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CASE REPORT

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Treatment with low-dose nintedanib and tacrolimus in patients with progressive fibrosing interstitial lung diseases with anti-ARS antibody-positive dermatomyositis

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Abstract

Nintedanib has been demonstrated to inhibit the rate of forced vital capacity decline in patients with progressive fibrosing interstitial lung diseases (PF-ILD) at a dose of 200 or 300 mg/day in the INBUILD trial. Although concomitant use of nintedanib with P-glycoprotein inhibitors reportedly increases the plasma concentrations of the former, tacrolimus, a P-glycoprotein inhibitor, is often used to treat connective tissue diseases-related interstitial lung diseases. The optimal dose of nintedanib in combination with tacrolimus for the treatment of PF-ILD with connective tissue disease is unknown. We herein present two patients with PF-ILD with anti-aminoacyl-tRNA synthetase antibody-positive dermatomyositis who were successfully treated with low-dose nintedanib (<200 mg/day) in combination with tacrolimus.

KEYWORDS

connective tissue diseases, nintedanib, P-glycoprotein, progressive fibrosing interstitial lung diseases, tacrolimus

INTRODUCTION

In the INBUILD trial,[1] nintedanib reduced the forced vital capacity (FVC) rate decline in patients with progressive fibrosing interstitial lung diseases (PF-ILD). The INBUILD study enrolled 108 (16%) Japanese patients, and the efficacy and safety of nintedanib in Japanese patients were consistent with the overall INBUILD study population. Nintedanib showed its efficacy at a dose of 200 or 300 mg/day but not at a low dose of <200 mg/day. Concomitant use of nintedanib with P-glycoprotein inhibitors reportedly increases the plasma concentrations of the former due to drug–drug interactions.[2] However, the optimal dose of nintedanib for concomitant use is unknown. We herein present two patients with PF-ILD with anti-aminoacyl-tRNA synthetase (ARS) antibody-positive dermatomyositis who were successfully treated with a combination of low-dose nintedanib and tacrolimus, a P-glycoprotein inhibitor.

CASE REPORT

Case 1

A previously healthy Japanese woman in her 60s was diagnosed with dermatomyositis (DM) based on the findings of mechanic's hands, organizing pneumonia and cellular nonspecific interstitial pneumonia (NSIP), myositis, and positive anti-ARS antibody; she received induction therapy with prednisolone 30 mg/day and tacrolimus (Figure 1). She exhibited decreased FVC and increased Krebs von den lungen-6 (KL-6) levels, which improved after treatment. The patient showed improvement and received maintenance therapy with low-dose prednisolone and tacrolimus. Three years after the diagnosis, her ILD gradually worsened and was treated with increasing doses of prednisolone and various immunosuppressive therapies (azathioprine, cyclosporine, and cyclophosphamide pulse therapy). However, 4 years after the diagnosis, her respiratory function

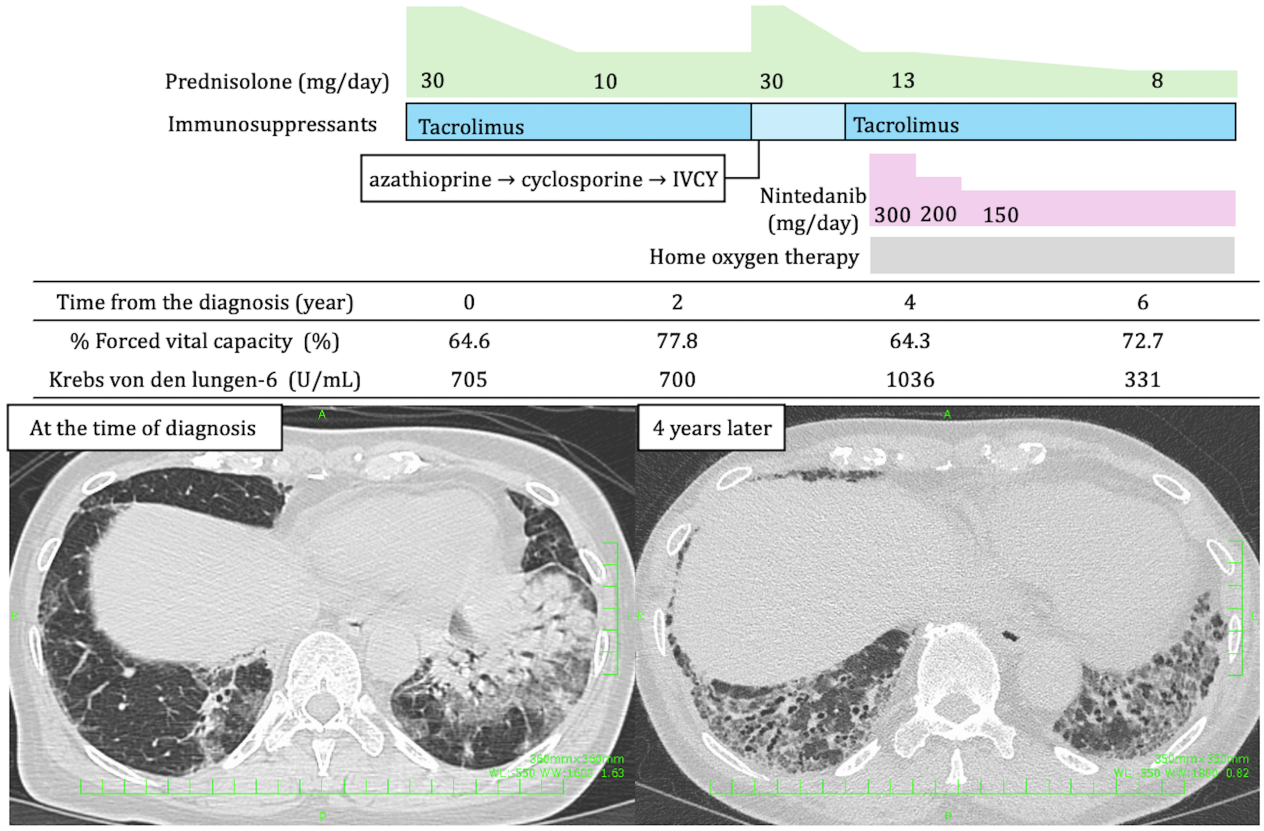
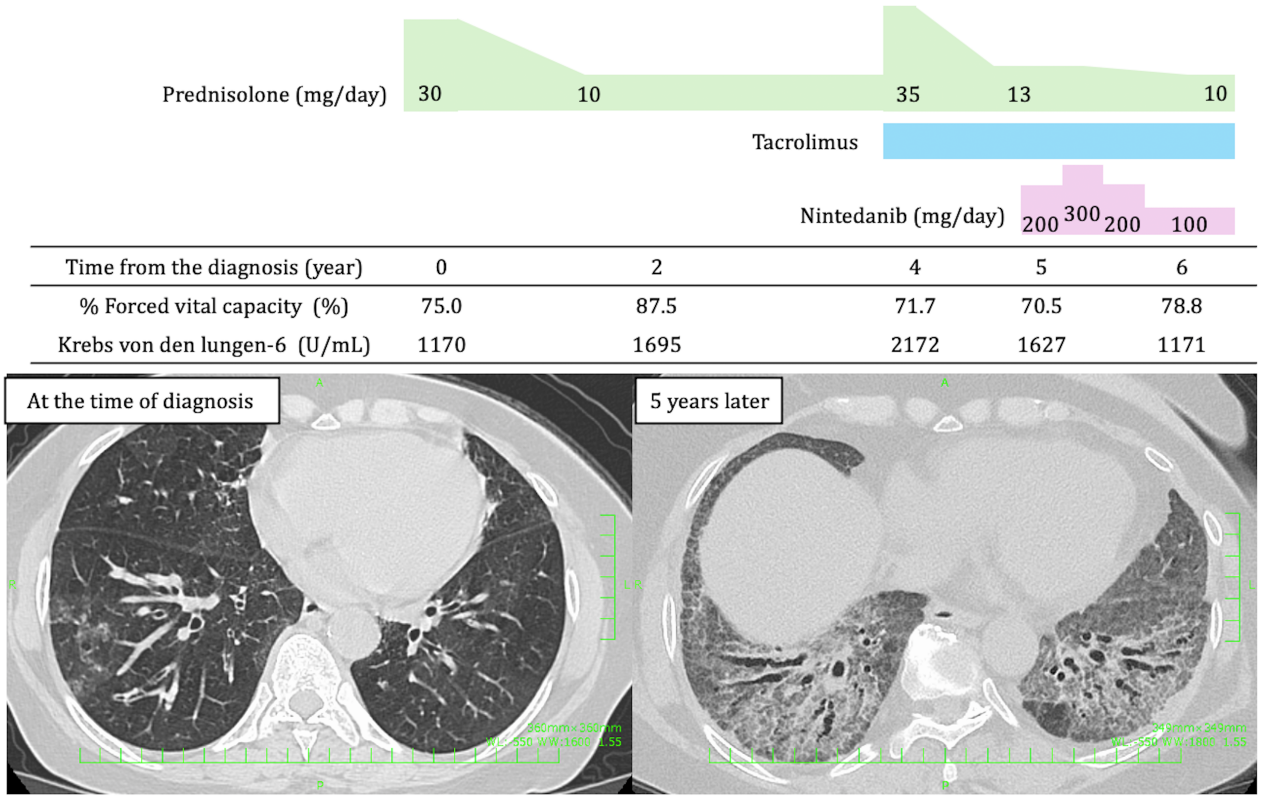


FIGURE 1 Clinical course and findings of the chest computed tomography of Case 1. High-resolution computed tomography (HRCT) of the chest at diagnosis shows infiltrative shadows around bronchovascular bundles and surrounding ground-glass opacity (GGO), findings consistent with organizing pneumonia and cellular nonspecific interstitial pneumonia (NSIP). HRCT of the chest obtained at the start of nintedanib administration (4 years after diagnosis) shows interstitial reticulation, GGO, and traction bronchiectasis, findings that are consistent with fibrotic NSIP. IVCY, intravenous cyclophosphamide.

gradually worsened, and she developed hypoxemia (percutaneous oxygen saturation < 90% during a short 2–3-min walk). High-resolution computed tomography (HRCT) of the chest confirmed the findings of fibrotic NSIP accompanied by ground-glass opacity (GGO), reticular abnormalities, and traction bronchiectasis. The relative decline in FVC was 17% since the %FVC had decreased from 77.8% to 64.3% over 24 months. These findings met the diagnostic criteria for PF-ILD. The patient's maintenance therapy, prednisolone 13 mg/day and tacrolimus 2 mg/day, was continued, and nintedanib 300 mg/day and home oxygen therapy were added. At the start of nintedanib administration, the patient weighed 53.3 kg, had a body mass index (BMI) of 20.6, and had no liver function abnormalities. Due to diarrhoea and weight loss, the dose of nintedanib was reduced to 150 mg/day. Six years after the diagnosis, low-dose nintedanib was continued at the same dose for 2 years. The prednisolone dose was reduced to 8 mg/day, and no worsening of pulmonary condition was observed. Furthermore, from the start of nintedanib to 2 years after treatment, FVC improved from 64.3% to 72.7%, and KL-6 decreased from 1036 U/mL to 331 U/mL. Tacrolimus was continued at the same dose, and the serum trough concentrations of tacrolimus were unchanged (4–6 ng/mL) before and after the nintedanib administration.

Case 2

A Japanese woman in her 70s receiving treatment with inhaled corticosteroid/long-acting β2 agonist for asthma developed a dry cough. HRCT of the chest revealed GGO in both lungs, a finding consistent with cellular NSIP. The cytology of bronchoalveolar lavage fluid revealed increased total cell count with lymphocyte predominance and no eosinophilia. Antinuclear antibodies, anti-SS-A, and anti-SS-B antibodies were negative. However, the patient had dry eyes and mouth, and a lip biopsy revealed chronic sialadenitis that met the diagnostic criteria for Sjogren's syndrome. The patient was diagnosed with Sjogren's syndrome and treated with prednisolone 30 mg/day. Her lung condition improved, and she received maintenance therapy with low-dose prednisolone (Figure 2). Two years after the diagnosis, KL-6 remained elevated, although respiratory symptoms had abated and FVC had normalized. Four years after the diagnosis, the patient developed



Time from the diagnosis (year)	0	2	4	5	6
% Forced vital capacity (%)	75.0	87.5	71.7	70.5	78.8
Krebs von den lungen-6 (U/mL)	1170	1695	2172	1627	1171

FIGURE 2 Clinical course and findings of the chest computed tomography of Case 2. High-resolution computed tomography (HRCT) of the chest at diagnosis shows ground-glass opacity (GGO) in both lungs, a finding consistent with cellular nonspecific interstitial pneumonia (NSIP). HRCT of the chest obtained at the start of nintedanib administration (5 years after diagnosis) shows interstitial reticulation, GGO, and traction bronchiectasis, findings that are consistent with fibrotic NSIP.

mechanic's hands, arthritis, and hypoxemia (percutaneous oxygen saturation < 90% during a short 2–3-min walk) and had positive anti-ARS antibody, but no myositis. She was diagnosed with amyopathic DM and treated with 35 mg/day and tacrolimus 2 mg/day, but her lung disease gradually worsened. Five years after the diagnosis, she complained of a worsening cough, and HRCT of the chest revealed fibrotic NSIP accompanied by diffuse GGO, reticular shadow, and traction bronchiectasis, satisfying the diagnostic criteria for PF-ILD. The patient's maintenance therapy, prednisolone 13 mg/day and tacrolimus 2 mg/day, was continued, and nintedanib 200 mg/day was added. At the start of nintedanib administration, the patient weighed 76.7 kg, had a BMI of 33.5, and had no liver function abnormalities. Due to diarrhoea, the dose of nintedanib was reduced to 100 mg/day. Six years after the diagnosis, low-dose nintedanib was continued at the same dose for 1 year. The prednisolone dose was reduced to 10 mg/day, and no worsening of pulmonary condition was observed. From the start of nintedanib to 1 year after treatment, FVC improved from 70.5% to 78.8%, and KL-6 decreased from 1627 U/mL to 1171 U/mL. Tacrolimus was continued at the same dose, and the serum trough concentrations of tacrolimus were unchanged (5–7 ng/mL) before and after nintedanib administration.

DISCUSSION

Managing adverse events is important for the long-term administration of nintedanib, which may require dose adjustments. In the INBUILD trial, the most common adverse events were diarrhoea (66.9%) and liver function abnormalities (11.4%). Such adverse events led to treatment discontinuation (19.6%) and permanent dose reduction (33.1%).[1] In a post-marketing survey of nintedanib in patients with idiopathic pulmonary fibrosis (IPF) in Japan, 50.1% of the patients discontinued treatment within 1 year, and half of the discontinuations were due to adverse events. The most common adverse events causing discontinuation were liver function abnormalities (18.8%) and diarrhoea (13.2%).[3] In our cases, nintedanib was reduced to a lower dose (<200 mg/day) due to diarrhoea and weight loss, after which nintedanib could be continued.

When nintedanib is concomitantly used with P-glycoprotein inhibitors, such as tacrolimus, the plasma concentrations of nintedanib are expected to be higher than when nintedanib is used alone. A post-marketing survey of patients with IPF showed more discontinuations in those receiving nintedanib with cyclosporine (odds ratio: 1.89; 95% confidence interval: 1.37–2.61).[3] Similar results were not obtained with the concomitant use of tacrolimus,

possibly because of the small number of tacrolimus-treated cases (1.3%) in the overall survey. A dose reduction of nintedanib to 200 mg/day is considered in patients with adverse events with or without tacrolimus, but a dose reduction to less than 200 mg/day is not common. When nintedanib is combined with tacrolimus, a dose reduction of nintedanib to 100 or 150 mg/day may be a potential treatment option. Other factors known to affect the metabolism of nintedanib include ethnicity, low body weight, advanced age, and smoking habit, but the effects are insignificant and do not require dose adjustments.[2] Although it was impossible to measure the plasma concentrations of nintedanib in our cases, the concomitant use of nintedanib with tacrolimus likely increased the plasma concentrations of the former.

Tacrolimus is often used to treat CTD-ILD. In particular, tacrolimus is frequently administered to patients with polymyositis/DM-related ILD because its addition to conventional therapy (prednisolone and/or cyclophosphamide) improves the prognosis.[4] Furthermore, one-third of patients with anti-ARS antibody-positive ILD have organizing pneumonia with fibrosis.[5] Nintedanib and tacrolimus may often be used together in the future.

We herein present two patients with PF-ILD who were successfully treated with low-dose nintedanib and tacrolimus. Further clinical trials or case series are warranted to confirm the efficacy of low-dose nintedanib when combined with P-glycoprotein inhibitors.

AUTHOR CONTRIBUTIONS

All authors meet the ICMJE authorship criteria. *Data curation*: Takeshi Kawaguchi, Motohiro Matsuda. *Writing–original draft preparation*: Takeshi Kawaguchi. *Writing–review & editing*: Takeshi Kawaguchi, Kunihiko Umekita, Taiga Miyazaki.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

Ethical approval for this case report was waived by the Ethics Committee of the University of Miyazaki. The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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