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Case report

Three cases of sequential treatment with nintedanib following pulsed-dose corticosteroids for acute exacerbation of interstitial lung diseases

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ABSTRACT

We describe three cases of acute exacerbation of interstitial lung diseases (ILDs) in which patients were treated with pulsed-doses of corticosteroids followed by nintedanib and maintenance doses of corticosteroids. All cases responded well to pulsed-dose corticosteroids. However, in conventional practice, corticosteroids can complicate adverse events, including opportunistic infections, diabetes, and osteoporosis. One of the cases reported here involved dermatomyositis-associated ILD with anti-EJ antibodies. Considering possible side effects of corticosteroids and the frequent recurrence of ILDs associated with anti-EJ antibodies, we decided to use nintedanib as a sequential treatment for acute exacerbation of ILDs. Nintedanib has just been approved for treatment of progressive fibrosing ILD, but to date, few reports of acute exacerbation of ILDs treated with nintedanib have been published. This case series may contribute to a more thorough discussion regarding the use and timing of nintedanib in treating acute exacerbation of ILDs.

1. Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases characterized by variable degrees of inflammation and fibrosis of the lung. In some cases, ILDs show a chronic course with progressive scarring of lung tissue. During the clinical course of ILDs, acute exacerbation (AE) can occur at any time and is associated with significant morbidity and mortality [1]. Initially, AE-ILD was described in idiopathic pulmonary fibrosis (IPF), the most severe form of progressive fibrosing interstitial lung disease of unknown etiology. The international working group for AE-IPF has revised the definition and diagnostic criteria for AE-IPF [2]: (a) Previous or concurrent diagnosis of IPF (b) Acute worsening or development of dyspnea, typically of <1 month duration (c) CT with new, bilateral ground-glass opacities (GGOs) and/or consolidation superimposed on a background pattern consistent with the usual interstitial pneumonia pattern (d) Deterioration not fully explained by cardiac failure or fluid overload. Similarly, AE-ILD manifests radiographically as emerging diffuse, bilateral, GGOs superimposed on a background of chronic fibrotic changes consistent with fibrosing ILDs on high-resolution CT imaging [2,3]. Because of the disease behavior, clinical trials for AE-ILDs are challenging, and there is little clinical evidence on which to base a treatment strategy for them [4].

Here, we describe three cases of AE-ILDs that were treated with pulsed doses of corticosteroids followed by nintedanib and a maintenance dose of corticosteroids. We discuss the rationale for this treatment with limitations and propose a new therapeutic strategy for AE-ILDs.

2. Case presentations

2.1. Case #1

An 88-year-old Japanese woman was admitted to Hamanomachi Hospital due to a worsening dry cough and progressive exertional dyspnea that arose within the previous 1 month. She was a non-smoker and had no family history of lung disease. There was no suspicion of pulmonary infection, connective tissue disease, or occupational exposure relevant to interstitial lung disease. She was diagnosed as having an ILD based on the usual interstitial pneumonia (UIP) pattern in chest CT findings for 13 years (Fig. 1C). Since then, she had been followed up without specific therapy for the ILD and had remained stable until 1 month prior.

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On admission day 1, she was initially diagnosed with exacerbation of chronic heart failure due to an upper airway infection. She was treated with furosemide and levofloxacin in addition to oxygen therapy. Even though the diuresis was sufficient, her oxygen saturation (SpO_2) deteriorated. On day 3, a chest X-ray revealed worsened bilateral infiltrative shadows (Fig. 1B), and a repeat chest CT showed new bilateral GGOs with traction bronchiectasis superimposed on the background UIP pattern (Fig. 2D), indicating AE-ILD. She was referred to the Department of Respiratory Medicine on the same day. Physical data at the time of referral were as follows: height, 145.5 cm; weight, 46.5 kg; and body surface area, 1.36 m^2. She had a temperature of 36.5 °C, blood pressure of 120/66 mmHg, a heart rate of 72 beats per minute, oxygen saturation of 92% under non-invasive positive pressure ventilation (NPPV) with oxygen fraction (FiO2) of 0.5. Physical examination revealed bilateral late inspiratory crackles in her back. A PCR test for SARS-CoV-2 was negative. Increased levels of C-reactive protein (CRP) (25.50 mg/dL), serum lactate dehydrogenase (LDH) (593 U/mL), and serum Krebs von den Lungen-6 (KL-6) (1121 U/mL; normal, <500 U/mL) were noted. Following admission, we ordered an additional serological examination to evaluate the etiology of ILDs: Anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), anti-citrullinated protein antibodies (ACPA), anti-Ro, anti-Scl-70, and anti-aminoacyl tRNA synthetase (ARS) antibodies were all negative. The rheumatoid factor (RF) level was 17 U/dL, which was not significant. Based on her CT findings and serological results, the patient was diagnosed as having IPF.

Pulsed-dose methylprednisolone (mPSL) was initiated from day 3 (Fig. 4). She responded well to the treatment. Her respiratory condition improved gradually. Levels of CRP and LDH peaked, and her chest X-ray showed improvement of bilateral infiltrative shadows. On day 7, the prednisolone (PSL) dose was reduced to a maintenance dose of 50 mg per day. On day 8, she no longer required oxygen at rest; however, long-term oxygen therapy with 2 L/min on exercise was initiated due to remaining exertional dyspnea and desaturation with SpO_2 under 90% on exercise. On day 11, the PSL dose was tapered to 30 mg per day, and 100 mg/day of nintedanib was initiated as a sequential treatment. The PSL dosage was further tapered to 12.5 mg/day. She was discharged on day 44, continuing with nintedanib and a PSL maintenance dose without significant side effects. She has not suffered a relapse in the one month since her discharge.

2.2. Case #2

A 55-year-old Japanese man was admitted to Hamanomachi Hospital due to progressive exertional dyspnea within 1 week. He had smoked 2 packs of cigarettes per day for 33 years and quit smoking last year. He had been treated for dermatomyositis and associated ILD for 6 years with maintenance-dose PSL and azathioprine. He had once suffered AE-ILD half a year before and was treated with pulsed-dose mPSL followed by nintedanib in combination with a PSL maintenance dose. However, nintedanib administration had been discontinued after 1 week because of an asymptomatic pulmonary embolism on a repeated chest CT. Three months of anticoagulation therapy were performed and pulmonary thrombi disappeared. On his last visit, one month before admission, he was in stable condition with 22.5 mg/day of PSL and 100 mg/day of azathioprine. There was no suspicion of pulmonary infection, new medications, or occupational exposure relevant to interstitial lung disease.

Admission data were: height, 153.7 cm; weight, 58.4 kg; and body

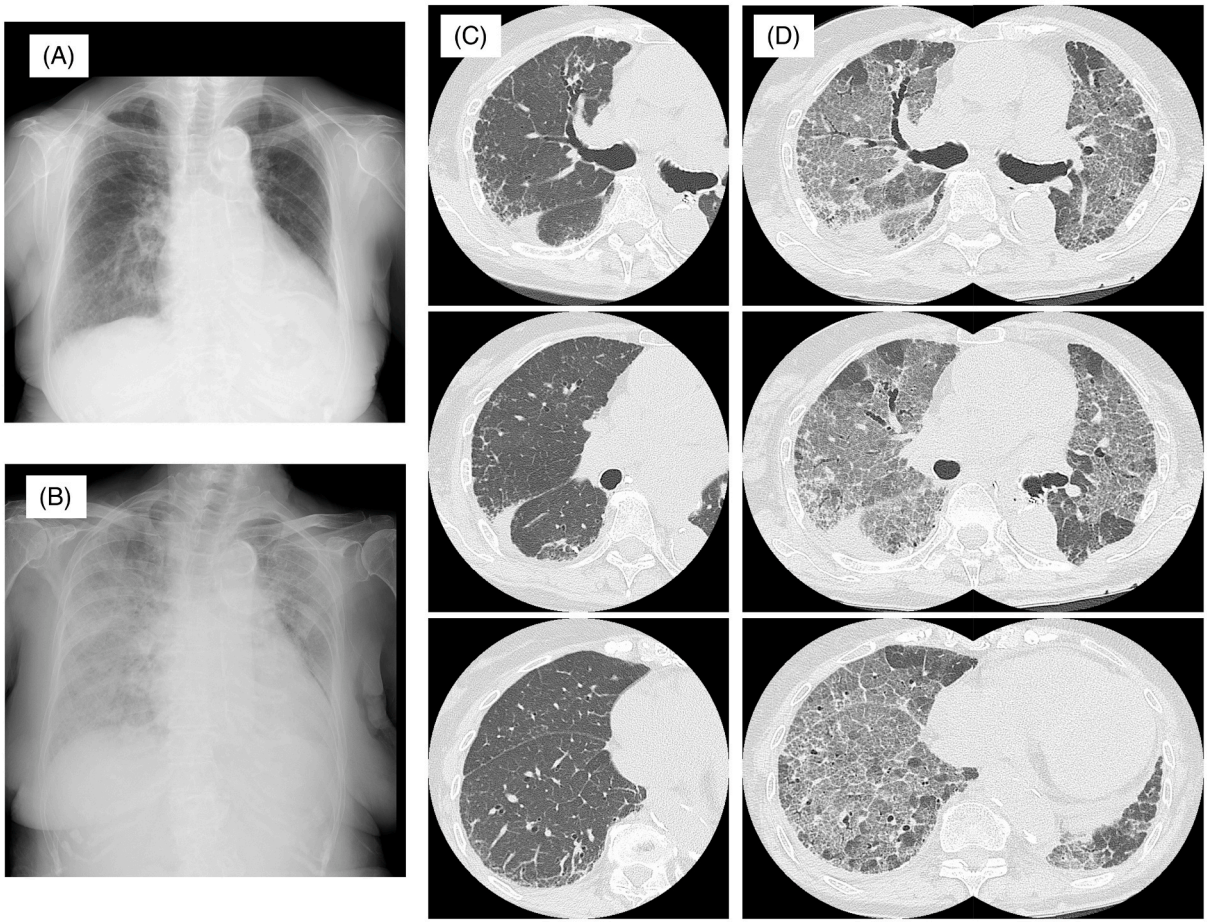

Fig. 1. Radiographic images of case #1. Chest X-ray images of the patient (A) before and (B) at the diagnosis of acute exacerbation of interstitial lung disease. Chest CT images of the patient (C) before and (D) at the diagnosis of acute exacerbation of interstitial lung disease.

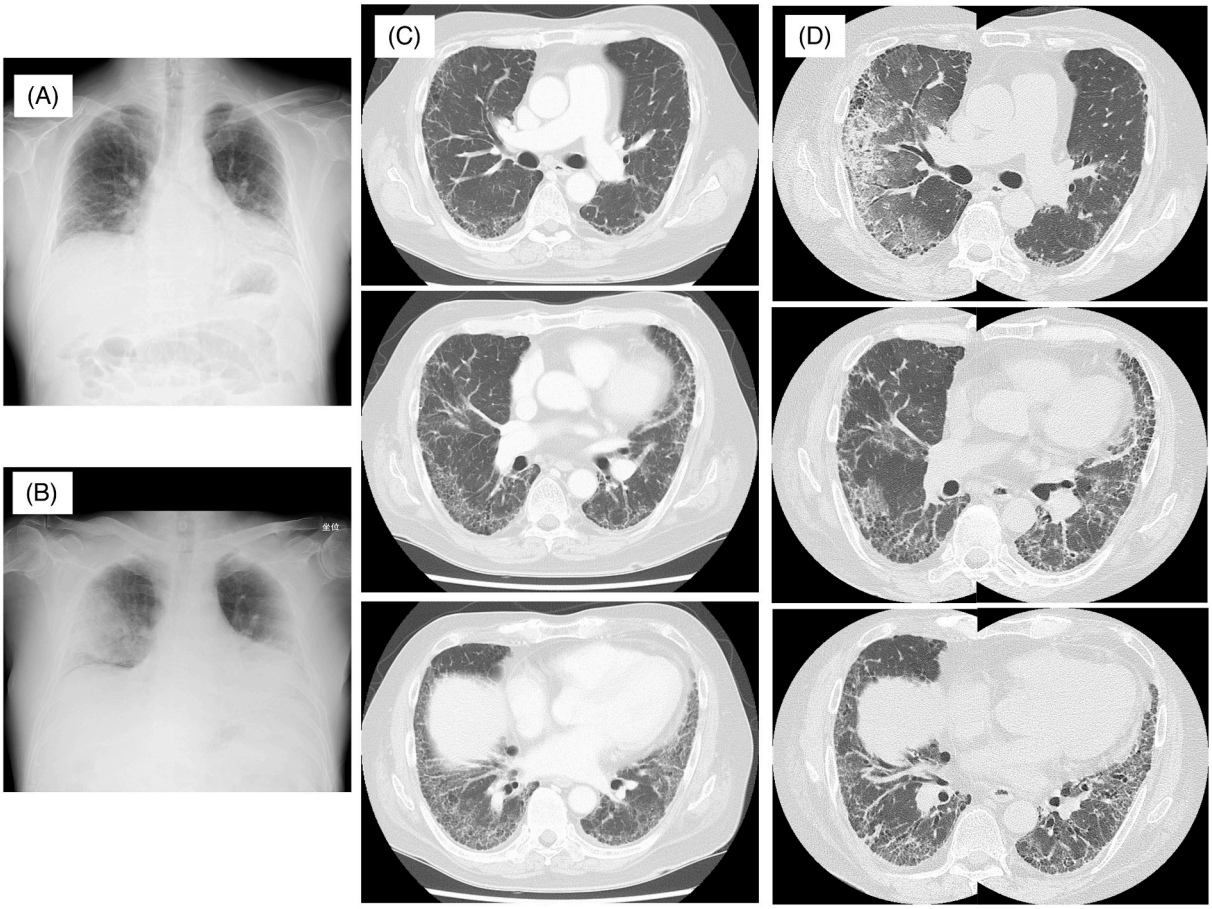

Fig. 2. Radiographic images of case #2. Chest X-ray images of the patient (A) before and (B) at the diagnosis of acute exacerbation of interstitial lung disease. Chest CT images of the patient (C) before and (D) at the diagnosis of acute exacerbation of interstitial lung disease.

surface area, 1.56 m^2. He had a temperature of 35.5 °C, blood pressure of 119/69 mmHg, a heart rate of 64 beats per minute, oxygen saturation of 99% under a non-rebreather reservoir bag oxygen mask 5L per minute. Physical examination revealed late inspiratory crackles in his right back. A chest X-ray (Fig. 2B) showed infiltrative shadows in the right lower lung fields. An HRCT scan revealed new GGOs in the right lung fields superimposed on a background of lung fibrosis (Fig. 2D). Increased levels of LDH and KL-6 were noted (610 U/mL, 841 U/mL, respectively). A PCR test for SARS-CoV-2 was negative.

He was diagnosed with AE-ILD due to infection, and pulsed-dose mPSL and revofloxacin were initiated on admission day 1 (Fig. 4). Intravenous immunoglobulin (IVIG) was added from day 2 to day 6. He responded well to the treatments. His respiratory condition improved gradually from day 2. Levels of CRP and LDH peaked, and his chest X-ray showed improvement of infiltrative shadows. On day 6, the PSL dose was reduced to a maintenance dose of 60 mg per day. On day 7, he no longer required oxygen. On day 12, the PSL dose was tapered to 40 mg per day. Additional serological examination was positive for anti-EJ antibodies. Considering the side effects of corticosteroids and the possibility of further recurrence of AE-ILD, 200 mg/day of nintedanib were initiated on day 13 as a sequential treatment. The PSL dose was tapered to 30 mg/day and he was discharged on day 20. On an outpatient basis, the PSL dose was further tapered to 20 mg/day with continuing nintedanib. Treatment with azathioprine had been continued through the course. He has not relapsed in the three months since his discharge.

2.3. Case #3

An 85-year-old Japanese man was admitted to Hamanomachi Hospital due to progressive exertional dyspnea that morning. He suffered a runny nose and dry cough 3 days before admission. He had smoked 2 packs of cigarettes per day for 45 years, but had quit 20 years earlier. He had a history of tuberculosis in his 30s. There were no new medications, and no connective tissue disease or occupational exposure relevant to ILD. He had been suspected of having an ILD and chronic obstructive pulmonary disease (COPD) based on clinical findings and a UIP pattern in a chest CT (Fig. 3C). He was followed up without specific therapy for his ILD and remained in stable condition until his previous visit, 1 month before admission.

Admission data were: height, 163.5 cm; weight, 50.9 kg; body surface area, 1.54 m^2. He had a temperature of 37.4 °C, blood pressure of 124/64 mmHg, a heart rate of 92 beats per minute, oxygen saturation of 98% under nasal O_2 1L per min.

Physical examination revealed bilateral late inspiratory crackles in his back. A chest X-ray (Fig. 3B) showed bilateral infiltrative shadows in the lower lung fields, which were worse than 1 month earlier (Fig. 3A). HRCT imaging revealed new, bilateral, multifocal GGOs superimposed on a background of emphysema and lung fibrosis (Fig. 3D). A PCR test for SARS-CoV-2 was negative. Increased CRP (11.22 mg/dL), LDH (245 U/mL), and KL-6 (783 U/mL) were noted. He was diagnosed with AE-ILD due to infection. Upon admission, we ordered an additional serological examination to evaluate the etiology of ILDs: ANCA, ANA, ACPA, anti-Ro, anti-Scl-70, and anti-ARS antibodies were all negative, and the level of RF was 35.9 U/dL, which were not significant findings. Based on CT findings and serological results, his ILD was diagnosed as IPF. Pulsed-dose mPSL (1000 mg) was initiated on admission day 1. He responded well to the treatment. His respiratory condition improved gradually. Levels of CRP and LDH peaked, and chest X-rays showed improvement

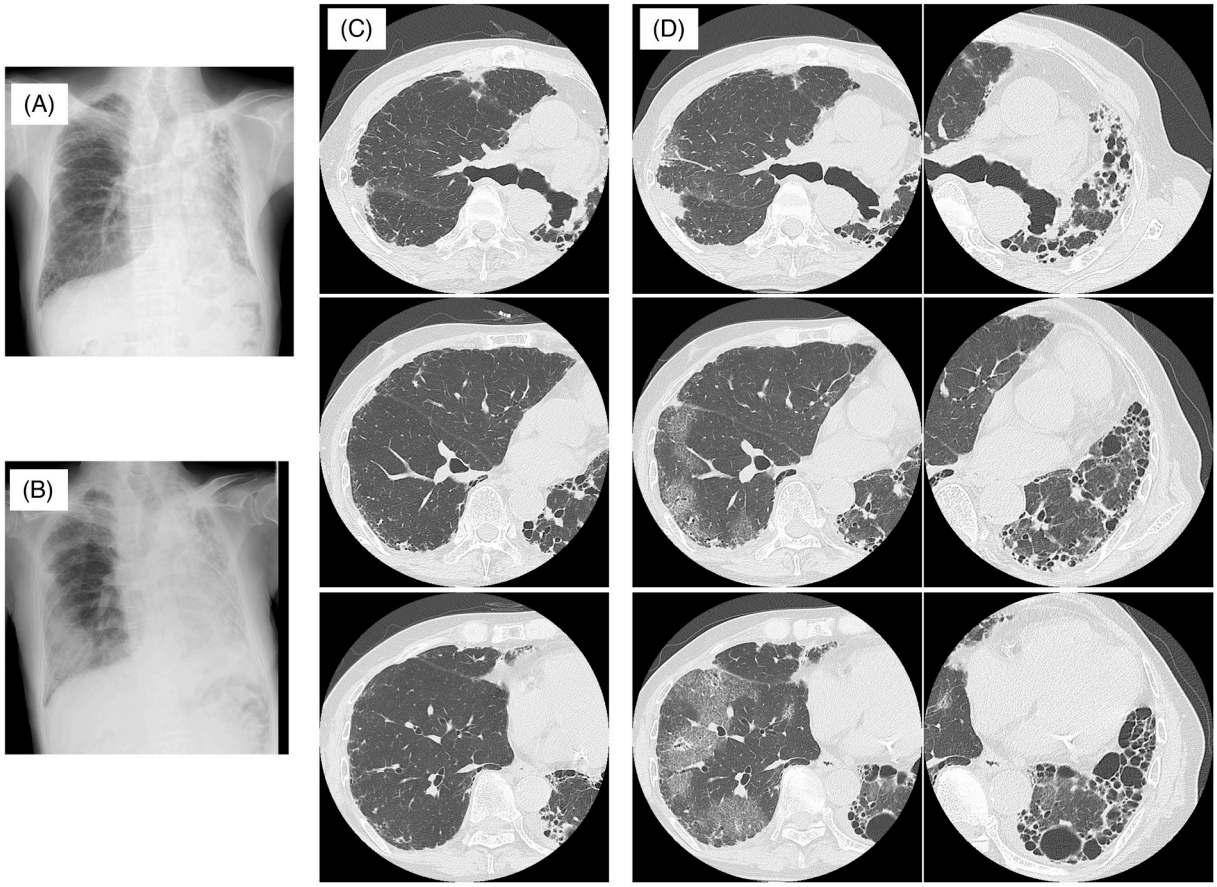

Fig. 3. Radiographic images of case #3. Chest X-ray images of the patient (A) before and (B) at the diagnosis of acute exacerbation of interstitial lung disease. Chest CT images of the patient (C) before and (D) at the diagnosis of acute exacerbation of interstitial lung disease.

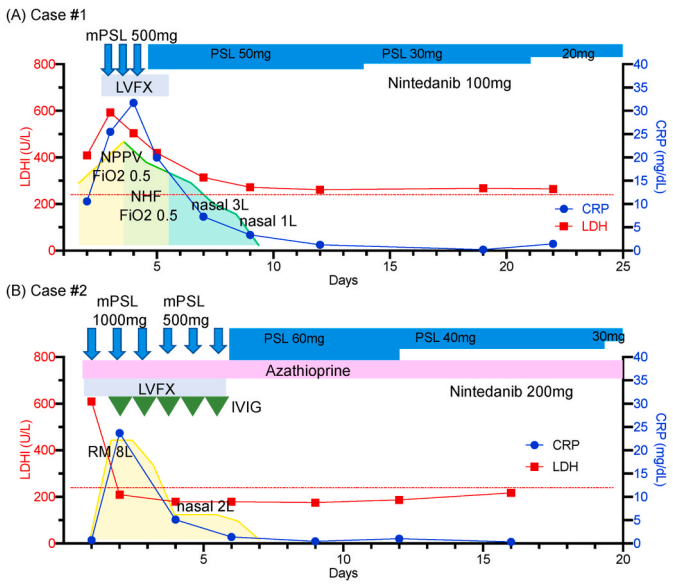

Fig. 4. Clinical courses of cases 1 and 2. mPSL: methylprednisolone, PSL: prednisolone, IVIG: intravenous immunoglobulin, LVFX: levofloxacin, CRP: C-reactive protein, LDH: lactate dehydrogenase, RM: reservoir mask, NHF: nasal high flow, FiO2: fraction of inspiratory oxygen.

of bilateral infiltrative shadows. On day 4, the PSL dose was reduced to a maintenance dose of 60 mg per day. On day 5, he no longer required oxygen at rest. On day 12, 100 mg/day of nintedanib were initiated. On day 18, the nintedanib dose was increased to 200 mg/day. The PSL dose was tapered to 7.5 mg/day and he was discharged on day 23. On an outpatient basis, the PSL dose was tapered off while continuing nintedanib. He has not relapsed and remains without significant side effects two month after discharge.

3. Discussion

We presented two cases of AE of IPF and one case of dermatomyositis-associated ILD that were treated with pulsed doses of corticosteroids followed by nintedanib and corticosteroid tapering. Corticosteroids are generally prescribed in AE-ILDs, including AE of IPF, based on historical evidence of beneficial results [2,5]. Long-term corticosteroid treatment, however, can induce several adverse side effects, such as immunocompromised infection. Indeed, patient case #3 had a history of tuberculosis and there was a serious concern that long-term corticosteroid treatment might cause tuberculosis relapse. Moreover, corticosteroids with immunosuppresive treatment are no longer recommended for stable IPF [6]. From these points of view, it might be less desirable to maintain corticosteroids long after remission of AE of IPF. On the other hand, relapse of AE of IPF is a major concern during rapid tapering of corticosteroids. Nintedanib is expected to slow progression of IPF as measured by forced vital capacity (FVC) beyond 4 years and might reduce the risk of AE-ILD [7–9]. Additionally, nintedanib may have therapeutic effects on AE-ILD by attenuating neutrophilic inflammation, normalizing alveolar permeability, and inhibiting profibrotic signals [10,11]. Thus, sequential treatment with nintedanib following pulsed-dose corticosteroids for AE of IPF is a reasonable strategy to reduce the risk of relapse during corticosteroid tapering.

Our patient in case #2 had anti-EJ antibodies and had suffered a

relapse of AE-ILD in the previous half a year. A high recurrence rate was reported in patients with dermatomyositis-associated ILDs having anti-EJ antibodies [12]. This suggests that an additional strategy may be required for standard therapy. Recently, we reported successful treatment with nintedanib and intensive immunosuppressive therapy for rapidly progressive ILD presenting anti-ARS antibodies [13]. In addition, a retrospective study in inflammatory myopathy-related ILDs showed that patients with nintedanib treatment had better prognoses and a lower incidence of rapidly progressive ILD [14]. These studies may support the additional use of nintedanib for the acute phase of dermatomyositis-associated ILDs, especially having anti-EJ antibodies. We thus believe that nintedanib may be able to prevent disease relapses when administered in combination with corticosteroids and immunosuppressive agents.

However, side effects occasionally become problematic when using nintedanib. The most serious involve hepatotoxicity and diverse gastrointestinal events, which could necessitate early termination of the therapy [15]. Small physique, Asian heritage, and advanced age are reported risk factors for these side effects [16–20]. In these three cases, we initiated nintedanib with low doses (100–200 mg/day) due to small patient physiques (all cases), Asian heritage (all cases), and advanced age (cases #1 and #3). This low-dosage strategy may avoid early termination due to side effects and appears to allow early tapering of corticosteroids. This strategy is supported by Ogura et al. [21], who recommended a low initial dose of nintedanib to prevent early termination. Therapeutic efficacy at a dose of 200 mg/day is based on two results. One is a retrospective study performed in Japan [21] and the other is an analysis of the INPULSIS-ON trial [22], both of which revealed no significant differences in FVC decline between patients treated with 200 mg/day and those receiving 300 mg/day. However, we could not measure the actual blood concentration of nintedanib in these patients with 100 mg/day or 200 mg/day.

Pirfenidone, another anti-fibrotic agent approved for treatment of IPF, can be an alternative option for AE of IPF. A retrospective study conducted by Furuya et al. revealed that three-month survival was better in patients treated with pirfenidone than in the control group for AE of IPF [23]. However, since the etiology of ILDs in patient #1 and #3 on admission were unknown and because nintedanib can be used for any type of ILDs that show progression and fibrosis, we chose nintedanib in these cases.

As a limitation, the observational periods may be too short to confirm that nintedanib therapy contributed to suppress the relapse of AE-ILDs. The most important point of the case series is, however, to contribute to a more thorough discussion regarding the use and timing of nintedanib in treating acute exacerbation of ILDs. We thus prioritized publishing the case series with the current observational periods rather than waiting for longer periods.

To summarize the main points, a low starting dose of nintedanib for AE-ILDs may enable early tapering of corticosteroids while simultaneously avoiding side effects of nintedanib, especially for patients of small physique, Asian ancestry, and advanced age, thus reducing side effects of steroids as well. We hope that this case report will contribute to a thorough discussion of the use and timing of nintedanib for AE-ILDs and that a standardized method of nintedanib use for AE-ILD will be established.

Patient consent for publication

Written, informed consent was obtained from all patients.

Declaration of competing interest

The authors declare that they have no conflicts of interest relative to this publication.

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