Respiratory Medicine Case Reports 31 (2020) 101272

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Nintedanib and intensive immunosuppressive therapy to treat rapidly progressive interstitial lung disease presenting anti-ARS antibodies

Toyoshi Yanagihara [a,b,*], Kunihiro Suzuki [b], Ayaka Egashira [a], Naruhiko Ogo [a], Tatsuma Asoh [a], Tsukasa Nara [a], Kensaku Takatsuki [c], Seiji Yoshizawa [c], Sy Giin Chong [d], Naoki Hamada [b], Takashige Maeyama [a]

[a] Department of Respiratory Medicine, And Department of Rheumatology, Hamanomachi Hospital, Fukuoka, 810-8539, Japan
[b] Research Institute for Diseases of the Chest, Kyushu University, Fukuoka, 812-8582, Japan
[c] Department of Rheumatology, Hamanomachi Hospital, Fukuoka, 810-8539, Japan
[d] Firestone Institute for Respiratory Health, Research Institute at St Joseph's Healthcare, Department of Medicine, McMaster University, Hamilton, ON, Canada

ARTICLE INFO

Keywords:
Rapidly progressive interstitial lung disease
Clinically amyopathic dermatomyositis
Anti-ARS antibody
Nintedanib
Progressive fibrosing interstitial lung disease

ABSTRACT

We describe a case of fulminant onset, rapidly progressive-interstitial lung disease (RP-ILD) with anti-ARS antibodies (anti-PL-7). The patient was successfully treated with nintedanib in addition to intensive immunosuppressive therapies, including intravenous cyclophosphamide. Nintedanib has just been approved for treatment of progressive fibrosing ILD, but to date, no reports of RP-ILD treated with nintedanib have been published. This case report may advance discussions regarding the use and timing of nintedanib in treating RP-ILD.

1. Introduction

Dermatomyositis (DM) is an autoimmune disease that mainly affects the skin and proximal muscles; however, some patients with DM have minimal or no muscle involvement, called clinically amyopathic DM (CADM) [1]. Interstitial lung disease (ILD) is a major complication of DM, with a poorer prognosis than DM without ILD [2]. Rapidly progressive ILD (RP-ILD) in CADM is a life-threatening subtype of myositis-associated ILD that tends to be resistant to high-dose glucocorticoid treatment and immunosuppressants. Anti-aminoacyl tRNA synthetase (ARS) antibodies and anti-melanoma differentiation-associated 5 (MDA5) antibodies have been reported with RP-ILD [3]. RP-ILD due to anti-MDA5 antibodies is often associated with worse outcomes than RP-ILD due to anti-ARS antibodies [4,5]. Here we report a case of severe onset RP-ILD associated with anti-ARS antibodies that was successfully treated with nintedanib in addition to intensive immunosuppressive therapies.

2. Case report

A 59-year-old Japanese man with no past medical history presented with worsening dyspnea of one-month duration. He was a construction worker and had 20 pack-years smoking history. He denied any contact with sick people and had not traveled. On admission, he had a temperature of 37.1 °C, blood pressure of 124/77 mmHg and a heart rate of 76 beats per minute. He was tachypneic with oxygen saturation of 93% with an oxygen mask delivering 8 L/min. Physical examination revealed fine bilateral crackles in his back, but no evidence of the skin rash that typifies dermatomyositis. He demonstrated evidence of "mechanic's hand" (roughening and cracking of the skin) (Fig. 1). An assessment of muscle power was not completed due to severe respiratory failure, but no obvious muscle weakness was observed.

A PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was negative. Increased levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer were noted (17.95 mg/dL, 478 U/L, 44.9 μg/mL, respectively). Krebs von den Lungen-6 (KL-6) was remarkably increased (3930 U/mL; normal <500 U/mL). Serum levels of creatine kinase (CK) and aldolase were not elevated (38 IU/L and 4.1U/L, respectively). Serological tests for atypical pathogens, including *Mycoplasma pneumoniae,* were negative. Chest computed tomography (CT) showed consolidations and ground-glass opacities (GGO), predominantly in the bilateral lower lobes with decreased lung volumes, suggesting a radiologic pattern of diffuse alveolar damage (DAD) imposed on non-specific interstitial pneumonia (NSIP) (Fig. 2A).

* Corresponding author. Department of Respiratory Medicine, and Department of Rheumatology, Hamanomachi Hospital, Fukuoka, 810-8539, Japan.
E-mail address: yanagiha@kokyu.med.kyushu-u.ac.jp (T. Yanagihara).

https://doi.org/10.1016/j.rmcr.2020.101272
Received 11 October 2020; Received in revised form 23 October 2020; Accepted 23 October 2020
Available online 28 October 2020

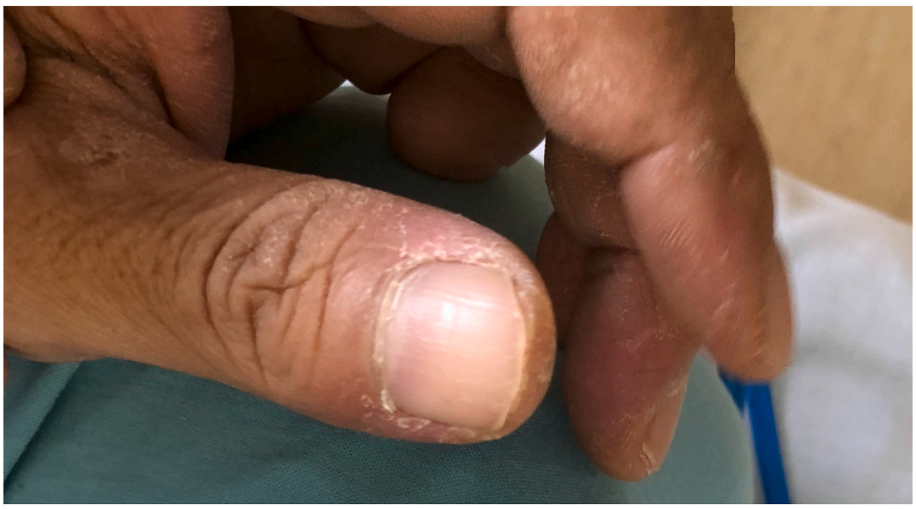

Fig. 1. The patient had rough, cracking skin on the tips and sides of the fingers ("mechanic's hand").

Contrast-enhanced CT showed no obvious pulmonary artery thromboembolism or deep vein thromboembolism.

In addition to broad-spectrum antibiotic therapy (intravenous meropenem and minocycline), pulse doses of methylprednisolone (mPSL) were initiated, followed by 50 mg/day of prednisolone (PSL). Further workup revealed positive anti-ARS antibodies (81.9 index; normal <24), which led to a final diagnosis of rapidly progressive interstitial lung disease (RP-ILD) associated with anti-ARS antibodies (The anti-ARS antibodies were later found to be anti-PL-7 antibodies). Despite a second course of mPSL pulses and additional tacrolimus and recombinant thrombomodulin therapy, which were started on day 7, his respiratory condition deteriorated. He was referred to Hamanomachi Hospital on day 11.

On arrival at Hamanomachi Hospital, his PaO_2 was 73 mmHg with

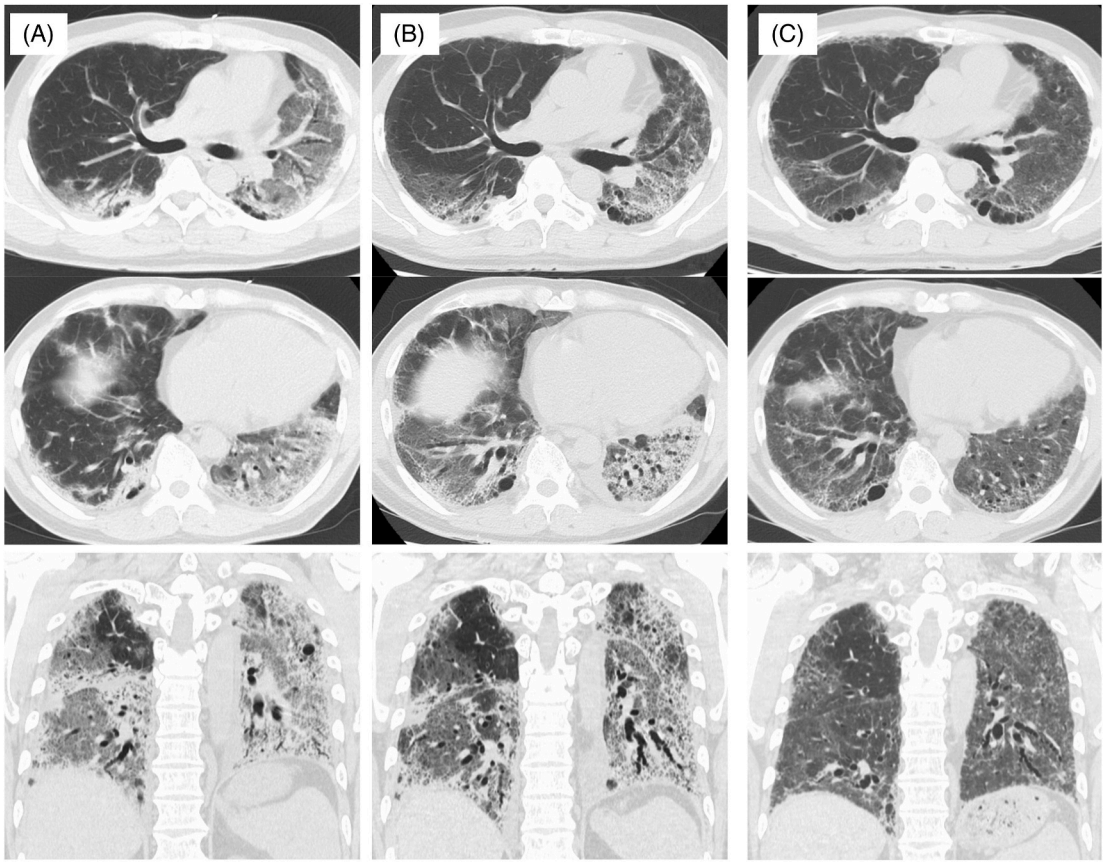

Fig. 2. Chest CT images of the patient. (A) On admission to the first hospital (day 1), chest CT images showed consolidations and ground-glass opacities (GGO), predominantly in the bilateral lower lobes with loss of lung volume, suggesting a radiologic pattern of diffuse alveolar damage (DAD) superimposed on non-specific interstitial pneumonia (NSIP). (B) On admission to Hamanomachi Hospital (day 11), chest CT images showed progression of the areas of GGO, consolidations, traction bronchiectasis, and decreased lung volume. (C) On day 40, chest CT images showed improvement of GGO and consolidations. Traction bronchiectasis in the peripheral area and loss of lung volume were partially reversed as well.

100% O_2 oxygen. Repeat chest CT showed a new development of mediastinal emphysema with worsening consolidation, GGO, traction bronchiectasis, and loss of lung volume, predominantly in the left lobes, suggesting progressive fibrosis (Fig. 2B). Nasal, high-flow oxygen therapy was started with initial fraction of inspiratory oxygen (FiO_2) at 1.0. His serum ferritin level was elevated at 771 ng/mL. Intravenous immunoglobulin (IVIG; 20g for 5 days) and intravenous cyclophosphamide (IVCY; 900 mg [500 mg/m^2]) was initiated. The dose of tacrolimus was increased to 0.05 mg/kg twice a day (8 mg/body), and the goal trough was set to 10 ng/mL. Due to suspicion of thrombotic microangiopathy in the pulmonary microvessels, based on his high levels of D-dimer, continuous intravenous dalteparin (5000 U/day) was started (Fig. 3).

On day 15, although laboratory tests showed improved levels of CRP and D-dimer, there was no improvement of chest X-ray images and the PaO_2/FiO_2 ratio. Serum KL-6 level was further elevated at 5380 U/mL. Therefore, nintedanib (200 mg/day) was started. The serum trough of tacrolimus reached 11.1 ng/mL on day 17. PSL was tapered to 40 mg/day for a week, followed by 30 mg/day. On day 25, dalteparin treatment was discontinued due to improvement of the D-dimer level. His respiratory condition further improved on day 34 with de-escalation of his oxygen requirement to a regular nasal canula with oxygen at 3 L/min. His chest CT, repeated on day 40, showed improvement of GGO and consolidations (Fig. 2C). Traction bronchieactasis in the peripheral area and lung volume was somewhat improved as well (Fig. 2C).

3. Discussion

We describe a case of fulminant RP-ILD associated anti-ARS antibodies, treated with nintedanib in addition to intensive immunosuppressive therapies. The recommended treatment for CADM-associated RP-ILD is corticosteroid therapy and/or immunosuppressive agents [6]. Immunosuppressive agents (IVCY and tacrolimus) may offer the main benefits in such a case. In addition to this standard therapy, we added nintedanib, based on the assumption that there should be significant fibrogenesis in the lung on day 15.

There are several publications regarding prognostic factors for inflammatory myositis-ILD. Fujisawa et al. reported that acute/subacute onset, older age, lower level of forced vital capacity (FVC), and a diagnosis of CADM predict a poor outcome in inflammatory myositis-ILD [7]. High levels of serum ferritin (>828 ng/mL) on admission constitute a poor prognostic factor in RP-ILD patients with anti-MDA5 antibodies, along with IL-6 [8]. Recently, a multicenter retrospective cohort of cases of myositis-associated ILD from 44 institutions across Japan was established, and several predictors of poor prognosis were reported: age at onset >60 years [hazard ratio (HR) = 4.3, 95% CI: 2.4, 7.5], CRP >1 mg/dL (HR = 2.6, 95% CI: 1.5, 4.8), peripheral capillary oxygen saturation <95% (HR = 2.0, 95% CI: 1.2, 3.4) and anti-MDA5 antibodies (HR = 7.5, 95% CI: 2.8, 20.2) [9]. Higher levels of KL-6 (>1000 U/ml) were an additional, independent risk factor (HR = 2.0, 95% CI: 1.2, 3.3; p = 0.01) [9]. In this case, acute onset with desaturation, extensive findings on chest CT, and higher levels of CRP and KL-6, except for the

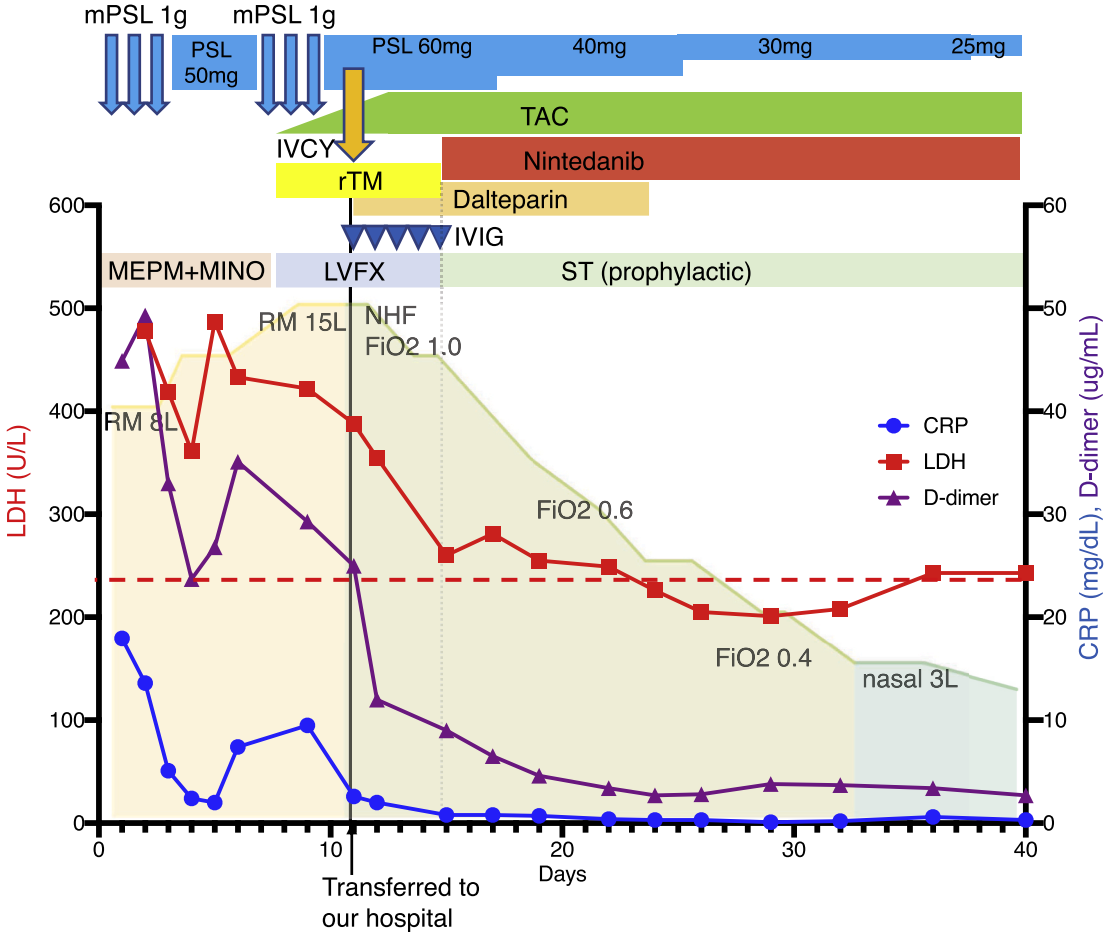

Fig. 3. A clinical course of the case.
The patient was transferred to Hamanomachi Hospital on day 11.
mPSL: methylprednisolone, PSL: prednisolone, IVCY: intravenous cyclophosphamide, TAC: tacrolimus, rTM: recombinant thrombomodulin, IVIG: intravenous immunoglobulin, MEPM: meropenem, MINO: minocycline, LVFX: levofloxacin, ST: sulfamethoxazole-trimethoprim, CRP: C-reactive protein, LDH: lactate dehydrogenase, RM: reservoir mask, NHF: nasal high flow, FiO2: fraction of inspiratory oxygen.

absence of anti-MDA5 antibodies, all suggested a poor prognosis and provided the rationale for intensive treatment.

The anti-ARS antibodies were later found to be anti-PL-7 antibodies. Marie et al. investigated clinical manifestations and outcomes of 15 patients with anti-PL-7 positive anti-synthetase syndrome [10]. They found that 93.3% (14/15) of anti-PL-7 patients exhibited ILD. 7.1% (1/14) showed acute onset of ILD. No patient had resolution of ILD, and 35.7% (5/14) of patients experienced deterioration [10]. This report suggests that additional therapies such as anti-fibrotic agents may be needed for disease remission.

It is becoming recognized that there is a progressive phenotype in non-idiopathic pulmonary fibrosis (IPF)—progressive fibrosing interstitial lung disease (PF-ILD)— the disease behavior of which is similar to IPF [11,12]. Thus, it is reasonable to consider application of antifibrotic agents—nintedanib or pirfenidone in PF-ILD, including myositis-associated ILD. A double-blind, placebo-controlled, phase 3 trial using nintedanib in patients with PF-ILD, including several cases of myositis-related ILD, have shown that nintedanib significantly reduced the decline in forced vital capacity (FVC) [13]. Based on this trial, nintedanib was recently approved for treatment of PF-ILD in the U.S.A., Canada, and Japan.

However, it is still unclear whether it is efficacious to use nintedanib on RP-ILD. Takada et al. investigated serum cytokine levels in patients with ILD related to anti-MDA5 antibody positive CADM [14]. They found that serum levels of vascular endothelial growth factor (VEGF) were correlated with the titer of anti-MDA5 antibodies and that fibroblast growth factor-2 (FGF-2) levels tended to be correlated, though not significantly [14]. These results indicate that nintedanib—a multi receptor kinase inhibitor for VEGF, FGF, and platelet-derived growth factor (PDGF), can be effective for CADM-ILD. Indeed, a recent preprint from a Chinese institution reported that nintedanib therapy might reduce the incidence of RP-ILD and might improve survival in inflammatory myositis-ILD patients [15].

Moreover, nintedanib has anti-inflammatory activity [16]. Nintedanib treatment suppresses interleukin (IL)-1β and KC in both bleomycin-treated lung and silica-treated lung in mice [17]. Nintedanib inhibits the release of mediators, including IL-2, IL-4, IL-5, IL-10, IL-12p70, IL-13 and interferon-γ from human peripheral blood mononuclear cells or T-cells [18]. Thus, nintedanib could have not only anti-fibrotic, but also anti-inflammatory effects, which should further contribute to favorable outcomes. Clinical trials using nintedanib in the acute phase of RP-ILD are warranted to assess and quantify the benefits of nintedanib. We hope that this case report will contribute to a thorough discussion of the use and timing of nintedanib for RP-ILD.

Patient consent for publication

Written, informed consent was obtained from the patient.

Declaration of competing interest

All authors of the manuscript declare that there are no conflicts of interest.

References

[1] R.D. Sontheimer, Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J. Am. Acad. Dermatol. 46 (2002) 626–636, https://doi.org/10.1067/mjd.2002.120621.

[2] V. Cottin, F. Thivolet-Béjui, M. Reynaud-Gaubert, J. Cadranel, P. Delaval, P. J. Ternamian, J.F. Cordier, P. Camus, I. Court-Fortune, B. Crestani, P. Delaval, G. Devouassoux, G. Mangiapan, M. Reynaud-Gaubert, B. Wallaert, Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis, Eur. Respir. J. 22 (2003) 245–250, https://doi.org/10.1183/09031936.03.00026703.

[3] Z. Betteridge, N. McHugh, Myositis-specific autoantibodies: an important tool to support diagnosis of myositis, J. Intern. Med. 280 (2016) 8–23, https://doi.org/10.1111/joim.12451.

[4] I.M.G. Piroddi, G. Ferraioli, C. Barlascini, C. Castagneto, A. Nicolini, Severe respiratory failure as a presenting feature of an interstitial lung disease associated with anti-synthetase syndrome (ASS), Respir, Investig 54 (2016) 284–288, https://doi.org/10.1016/j.resinv.2016.01.005.

[5] S.H. Kim, I.N. Park, Acute respiratory distress syndrome as the initial clinical manifestation of an Antisynthetase syndrome, Tuberc. Respir. Dis. 79 (2016) 188–192, https://doi.org/10.4046/trd.2016.79.3.188.

[6] T. Yanagihara, Y. Inoue, Insights into pathogenesis and clinical implications in myositis-associated interstitial lung diseases, Curr. Opin. Pulm. Med. 26 (2020) 507–517, https://doi.org/10.1097/MCP.0000000000000698.

[7] T. Fujisawa, H. Hozumi, M. Kono, N. Enomoto, D. Hashimoto, Y. Nakamura, N. Inui, K. Yokomura, N. Koshimizu, M. Toyoshima, T. Shirai, K. Yasuda, H. Hayakawa, T. Suda, Prognostic factors for myositis-associated interstitial lung disease, PloS One 9 (2014) 10–13, https://doi.org/10.1371/journal.pone.0098824.

[8] T. Gono, S. Sato, Y. Kawaguchi, M. Kuwana, M. Hanaoka, Y. Katsumata, K. Takagi, S. Baba, Y. Okamoto, Y. Ota, H. Yamanaka, Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis, Rheumatol. (United Kingdom) 51 (2012) 1563–1570, https://doi.org/10.1093/rheumatology/kes102.

[9] S. Sato, K. Masui, N. Nishina, Y. Kawaguchi, A. Kawakami, M. Tamura, K. Ikeda, T. Nunokawa, Y. Tanino, K. Asakawa, Y. Kaneko, T. Gono, T. Ukichi, S. Kaieda, T. Naniwa, M. Kuwana, Y. Okano, Y. Yamaguchi, Y. Taniguchi, J. Kikuchi, M. Kubo, M. Watanabe, T. Harada, T. Kazuyori, H. Kameda, M. Kaburaki, Y. Matsuzawa, S. Yoshida, Y. Yoshioka, T. Hirai, Y. Wada, K. Ishii, S. Fujiwara, T. Saraya, K. Morimoto, T. Hara, H. Suzuki, H. Shibuya, Y. Muro, R. Aki, T. Shibayama, S. Ohshima, Y. Yasuda, M. Terada, Y. Kawahara, Initial predictors of poor survival in myositisassociated interstitial lung disease: a multicentre cohort of 497 patients, Rheumatol. (United Kingdom) 57 (2018) 1212–1221, https://doi.org/10.1093/rheumatology/key060.

[10] I. Marie, S. Josse, O. Decaux, E. Diot, C. Landron, P. Roblot, S. Jouneau, P. Y. Hatron, E. Hachulla, O. Vittecoq, J.F. Menard, F. Jouen, S. Dominique, Clinical manifestations and outcome of anti-PL7 positive patients with antisynthetase syndrome, Eur. J. Intern. Med. 24 (2013) 474–479, https://doi.org/10.1016/j.ejim.2013.01.002.

[11] A. Wongkarnjana, C. Scallan, M.R.J. Kolb, Progressive fibrosing interstitial lung disease: treatable traits and therapeutic strategies, Curr. Opin. Pulm. Med. 26 (2020) 436–442, https://doi.org/10.1097/mcp.0000000000000712.

[12] M. Wijsenbeek, V. Cottin, Spectrum of fibrotic lung diseases, N. Engl. J. Med. 383 (2020) 958–968, https://doi.org/10.1056/NEJMra2005230.

[13] K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, K.K. Brown, INBUILD trial investigators, nintedanib in progressive fibrosing interstitial lung diseases, N. Engl. J. Med. 54 (2019) 1900161, https://doi.org/10.1056/NEJMoa1908681.

[14] T. Takada, A. Aoki, K. Asakawa, T. Sakagami, H. Moriyama, I. Narita, S. Sato, Serum cytokine profiles of patients with interstitial lung disease associated with anti-CADM-140/MDA5 antibody positive amyopathic dermatomyositis, Respir. Med. 109 (2015) 1174–1180, https://doi.org/10.1016/j.rmed.2015.07.004.

[15] J. Liang, Real-world experience of nintedanib therapy in idiopathic inflammatory myopathy-related interstitial lung disease: efficacy and tolerability, Res. Sq (2020), https://doi.org/10.21203/rs.3.rs-52262/v1.

[16] L. Wollin, J.H.W. Distler, E.F. Redente, D.W.H. Riches, S. Stowasser, R. Schlenker-Herceg, T.M. Maher, M. Kolb, Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases, Eur. Respir. J. 54 (2019), https://doi.org/10.1183/13993003.00161-2019.

[17] L. Wollin, I. Maillet, V. Quesniaux, A. Holweg, B. Ryffel, Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosiss, J. Pharmacol. Exp. Therapeut. 349 (2014) 209–220, https://doi.org/10.1124/jpet.113.208223.

[18] L. Wollin, A. Ostermann, C. Williams, Nintedanib inhibits pro-fibrotic mediators from T cells with relevance to connective tissue disease-associated interstitial lung disease, in: Diffus. Parenchymal Lung Dis, European Respiratory Society, 2017, p. PA903, https://doi.org/10.1183/1393003.congress-2017.PA903.