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Case Report

Improvement in idiopathic interstitial pneumonia by adding macitentan to a patient unresponsive to nintedanib

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ABSTRACT

A 69-year-old woman was diagnosed with idiopathic interstitial pneumonia (IIP). The patient underwent a combination therapy of steroid therapy and intravenous cyclophosphamide, long-term oxygen therapy, and the initiation of Nintedanib. However, there was no improvement in IIP, and as a result, the activities of daily living also declined. As one of the various examinations conducted, the results of the right heart catheterization diagnosed the patient with mild pulmonary hypertension, and Macitentan therapy was initiated. The subsequent clinical course appeared to show an improvement in Idiopathic Interstitial Pneumonia (IIP) by adding Macitentan therapy to Nintedanib therapy.

List of abbreviations

IP	interstitial pneumonia
IIP	idiopathic interstitial pneumonia
PAP	pulmonary artery pressure
pulmonary hypertension	PH
tricuspid regurgitation	TR
idiopathic pulmonary fibrosis	IPF
right heart catheterization	RHC
activities of daily living	ADL
pulmonary artery pressure	PAP
pulmonary artery wedged pressure	PAWP
pulmonary vascular resistance	PVR
modified medical research council	mMRC
Saint George's respiratory questionnaire	SGRQ
6-min walk distance	6WMD
vital capacity	VC

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forced vital capacity FVC
forced expiratory volume in one second FEV1
forced expiratory volume % in one second FEV1.0%
intravenous cyclophosphamide IVCY
long term oxygen therapy LTOT
treadmill exercise test TMET
tricuspid regurgitant pressure gradient TRPG
Right ventricular fractional area change RVFAC
tricuspid annular plane systolic excursion TAPSE
right ventricle total ejection isovolumetric index RVTEI index

1. Introduction

Idiopathic Interstitial Pneumonia (IIP) is a refractory and sometimes progressive disease. It is occasionally treated with steroids, immunosuppressants, anti-fibrotic drugs, and more, but there is no established highly effective treatment. Moreover, Interstitial Pneumonia (IP) is frequently comorbid with Pulmonary Hypertension (PH). Since PH is linked to reduced exercise capacity, diminished quality of life (QOL), and higher mortality rates [1–4], it is clinically crucial to assess these patients for the presence of PH.

Endothelin, which is considered to be involved in the progression of PH, has been reported to be associated with lung injury and is also reported to have an impact on fibrosis [5]. In patients with idiopathic pulmonary fibrosis (IPF), an increase in endothelin levels in both serum and bronchoalveolar lavage fluid (BAL) has been observed, along with excessive expression of endothelin receptors and ET-1 in lung tissue [6,7].

Ambrisentan, an endothelin receptor antagonist, has been considered clearly harmful as a treatment option for interstitial pneumonia (IP). However, it remains unclear whether other endothelin receptor antagonists could benefit IP patients [8–10]. In the management of IP, the relationships between pulmonary hypertension (PH) and endothelin, as well as the impact of PH treatments including endothelin receptor antagonists on IP, remain uncertain. Here, we report a case where combining macitentan with nintedanib resulted in beneficial effects in a patient with idiopathic interstitial pneumonia (IIP) who had an inadequate response to nintedanib alone.

2. Case presentation

A 69-year-old woman, who was scheduled to undergo laparoscopic surgery for appendicitis, was found to have interstitial pneumonia (IP) shadows on a chest CT scan. She was referred to the respiratory department in July 2015. The chest CT examination revealed clustered cystic structures predominantly in the bilateral lower lobes and peripheral regions, along with thickening of the interlobular septa and features of traction bronchiectasis, resulting in a ground-glass-like shadow. In September 2015, a bronchoscopy was performed. Bronchoalveolar lavage fluid showed a predominance of lymphocytes, and in transbronchial lung biopsies performed in the upper, middle, and lower lobes of the right lung, a predominance of lymphocytes was observed, along with evidence of obstructive, somewhat older fibrosis with lymphocytic infiltration in the alveolar spaces, as well as active organizing fibrosis. These findings led to the diagnosis of Chronic Active Fibrosing Alveolitis. No findings suggesting collagen vascular diseases were observed in the blood tests (Table .1).

Based on the above results and considering the results of examinations by dermatologists and rheumatologists, we clinically diagnosed IIP (cannot rule out FOP but NSIP).

From September 2015, treatment was initiated with prednisolone at 30mg, which was subsequently tapered. However, the disease progression could not be controlled, and from March 2016, intravenous cyclophosphamide (IVCY) was administered in a total of 10 doses. (Table .2, Fig. 1).

Gradual progression of IP lesions on imaging, a decline in lung function, worsening respiratory condition, severe coughing, and increased breathlessness were observed. In July 2020, long-term oxygen therapy (LTOT) was introduced (a flow rate of 2 L per minute throughout the day and 3 L per minute during bathing). Furthermore, based on the progressive fibrosis observed on imaging (Fig. 1) and the ongoing decline in lung function over time (Table .2), a diagnosis of progressive pulmonary fibrosis (PPF) in interstitial lung disease (ILD) was made [11]. In November 2020, Nintedanib therapy was initiated. However, despite efforts, the disease progression could not be controlled. The symptoms of breathlessness were so severe that even conducting a respiratory function test was not possible.

In an attempt to identify the cause of worsening symptoms, a right heart catheterization (RHC) was conducted in November 2021. The results showed mild pulmonary hypertension (mPAP23 mmHg), along with an exercise-induced elevation of PAP reaching mPAP35 mmHg during light handgrip exercises. Despite the patient's pulmonary hypertension being very mild, there was concern that even a slight increase in PAP could contribute to a significant decline in activities of daily living (ADL), equivalent to WHO functional class IV. Therefore, oral macitentan was initiated at a dose of 10 mg per day, with the hope of achieving some improvement in respiratory symptoms. The intention is to discontinue macitentan treatment at any time if its effectiveness is limited.

Just four weeks after starting Macitentan therapy, the cough symptoms vanished. Imaging revealed improvement in the ground-glass-like shadow and infiltration in the alveoli, as well as thickening of the alveolar septa. There was an enhancement in activities of daily living (ADL), a reduction in KL-6 levels, and by May 2023, lung function demonstrated improvement. The required oxygen flow rate decreased, and at rest, breathing transitioned to room air without the need for oxygen inhalation. (Table .2)(Figs. 1 and 2, Fig. 3).

Table 1
Blood data at the Time of IIP Diagnosis.

White Blood Cells (mm^3)	8320
Red Blood Cells ($\times 10^6/\mu l$)	4.77
Hemoglobin (g/dl)	13.9
Hematocrit (%)	40.6
Platelets ($\times 10^4/mm^3$)	26.6
AST (U/l)	23
ALT (U/l)	14
LDH (U/l)	199
ALP (IU/l)	264
γ-GTP (U/l)	13
CPK (IU/l)	115
T-Bil (mg/dl)	0.5
BUN mg/dl	11.7
Cre (mg/dl)	0.52
Na (mEq/L)	140
K (mEq/L)	4.1
Cl (mEq/L)	107
Total Protein (g/dl)	7.4
Albumin (g/dl)	3.7
C-Reactive Protein (mg/dl)	0.19
BNP (pg/ml)	9.50
KL-6 (U/ml)	880
SP-D (ng/ml)	124.6
ANA (EIA)	15.7
MMP-3 (ng/ml)	40.7
Anti-CCP Ab (U/ml)	1.0
Anti-DNA Ab (RIA)	4.4
Anti-RNP Ab (EIA)	<5.0
Anti-Sm Ab (EIA)	<5.0
Anti-SS-A Ab (EIA)	<5.0
Anti-SS-B Ab (EIA)	<5.0
Anti-Scl70 Ab (EIA)	0.7
Anti-Jo-1 Ab (EIA)	<0.5
Anti-cardiolipin Ab (U/ml)	1
Anti-centromere Ab	<5.0
MPO-ANCA(U/ml)	1.3
PR3-ANCA(U/ml)	<0.5
Anti-GBM Ab(U/ml)	1.1
Anti-ARS Ab (Index)	5.7
Anti-CCP Ab (U/ml)	0.6

3. Discussion

Clinical discussion: Treatment for IIP includes interventions such as anti-fibrotic drugs that aim to slow down the progression of the disease, but there is still no treatment that can provide sufficient efficacy. Considering the previously reported negative results with endothelin receptor antagonists in patients with IPF-PAH [12] and in patients with IIP [10], our patient was likely to have a mild form of pulmonary hypertension (PH) associated with IIP. This led to the hypothesis that Macitentan could bring about improvements. Unexpectedly, macitentan not only improved pulmonary hypertension but also appeared to follow a clinical course with a stabilizing effect on interstitial pneumonia (IP), which was unprecedented in this case.

Pathologic discussion and Brief review of literature: There are several potential reasons for improvement of IP in our patient with macitentan therapy. First, it is possible that the test findings, which were initially interpreted as deterioration of interstitial pneumonia (IP), may have been influenced by the effects of pulmonary hypertension (PH).

Second, it is possible that both IP and PH are attributable to the same underlying condition, such as a cardiovascular disease (CVD), and this common etiology may have contributed to the deterioration of PH, thereby triggering exacerbations of IP.

Finally, macitentan with or without nintendanib may have the potential to improve IP or arrest the progression of IP.

In this case, there were no significant exacerbations of PH evident in the past from BNP values or imaging. Additionally, at the time of Macitentan administration, PH is not considered severe. It is more on the mild side. Furthermore, results from consultations with rheumatologists and dermatologists, as well as hematological findings, did not indicate an underlying disease that would cause both PH and IP.

It has been reported that the concentration of endothelin, which is the most potent factor among endogenous vasoconstrictors involved in pulmonary arterial hypertension (PAH), is elevated in the lungs and plasma of patients with IP diseases. The pathogenesis of PH occurring in conjunction with IP is believed to involve not only the organic progression of lung diseases but also elements related to PAH. Furthermore, PH is also a prognostic factor for IP.

Table 2
Clinical course.

Peripheral blood	WBC /μl	LDH U/l	CRP mg/dl	KL-6 U/ml	BNP pg/ml
at initiation of IVCY (March 2016)	11,880	247	0.09	1038	<5.8
After 10th of IVCY (December 2018)	8390	201	0.20	1059	11.22
at initiation of LTOT (July 2020)	8200	234	0.43	865	7.05
at initiation of nintedanib (November 2020)	6600	227	0.23	795	<5.8
at initiation of Macitentan (November 2021)	5900	199	0.30	789	<5.8
After 4 weeks of Macitentan (December 2021)	5000	186	0.38	643	<5.8
After 1 year of Macitentan (November 2022)	5500	154	4.97	217.9	<5.8
After 2 years of Macitentan (November 2023)	5800	154	3.50	322.9	<5.8

ADL	mMRC	SGRQ (total)	6MWD m	TMET METs	O2 FLOW At rest/during exertion L/min
at initiation of IVCY (March 2016)	3	–	–	–	room/room
After 10th of IVCY (December 2018)	3	–	–	–	room/room
at initiation of LTOT (July 2020)	4	–	0	–	room/room
at initiation of nintedanib (November 2020)	4	–	200	–	2/2
at initiation of Macitentan (November 2021)	4	78	180	2.9	2/2
After 4 weeks of Macitentan (December 2021)	3	–	–	–	2/2
After 1 year of Macitentan (November 2022)	3	–	–	–	2/2
After 2 years of Macitentan (November 2023)	3	72	190	2.9	room/2

Pulmonary function test	FVC L (%predicted)	FEV1 L(%predicted)	FEV1.0/FVC %
6 months before nintedanib (May 2020)	0.95(41.9)	0.95(56.5)	100.0
at initiation of nintedanib (November 2020)	0.79(35.0)	0.79(47.3)	100.0
at initiation of Macitentan (November 2021)	not feasible	not feasible	not feasible
After 1 year of Macitentan (November 2022)	0.99(44.0)	0.97(58.4)	98.0
After 2 years of Macitentan (November 2023)	1.03(45.8)	1.00(60.2)	97.1

RHC	PAP Systolic/diastolic (mean) mmHg	PAWP (mean) Systolic/diastolic (mean) mmHg	CO L/min	CI L/min	PVR Woods
at initiation of Macitentan (November 2021)	27/19 (23)	5/0 [3]	4.10	2.90	4.88
After 2 years of Macitentan (November 2023)	34/14 (24)	10/2 [6]	4.81	3.73	3.74

TTE	TRPG mmHg	RVFAC %	TAPSE cm	RVTEI index
at initiation of Macitentan (November 2021)	not assessable	44	2.1	0.71
After 4 weeks of Macitentan	–	–	–	–
After 1 year of Macitentan	not assessable	27.2	2.2	0.21
After 2 years of Macitentan (November 2023)	42	41	2.76	0.10

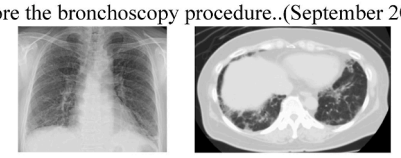
Abbreviations: RHC, right heart catheterization; ADL, activities of daily living; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedged pressure; PVR, pulmonary vascular resistance; mMRC, modified medical research council; SGRQ, Saint George's respiratory questionnaire; 6WMD, 6-min walk distance; VC, vital capacity; FVC, forced vital capacity; FEV1 (V), forced expiratory volume in 1 s; FEV1.0%, forced expiratory volume % in 1 s; IVCY, intravenous cyclophosphamide; LTOT, long term oxygen therapy; TMET, treadmill exercise test; TRPG, tricuspid regurgitant pressure gradient; RVFAC, Right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; RVTEI index, right ventricle total ejection isovolumetric index.

In the past, while negative results have been explicitly demonstrated for the selective endothelin A receptor inhibitor Ambrisentan in the context of IP, in contrast, reports on the effects of non-selective endothelin receptor antagonists, inhibiting both endothelin A and B receptors, on IP or IP combined with PH are inconclusive, with some indicating unclear outcomes and others reporting positive effects [12–17].

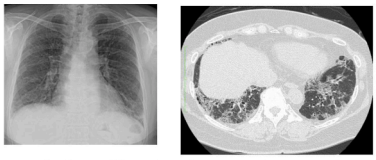
Furthermore, the BUILD-3 study, a phase III randomized trial of bosentan, a non-selective endothelin receptor inhibitor, in patients with idiopathic pulmonary fibrosis (IPF), failed to demonstrate the efficacy of bosentan in suppressing the progression of IPF or reducing mortality from IPF. However, it was observed that IPF did not worsen in some cases among those receiving bosentan compared to those receiving a placebo [10]. Additionally, the BUILD-I trial, which served as the basis for the design of the BUILD-III trial, also identified cases where Bosentan could have a positive effect on the IP pathology [9].

This case is currently enrolled as one of the subjects in the clinical study we are conducting (UMIN000042159). In both our past clinical studies and the ongoing one, the prognosis for patients with idiopathic pneumonia (IP) complicated by severe PH remains very poor, irrespective of the administration of PAH therapeutic agents. However, among the subgroup of cases where PH complicating IP, especially those intervened with endothelin receptor antagonists in the non-severe and early stages, there are instances suggesting a favorable impact on the IP pathology.

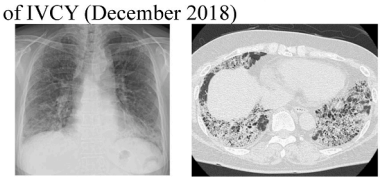
a. Chest X-ray and chest CT
shortly before the bronchoscopy procedure..(September 2015)



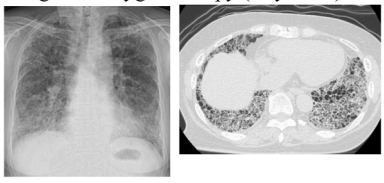
b . Chest X-ray and chest CT Shortly before the initiation of IVCY
(March 2016)



c. Chest X-ray and chest CT after the completion of
10 sessions of IVCY (December 2018)



d. Chest X-ray and chest CT
at the start of long-term oxygen therapy (July 2020)



e. Chest X-ray and chest CT at the initiation of Nintedanib therapy
(November 2020)

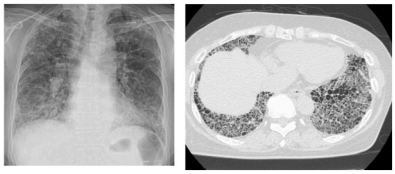


Fig. 1. Imaging changes in idiopathic interstitial pneumonia prior to the introduction of Macitentan therapy:
Fig 1a. Chest X-ray and chest CT shortly before the bronchoscopy procedure. (September 2015)
Fig 1b. Chest X-ray and chest CT Shortly before the initiation of IVCY (March 2016)
Fig 1c. Chest X-ray and chest CT after the completion of 10 sessions of IVCY (December 2018)
Fig 1d. Chest X-ray and chest CT at the start of long-term oxygen therapy (July 2020)
Fig 1e. Chest X-ray and chest CT at the initiation of Nintedanib therapy (November 2020)
Over time, fibrosis in the lungs progressed, and there was a worsening of infiltrative shadows within the alveoli, as well as thickening of the alveolar septa.

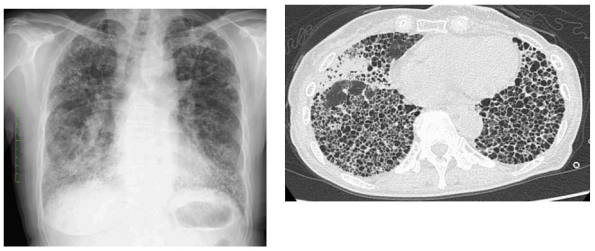
In this case, TBLB was performed only once to establish the clinical diagnosis of IIP, making it difficult to determine precisely how macitentan affected the imaging and pathophysiology of IIP. Although no newly recognizable pathophysiology was observed in the clinical course of this case, it was noted that the progressive nature of IIP consistently improved in symptoms and imaging during the administration of macitentan. While there are reports implicating endothelin in the exacerbation of ALI and ARDS [18], and the possibility that macitentan, an endothelin receptor antagonist, may be involved in the reduction of GGA and consolidation in this case, it remains speculative.

Considering the clinical course in this instance, the patient was considered a case where the administration of Macitentan not only improved pulmonary hypertension but also, particularly, ameliorated the pathology of interstitial lung disease, especially when the effects of Nintedanib treatment alone were found to be insufficient.

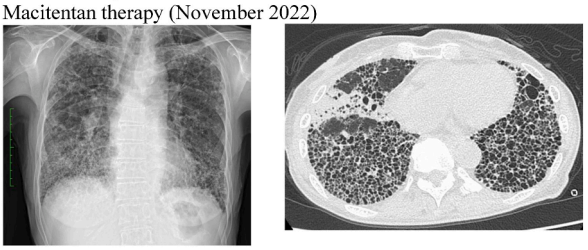
There is a possibility that the combination therapy of Nintedanib and Macitentan may bring about improvements in the IP pathology.

On the other hand, PAH is classified as group 1, and respiratory disease-associated PH is classified as group 3 in the Nice classification of pulmonary hypertension (PAH). It is worth noting that the prognosis of group 1 PH has significantly improved with the availability of three classes of PAH-specific therapeutics, including prostacyclins, endothelin receptor antagonists, and phosphodiesterase

a. Chest X-ray and chest CT at the initiation of Macitentan therapy (November 2021)



b. Chest X-ray and chest CT at one year after the initiation of Macitentan therapy (November 2022)



c. Chest X-ray and chest CT at one year after the initiation of Macitentan therapy (November 2023)

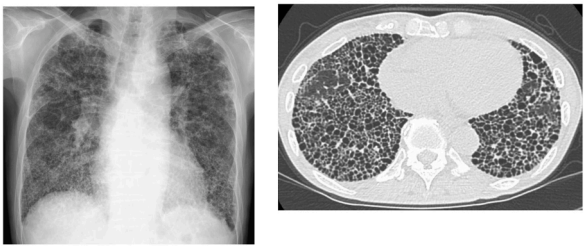


Fig. 2. Imaging changes in idiopathic interstitial pneumonia following the introduction of Macitentan therapy
Fig 2a. Chest X-ray and chest CT at the initiation of Mcitentan therapy (November 2021)
Fig 2b. Chest X-ray and chest CT at one year after the initiation of Macitentan therapy (November 2022)
Fig 2c. Chest X-ray and chest CT at one year after the initiation of Macitentan therapy (November 2023)
Since the initiation of Macitentan therapy, there has been a gradual resolution of infiltrative shadows within the alveoli and thickening of the alveolar septa over time.

type 5 (PDE-5) inhibitors [19]. However, dual endothelin receptor antagonists like Macitentan and Bosentan are yet to be evaluated for their efficacy against IP, and their indications are yet to be established [8].

Imaging discussion: While it is difficult to conclude from this case alone that macitentan may have the potential to control IP, currently, it remains unclear who, of all patients with IP, may benefit from macitentan as a treatment option for IP [8]. However, considering that the clinical, x-ray/CT findings, and the clinical course of our patient indicated that Macitentan alone or in combination with Nintedanib might be effective in controlling IIP, which is unlikely to be solely due to PH, we believe that this case is worth reporting as it provides evidence of Macitentan's efficacy in IP.

Conclusion: What type of interstitial pneumonia (IP) responds to Macitentan administration?

Was the efficacy of Macitentan observed in this case due to the early stage of pulmonary hypertension (PH) pathology at the time of administration, and whether there may come a time in the future when Macitentan should be discontinued based on the progression of IP pathology?

Was the efficacy of Macitentan observed in this case due to a synergistic effect with nintedanib?

Further study is required in a larger population of PH and IP patients to explore the comprehensive pharmacological profile of macitentan, including its efficacy against IP-related PH and IP.

Disclosure statement

The authors have no conflict of interest to declare. Appropriate written informed consent was obtained for publication of this case report and accompanying images.

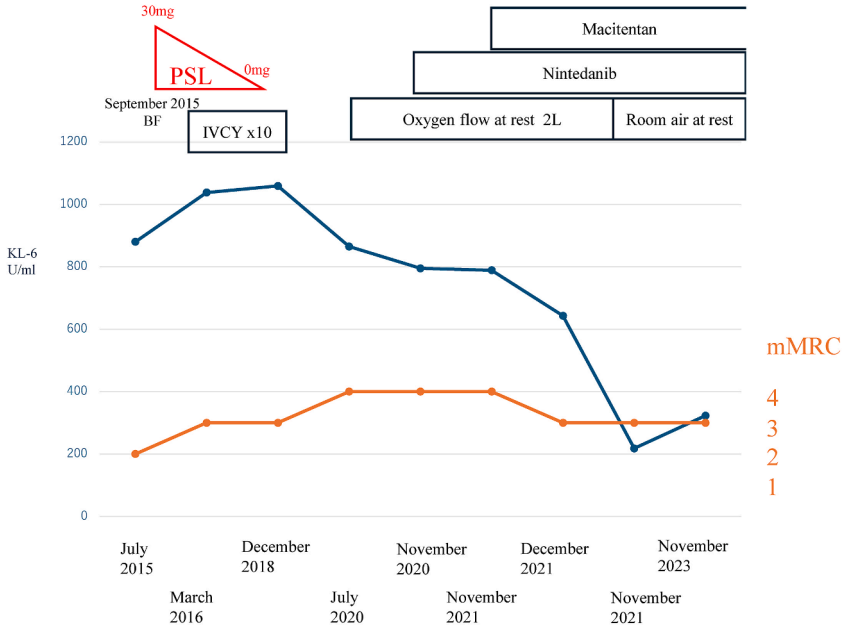


Fig. 3. Treatment course.

CRediT authorship contribution statement

Yosuke Tanaka: Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shota Kaburaki:** Investigation. **Toru Tanaka:** Investigation. **Koichiro Kamio:** Supervision, Methodology, Investigation. **Tetsuya Okano:** Supervision, Methodology, Investigation. **Masahiro Seike:** Supervision, Methodology, Investigation.

Declaration of competing interest

No conflict of interest to declare.

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