapeutic value of nintedanib is of great importance and may possibly provide insights into new therapeutic strategies.

Materials and methods

Patient selection

We carried out a retrospective analysis of patients diagnosed with anti-MDA5+ DM at the Rheumatology Department of the China-Japan Friendship Hospital between January 2015 and June 2022. The diagnosis of anti-MDA5+ DM was established based on the Bohan and Peter criteria (11) and was confirmed retrospectively by two experienced rheumatologists, according to the 2017 EULAR/ACR IIM classification criteria (12) or the 2018 ENMC DM criteria (13). The study encompassed all patients aged 18 years or older, while cases that had received nintedanib treatment for less than three months were excluded from the analysis. Patients who were administered nintedanib for a duration exceeding three months were categorised as the nintedanib+ group, whereas those who did not receive nintedanib were classified as the nintedanib- group. The patient selection process is shown in Supplementary Figure S1.

The MSA profile which included the anti-MDA5 antibody, was identified by immunoblotting according to the manufacturer's instructions (Euroimmun, Lübeck, Germany). The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital (reference number: 2022-KY-156). Patient written informed consent was waived for this retrospective study.

Propensity score methods

The study used propensity score matching to assemble a cohort in which the

Table I. General information of matched nintedanib-treated patients with anti-MDA5+ DM.

No.	Age/ Gender	RPILD	Refractory case	Initial treatment	Administration of nintedanib				Follow up time (months)
					Dose	Interval	Treatment time (months)	Adverse effects	
1	48/F	Yes	Yes	MP, CsA, IVIG	100 mg	Twice daily	17	Nausea and vomiting	20
2	31/F	Yes	Yes	Pred, Tac, IVIG	100 mg	Twice daily	35	Diarrhoea	42
3	67/F	No	No	Pred, Tac, HCQ, IVIG	100 mg	Twice daily	3	Elevated transaminases	15
4	60/F	Yes	Yes	MP, CTX, IVIG	150 mg	Twice daily	17	No	21
5	59/F	Yes	No	MP, CsA, IVIG	150 mg	Twice daily	16	No	19
6	68/M	No	No	MP, Tac, IVIG	150 mg	Twice daily	36	No	47
7	54/M	Yes	Yes	Triamcinolone, Tac, IVIG	150 mg	Twice daily	12	No	15
8	46/F	No	No	MP, Baricitinib	150 mg	Twice daily	12	No	24
9	51/F	No	No	Pred, Tac	150 mg	Twice daily	6	No	12
10	44/M	Yes	No	PMT, MP, CTX, IVIG	150 mg	Twice daily	4	No	13
11	46/M	Yes	Yes	MP, CTX, HCQ, IVIG	150 mg	Twice daily	3	No	6
12	39/F	No	No	MP, CTX	150 mg	Twice daily	5	No	9
13	62/F	Yes	No	MP, CTX	150 mg	Twice daily	3	No	76
14	46/F	Yes	No	PMT, MP, CTX	150 mg	Twice daily	3	Diarrhoea	6

CsA: ciclosporin; CTX: cyclophosphamide; F: female; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulin; M: male; MP: methylprednisolone; PMT: pulse methylprednisolone therapy; Pred: prednisolone; Tac: tacrolimus.

Table II. Comparison of clinical characteristics between anti-MDA5+ DM patients receiving nintedanib and those not receiving nintedanib after a minimum of 3 months of treatment duration.

Parameters	Propensity score-matched cohort		*p*-value
	Nintedanib+ (n=14)	Nintedanib- (n=56)	
Clinical manifestations			
Myalgia	3 (21.4)	18 (32.1)	0.529
Muscle weakness	3 (21.4)	25 (44.6)	0.113
Heliotrope	6 (42.9)	47 (83.9)	**0.003**
Gottron's sign	10 (71.4)	47 (83.9)	0.277
Arthritis	2 (14.3)	26 (46.4)	**0.028**
Fever	4 (28.6)	28 (50.0)	0.150
Laboratory findings			
Neutrophil, $\times 10^9$/L	4.44 (2.60, 7.49)	4.01 (2.49, 5.45)	0.454
Lymphocyte, $\times 10^9$/L	1.03 (0.76, 1.69)	0.75 (0.52, 1.02)	**0.014**
$CD4^+$ T cell, $\times 10^6$/L	678.5 (364.5, 930.5)	330.0 (221.5, 460.5)	**0.004**
$CD8^+$ T cell, $\times 10^6$/L	462.0 (296.5, 722.3)	156.0 (84.5, 272.0)	**< 0.001**
Creatine kinase, IU/L	66.5 (45.0, 106.8)	49.0 (28.3, 123.8)	0.618
Lactate dehydrogenase, IU/L	267.5 (223.3, 343.3)	287.0 (246.8, 388.5)	0.419
Ferritin, ng/ml	144.4 (37.0, 717.5)	509.8 (168.3, 1262.9)	**0.031**
CRP, mg/dl	0.354 (0.175, 0.852)	0.354 (0.170, 0.829)	0.887
ESR, mm/h	22 (13, 39)	19 (10, 41)	0.754
Pulmonary function test			
FVC%	86.1 ± 20.3†	82.1 ± 17.6#	0.570
FEV1%	81.3 ± 20.9†	78.1 ± 16.3#	0.637
FEV1%/FVC%	79.0 ± 7.3†	82.7 ± 7.5#	0.203
DLCO%	57.4 ± 8.5†	60.1 ± 14.8#	0.520
HRCT score% (100-600)	112.5 (105.8, 162.5)	115.0 (108.0, 140.0)*	0.873
Pulmonary VAS (0-10)	1.5 (1.0, 6.0)	2.0 (1.0, 4.0)	0.742

Values are expressed as mean ± SD, median (interquartile range) or number (%).
†Data available for 9 patients. #Data available for 29 patients. *Data available for 51 patients.
CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; VAS: visual analogue scales.

patients treated or not treated with nintedanib would be balanced according to key baseline covariates. The selected independent covariates in our study encompassed age, gender, smoking history, the presence of RP-ILD, pulmonary infection, relevant past medical history (such as hypertension, diabetes mellitus, cancer, and other connective tissue diseases), and the treatment regimen received prior to admission. The treatment regimen included factors like pulse methylprednisolone therapy, initial dose of glucocorticoid, use of multiple immunosuppressants, and intravenous immunoglobulin administration.

We estimated the propensity score for each patient treated with nintedanib using a non-parsimonious multivariable logistic regression model. For the matched cohort analysis, the nintedanib+ group were matched with the nintedanib- group according to the propensity score, using a 1:4 matching ratio without replacement and a calliper width of 0.1. As recommended, this resulted in a relatively narrow difference between the matched variables (14). The distribution of the propensity score and standardised bias across the covariates are shown in Supplementary Figure S2.

Data collection

All patient-related demographic data, laboratory tests, and therapy information were recorded. The laboratory tests included counts of neutrophils, lymphocytes, $CD4^+$ T-cells, and CD8+ T-cells, the levels of creatine kinase, serum ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR). The pulmonary function tests (PFTs) included the predictive values for forced vital capacity of the (FVC%), forced expiratory volume in one second (FEV1%),

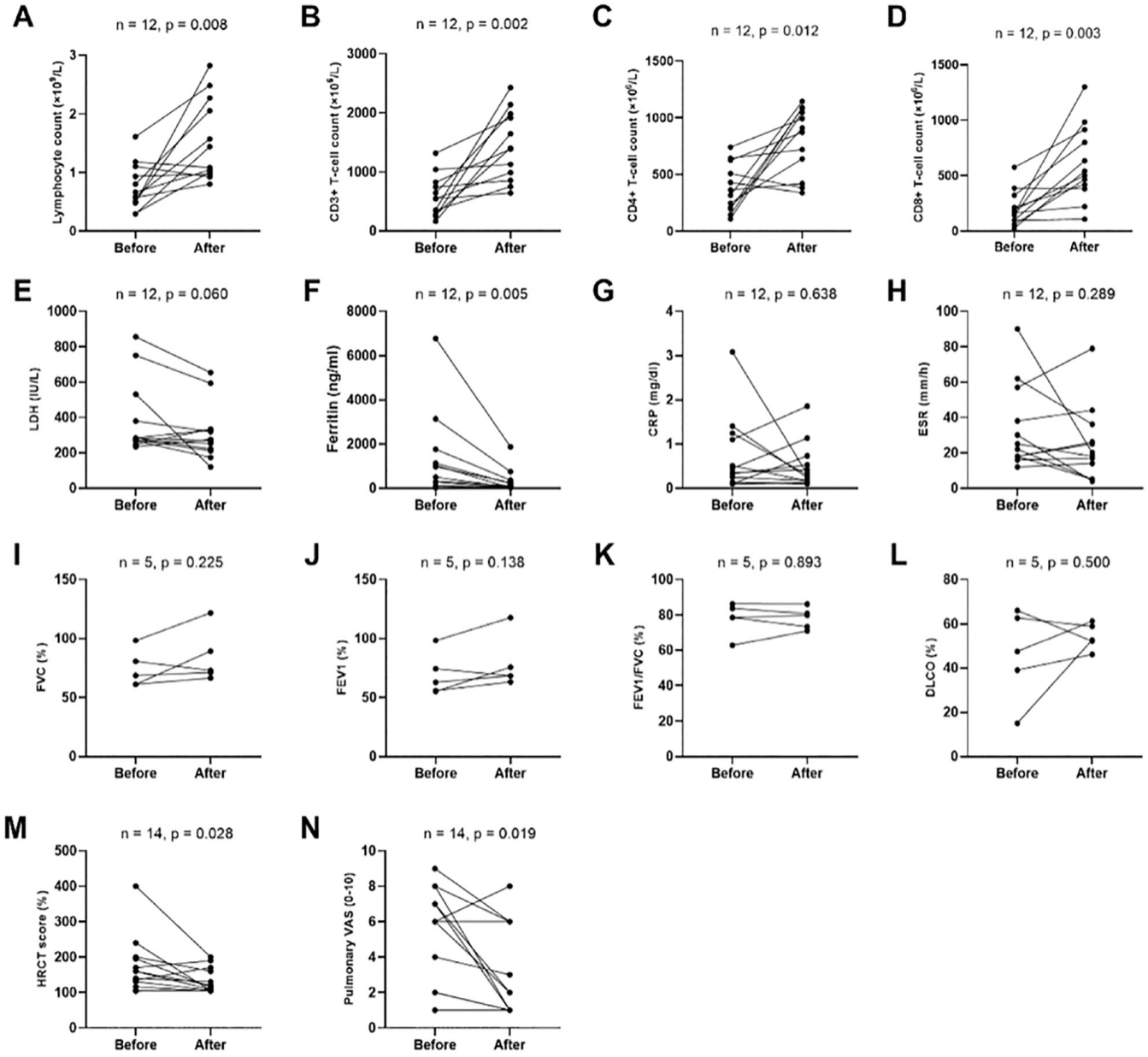

Fig. 1. Changes in laboratory indicators, pulmonary function test, HRCT score, and pulmonary disease activity in anti-MDA5+ DM patients before and after nintedanib treatment. Longitudinal study showed that lymphocytes (**A**), $CD3^+$ T-cells (**B**), $CD4^+$ T-cells (**C**), and $CD8^+$ T-cells (**D**) increased significantly after nintedanib treatment. The serum levels of ferritin (**F**), HRCT score (**M**), and pulmonary VAS (**N**) decreased significantly after nintedanib treatment. There were no statistical differences in LDH (**E**), CRP (**G**), ESR (**H**), and pulmonary function tests (**I-L**) after nintedanib treatment.
CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; VAS: visual analogue scales.

diffusing capacity of the lung for carbon monoxide (DLCO%), and FEV1%/FVC%. ILD was evaluated using chest radiography or high-resolution computed tomography (HRCT). These indicators were measured at baseline, and subsequent assessments were performed at least 3 months post-initiation of nintedanib treatment or routine immunosuppressive therapy, respectively. The American Thoracic Society's terminology for progressive disease in idiopathic pulmonary fibrosis (15) was used to define anti-MDA5+ DM-associated RP-ILD as either worsening dyspnoea or chest imaging within 1 month or deterioration to respiratory failure within 3 months since the onset of respiratory symptoms. Patients who did not conform to the aforementioned criteria were classified as having non-RP-ILD. Refractory cases are defined as patients who exhibit an inadequate response to the prescribed treatment regimen comprising of glucocorticoids and one or more immunosuppressants, for a duration of at least three months.

Radiological analysis and pulmonary disease activity

All the lung radiology images were reviewed independently by two radiologists. We determined the overall HRCT score based on the classification of Ichikado (16), as follows: score of 1, normal attenuation; score of 2, ground-glass

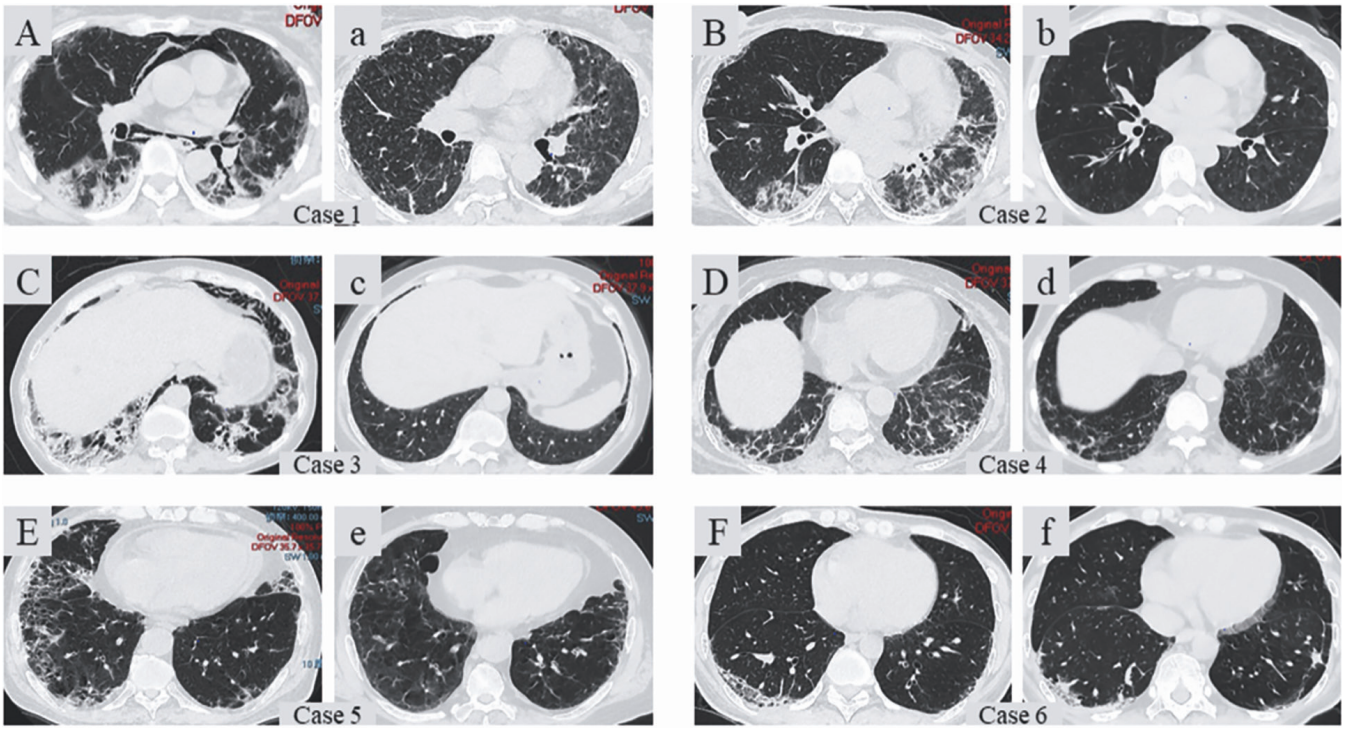

Fig. 2. Chest HRCT images of patients with anti-MDA5+ DM before and after receiving nintedanib treatment. **A-F**: Corresponding HRCT images of cases 1-6 before receiving nintedanib treatment; **a-f**: The corresponding HRCT images of cases 1-6 after receiving nintedanib treatment.

attenuation; score of 3, consolidation; score of 4, ground-glass attenuation with traction bronchiolectasis or bronchiectasis; score of 5, consolidation with traction bronchiolectasis or bronchiectasis; and score of 6, honeycombing. The overall CT score was obtained by adding the six averaged scores (three zones in each lung). Pulmonary disease activity was assessed using 10-cm visual analogue scales (VAS).

Follow-up study

The follow-up period was calculated from the onset of symptoms to death (primary outcome) or the last investigation/visit by the patient. All the follow-up examinations were completed by September 2022, with the date of the last follow-up or death recorded for each patient.

Statistical analysis

SPSS software (version 23.0, Chicago, IL, USA) and Stata software (v. 15.0, Stata Corporation, College Station, Texas, USA) were used for the statistical analyses. The data were expressed as mean ± SD, median (interquartile range), or number (percentage) when appropriate. Comparisons between groups were performed using the independent-samples t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The Mann-Whitney U-test was used to analyse data with a non-normal distribution and the Wilcoxon signed rank test was used on paired data when appropriate. The survival of patients treated or not treated with nintedanib were evaluated by the Kaplan-Meier method with a log-rank test. Two-sided *p*-values of <0.05 were considered statistically significant.

Results

Clinical characteristics and treatment of patients with anti-MDA5+ DM

We identified 394 eligible patients, including 15 patients with anti-MDA5+ DM who received nintedanib and 379 patients who did not receive nintedanib. The baseline characteristics of these unmatched groups are shown in Table S1. A propensity score model was then derived using 13 variables measured at baseline. The nintedanib+ group and nintedanib- group were matched 1:4 to create the final cohort consisting of 70 patients with 14 and 56 patients in each group, respectively. After matching, all the imbalanced baseline characteristics were well-balanced so that no significant differences remained.

Information on the general characteristics, initial treatment, nintedanib dose, frequency, duration of treatment, and adverse effects for the 14 patients who received nintedanib is shown in Table I. Notably, five patients were refractory cases. Nintedanib was then added to the conventional immunosuppressive therapy. During nintedanib treatment, 3 patients had a reduction in the dose of nintedanib to 100 mg twice daily because of nausea and vomiting, diarrhoea, or elevated serum transaminase levels. Another patient developed mild diarrhoea, but did not reduce the dosage or discontinue the drug. Overall, adverse events occurred in 28.6% (4/14) of patients.

Therapeutic effects of nintedanib in anti-MDA5+ DM

Following a 3-month treatment period, a comparative analysis was conducted on the clinical manifestations and laboratory indicators of the nintedanib+ and nintedanib- groups. The results, presented in Table II, revealed significant

differences favouring the nintedanib+ group. This group exhibited lower incidence of heliotrope (42.9% *vs*. 83.9%, *p*=0.003) and arthritis (14.3% *vs*. 46.4%, *p*=0.028), along with higher lymphocyte counts (1.03×10^9/L *vs*. 0.75×10^9/L, *p*=0.014), and lower serum ferritin levels (144.4 ng/mL *vs*. 509.8 ng/mL, *p*=0.031) compared to the nintedanib- group. However, there were no statistically significant differences observed in the pulmonary function test, HRCT score, or pulmonary VAS between the two groups (*p* all >0.05).

In our longitudinal study, a minimum of 3-month treatment of nintedanib resulted in significant improvements in various parameters. Notably, there were significant increases in lymphocyte counts (*p*=0.008), specifically in $CD3^+$ T-cells (=0.002), $CD4^+$ T-cells (*p*=0.012), and $CD8^+$ T-cells (*p*=0.003). Moreover, serum ferritin levels showed a significant decrease (*p*=0.005). Additionally, improvements were observed in HRCT scores (*p*=0.028) and pulmonary VAS (*p*=0.019) as depicted in Figure 1. In addition, chest imaging also showed significant recovery after nintedanib treatment (Fig. 2). Probably due to the small sample size, no significant difference in the pulmonary function test was found (*p* all 0.05). Taken together, these results indicate that nintedanib was effective for improving inflammatory indicators and alleviating lung lesions in patients with anti-MDA5+ DM.

Survival analysis

For the 12-month survival analysis, 8 patients in the post-matching cohort were lost to follow-up. We observed statistically significant differences in survival rates between the anti-MDA5+ DM patients who received nintedanib and those who did not receive nintedanib (100% *vs*. 73.2%, *p*=0.0344) (Suppl. Fig. S3). We then conducted a stratified analysis based on the presence of RP-ILD and patients classified as refractory cases. Intriguingly, our findings revealed that individuals who received nintedanib treatment within both the RP-ILD group and refractory group demonstrated substantially higher survival rates compared to their respective counterparts (100% *vs*. 54.5%, *p*=0.0188; 100% *vs*. 26.3%, *p*=0.008) (Fig. 3).

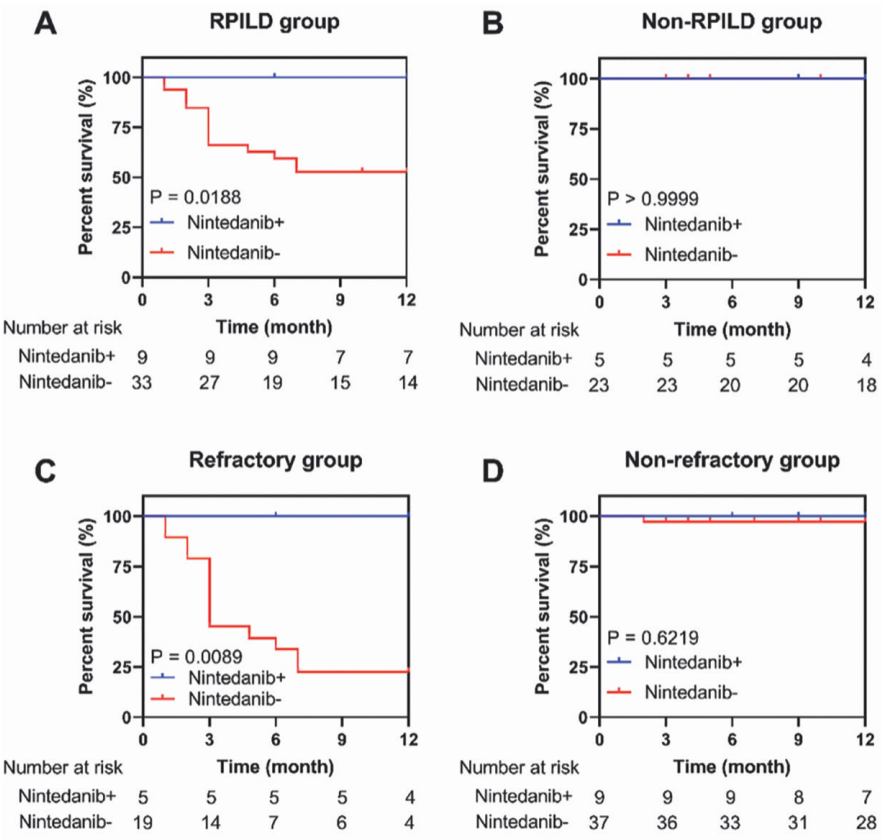

Fig. 3. Kaplan-Meier curves of patients receiving or not receiving nintedanib therapy. (**A**) Nintedanib+ group exhibited significantly higher survival rates compared to nintedanib- group within the RP-ILD group (log-rank, *p*=0.0188). (**B**) There was no significant difference in survival rates between nintedanib+ and nintedanib- groups within the non-RP-ILD group (log-rank, *p*>0.9999). (**C**) Nintedanib+ group demonstrated significantly higher survival rates compared to nintedanib- group within the refractory group (log-rank, *p*=0.0089). (**D**) There was no significant difference in survival rates between nintedanib+ and nintedanib- groups within the non-refractory group (log-rank, *p*=0.6219).

Subsequent analysis of patients receiving nintedanib demonstrated no significant differences in age, disease duration, and treatment regimens between the RP-ILD and non-RP-ILD groups (Supplementary Table S2), as well as refractory and non-refractory groups (Supplementary Table S3). These findings underscore the autonomous potential efficacy of nintedanib in enhancing survival outcomes within these distinct patient subgroups, irrespective of the influence of other factors.

Discussion

Findings from this study demonstrated that nintedanib was effective for improving clinical symptoms (heliotrope and arthritis), laboratory parameters (lymphocyte count and serum ferritin level) and survival in patients with anti-MDA5+ DM. Although statistical evidence of the benefit of nintedanib on lung function could not be provided, a longitudinal study suggests that the addition of nintedanib to conventional therapy can slow or even reverse the progression of anti-MDA5+ DM-ILD, as observed by a chest HRCT. Furthermore, nintedanib shows potential as a treatment option for patients with RP-ILD or refractory cases, indicating its therapeutic benefits in these populations.

Anti-MDA5+ DM is characterised by dermatomyositis rashes, amyopathic or hypomyopathic muscle involvement, and notable ILD, frequently as a rapid progressive course (17). Many previous studies have investigated factors associated with poor prognosis in anti-MDA5+ DM, including older age, male gender, RP-ILD, and inappropriate therapeutic strategies (18-20). In

order to exclude the interference of these confounding factors, we used a robust propensity-score matching design to balance 13 key baseline covariates. This allowed us to directly assess the independent therapeutic effect of nintedanib in anti-MDA5+ DM.

After treatment, our study revealed that the nintedanib+ group exhibited a lower incidence of heliotrope and arthritis, along with increased lymphocyte counts and decreased serum ferritin levels compared to the nintedanib- group. A previous study by Cope *et al*. (21) suggested that T-cells release pro-inflammatory and pro-fibrotic mediators that initiate and enhance the progression of fibrosis in autoimmune diseases. In this regard, Zuo *et al*. (22) showed that serum ferritin, a biomarker of macrophage activation, was elevated significantly in anti-MDA5+ DM patients, with extensive infiltration of CD163-positive macrophages into the alveolar space. This provides further evidence that macrophages may be involved in the pathogenesis of anti-MDA5+ DM-ILD. Therefore, we speculate that nintedanib may improve clinical symptoms and alleviate lung lesions in patients with anti-MDA5+ DM by acting on lymphocytes, macrophages, and other targets not yet identified.

Nintedanib has previously been shown to have therapeutic value by reducing lung function decline and acute exacerbation in IPF patients (7, 8). However, the efficacy of nintedanib in IIM-ILD, anti-MDA5+ DM-ILD in particular, has not been clarified. In this study, all patients included in the nintedanib+ group had a diagnosis of ILD. Owing to the constrained sample size of patients who underwent lung function testing and chest CT examinations, no statistically significant disparities were detected in lung function, HRCT scores, or lung VAS between the nintedanib+ and nintedanib- groups. Nevertheless, our longitudinal analysis showed a remarkable amelioration in HRCT scores and lung VAS among patients who received nintedanib treatment, thereby suggesting the potential therapeutic efficacy of nintedanib.

In addition to alleviating lung lesions, we also observed that nintedanib could improve survival in patients with anti-MDA5+ DM-ILD. The survival analysis revealed a statistically significant difference in the 12-month survival rate between the nintedanib+ and nintedanib- groups, particularly among patients with RP-ILD and those categorised as refractory cases. This finding reveals a partial divergence from the research conducted by Ting Li *et al*. (23), who observed a significantly higher survival rate in the pirfenidone treatment group within the subacute ILD subgroup (duration of 3-6 months) of CADM patients when compared to the control group. However, no such disparity was noted in the acute ILD and chronic ILD subgroups. Clinically, refractory cases have consistently presented significant challenges due to their limited response to conventional immunosuppressive therapy, resulting in higher mortality rates. Intriguingly, our study demonstrated that the nintedanib+ group of refractory cases with anti-MDA5+ DM exhibited a significantly higher survival rate than the nintedanib- group. Taken together, these findings suggest that nintedanib may be more suitable for individuals diagnosed with RP-ILD and refractory cases.

During the course of nintedanib therapy, 28.6% of anti-MDA5+ DM patients suffered from adverse events, a prevalence considerably lower than that reported by previous clinical trials (60-80%) (7, 8). Consistent with previous reports (7, 8, 10), diarrhoea was the most common adverse event. Three patients in our cohort required a reduction in the dose of nintedanib because of nausea and vomiting, diarrhoea, or elevated serum levels of transaminases. Therefore, monitoring of liver function and timely symptomatic treatment should be emphasised in anti-MDA5+ DM-ILD patients, although in general, nintedanib is tolerable in the majority of these patients.

Several limitations of our study need to be considered. First, this was a single-centre retrospective study and therefore, intrinsic bias could not be avoided completely. Second, given the retrospective nature of the study, despite the rigorous propensity score matched design to assemble cohorts that were well balanced on all measured baseline covariates, hidden bias may remain because of the influence of potential unmeasured confounders. Third, due to missing data, such as pulmonary function test results and the small sample size, the results of this study should be interpreted with caution.

Conclusion

Nintedanib may be effective for improving clinical symptoms, laboratory parameters, lung lesions, and survival in patients with anti-MDA5+ DM. In addition, diarrhoea was the most common adverse event in patients with anti-MDA5+ DM, although most patients did not discontinue nintedanib due to these adverse reactions.

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