EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2021.21102

Literature Review

# Antifibrotic therapies in rheumatoid arthritis associated interstitial lung disease

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## Abstract

Interstitial lung disease (ILD) is one of the common extra-articular manifestations of rheumatoid arthritis (RA) and it is associated with high mortality rate. The usual interstitial pneumonia (UIP) pattern of RA associated ILD (RA-ILD) shows some similarities to idiopathic pulmonary fibrosis, suggesting that antifibrotic therapies may have potential positive affects. In this review, we discuss the effectiveness of antifibrotic therapy for RA-ILD.

**Keywords:** Lung diseases, interstitial, arthritis, rheumatoid, therapeutics

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**Cite this article as:** Bes C, Köybaşı G, İçaçan OC, Mutlu MY, Yıldırım F. Influence of anti-TNF-α treatment on liver and kidney functions in patients with ankylosing spondylitis: A retrospective longitudinal study. *Eur J Rheumatol.* 2022;9(3):176-179.

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Submitted: May 10, 2021
Accepted: June 30, 2021
Available Online Date: December 28, 2021



## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting 0.5-1% of the population worldwide.[1] Although RA most commonly affects the joints, it is also associated with a variety of extra-articular organs and systems; the most common of which is lung involvement. The pulmonary involvement in RA may vary, including interstitial lung disease (ILD), pleural disease, rheumatoid nodules, bronchiectasis, and vasculitis. ILD is a particular type of pulmonary involvement associated with significant morbidity and mortality. The exact incidence of RA-ILD is unknown due to lack of routine screening recommendations and a standard screening method, but it has been reported that the symptomatic RA-ILD incidence is 5-10%.[2-6] High-resolution computed tomography (HRCT) has been accepted as the gold standard noninvasive imaging method in the diagnosis of ILD in patients with RA. The most common HRCT findings in patients with RA-ILD are usual interstitial pneumonia (UIP) (particularly the fibrosing form), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia, organizing pneumonia (OP), diffuse alveolar damage, respiratory bronchiolitis, and desquamative interstitial pneumonia.[7] Histopathologic and/or radiologic phenotypes play a major role in the prognosis of RA-ILD. Certain ILD subtypes, such as NSIP and OP, may have a better response to corticosteroids than others. When corticosteroid doses need to be reduced, additional immunosuppressive agents may be required. For this purpose, corticosteroids may be combined with azathioprine, cyclophosphamide, mycophenolate mofetil, or rituximab.[8-10]

The prognosis of RA-ILD-associated UIP is poor and similar to idiopathic pulmonary fibrosis, and the response to standard immunosuppressive therapy is insufficient.[11,12] Due to its similarity with idiopathic pulmonary fibrosis (IPF), antifibrotic drugs have come to the forefront in the treatment of UIP pattern of RA-ILD. Although antifibrotic drugs are not widely used in RA-ILD yet, clinical outcomes are promising.

### Antifibrotic therapies for rheumatoid arthritis associated interstitial lung disease

The antifibrotics pirfenidone and nintedanib were indicated for the treatment of IPF, and these agents have demonstrated clinical efficacy to reduce the rate of respiratory functional decline and disease progression.[13] The fibrotic process is triggered by chronic epithelial damage or inflammation and activation of alveolar epithelial cells. This activation causes increased migration, proliferation, and differentiation of fibroblasts into myofibroblasts. Synthesis of an excessive amount of extracellular matrix proteins results in destruction of the lung tissue.[14] Antifibrotic drugs demonstrate their effect by modulating the pathways of this fibrotic process.

### Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally active synthetic molecule that exhibits antifibrotic, antioxidant, and anti-inflammatory features. Although the exact mechanism of action has not been

fully revealed, it mainly acts by inhibiting transforming growth factor $\beta$ induced differentiation of human lung fibroblasts and modulating procollagen synthesis.[15]

*In vitro* studies and animal models showed that pirfenidone inhibits fibroblast differentiation collagen synthesis and its deposition. Initial trials were conducted to elucidate the therapeutic effect of pirfenidone in patients with IPF.[16,17] Following the phase 2 trials showed the potential beneficial effects of pirfenidone in IPF patients, the phase 3 randomized, double-blinded, placebo-controlled CAPACITY studies (004 and 006) were conducted to investigate the efficacy and safety. The CAPACITY 004 study showed a reduction in forced vital capacity (FVC) decline in the pirfenidone group (193 mL vs 235 mL, $P = .001$). However, no significant difference was observed in the CAPACITY 006 study ($P = .44$).[18] According to the following multinational placebo-controlled phase 3 ASCEND study, pirfenidone reduced the disease progression, but there was no significant difference between the two groups in all-cause or IPF-related mortality.[19] However, a pooled analysis of the results of these trials (CAPACITY 1, CAPACITY 2, and ASCEND) showed that there was a significant decline in mortality rates and FVC decline in the pirfenidone group. Additional benefits for progression-free survival, dyspnea, and 6-minute walk distance were reported.[20]

Although pirfenidone is generally well tolerated, treatment was associated with significant side effects. Among them, the most common is nausea (21.6%), followed by diarrhea (12.3%) and photosensitivity/rash (11.6%). Patients should be monitored for potential risk of hepatotoxicity under pirfenidone treatment. These side effects are usually manageable with symptomatic treatment, dose reduction, or temporary discontinuation of therapy, but in some cases, permanent discontinuation may be required.[21,22]

## Main Points

- Prognosis of usual interstitial pneumonia associated with rheumatoid arthritis same with idiopathic pulmonary fibrosis.
- Response to immunsupressive therapies for usual interstitial pneumonia associated with rheumatoid arthritis is poor.
- Antifibrotic therapies shows promise in the treatment of rheumatic interstitial lung disease.

### Nintedanib

Nintedanib (6-methoxycarbonyl-substituted indolinone) is a potent inhibitor of receptor-tyrosine kinases, including fibroblast growth factor (FGF), platelet-derived growth factor, and vascular endothelial growth factor (VEGF) receptors. Indolinone-type kinase inhibitors were initially evaluated as antiangiogenic molecules, and nintedanib was originally developed for cancer treatment due to its inhibitory effect on FGF and VEGF receptors.[23] Since these receptors also have an important role in the pathogenesis of progressive fibrosis, it was considered that nintedanib might be effective in the treatment of IPF. Preclinical studies showed that nintedanib has an inhibitor effect on fibrotic processes, including fibroblast proliferation, their migration and differentiation into myofibroblasts, and extracellular matrix deposition.[24] The safety and efficacy of nintedanib was investigated in phase 2 TOMORROW study and in phase 3 INPULSIS studies (INPULSIS 1 and INPULSIS 2). The TOMORROW study, which is a randomized, placebo-controlled, dose-finding trial, revealed that treatment with nintedanib is associated with a reduced annual rate of decline in FVC, decreased risk of further acute exacerbations, and a decrease in St. George's Respiratory Questionnaire total score.[25] Subsequently, phase 3, randomized, double-blind, multicenter, placebo-controlled INPULSIS trials also showed a beneficial effect of nintedanib on disease progression by reducing the decline in FVC over a period of 52 weeks.[26] The pooled data confirmed that nintedanib reduced the rate of decline in FVC (difference: 110.9 mL year$^{-1}$; 95% CI: 78.5 to 143.3; $P < .001$) and the risk of acute exacerbation (HR: 0.53; 95% CI: 0.34 to 0.83; $P = .004$). Although there was a trend toward lower all-cause mortality, it did not reach statistical significance (HR: 0.70; 95% CI: 0.46 to 1.08; $P = .09$).[27]

The most common adverse event associated with nintedanib is diarrhea (62.4%), which is manageable by symptomatic treatment and can be resolved without the need for dose reduction or interruption of treatment. According to pooled data from the INPULSIS trials, only 4.4% of the patients discontinued the medication due to this side effect. Other common adverse events are nausea (24%), vomiting (11.6%), weight loss (9.7%), and increased liver enzymes (14%). Bleeding and cardiac events were reported as rare side effects, but there was no significant difference between the placebo group and the nintedanib group. It is recommended to be used with caution in patients having a risk of bleeding, such as patients under anticoagulant therapy.[28]

Despite the fact that there is a clinical and etiological heterogeneity in ILD, the pathophysiological processes of pulmonary fibrosis share a common pathway. In this regard, antifibrotic agents have been evaluated for the therapeutic effect on other fibrotic ILD, such as systemic sclerosis (SSc)-associated ILD, RA-ILD, and hypersensitivity pneumonitis.[29-32]

Nintedanib and pirfenidone were both approved by the US Food and Drug Administration (FDA) in October 2014 for the treatment of IPF following the phase 3 trials (INPULSIS 1-2 and ASCEND). In September 2019, nintedanib had an approval for SSc-associated ILD based on the efficacy and safety data from the SENSCIS trial.[33] Subsequently, nintedanib was approved in March 2020, based on the INBUILD trial, which evaluated the efficacy, safety, and tolerability of nintedanib in patients with chronic fibrosing ILD with a progressive phenotype.[34] On the other hand, evidence of the efficacy of pirfenidone in these groups is not equally compelling. The existing findings will support further research.[35]

### Pirfenidon therapy for RA-ILD

The use of antifibrotic drugs in the treatment of RA-ILD has recently become a popular topic. In particular, RA-ILD with the UIP pattern has similarities with IPF in terms of pathogenetic mechanisms, clinical course, and survival time.[36-40]

It was shown that some patients who were diagnosed with IPF based on isolated lung manifestations and were initially treated successfully with pirfenidone subsequently developed joint complaints, autoantibodies were identified in the follow-up, and the patients were eventually diagnosed with RA.[41] Maher et al[42] conducted a multicenter, placebo-controlled, randomized, double-blind, phase 2 study, investigated the efficacy and safety of pirfenidone in patients who have unclassifiable progressive fibrotic ILD, and published beneficial results in *The Lancet Respiratory Medicine* in 2019. There are also other studies investigating the use of pirfenidone in SSc-associated ILD.[43,44] All these experiences have formed the basis for the idea that pirfenidone, which is an antifibrotic agent, can also be used in RA-ILD. However, there is no randomized controlled study that has been completed on this subject yet.

The TRAIL1 study, which is a randomized, double-blind, phase 2 study, is the only study investigating the efficacy and safety of pirfenidone in RA-ILD and is still ongoing.[45] It was planned to enroll 270 patients who have parenchymal fibrosis findings of more than

10%, which cannot be explained by alternative diagnosis in lung imaging. Inclusion criteria also include the results of FVC ≥ 40% and Diffusing Capacity Of The Lungs For Carbon Monoxide (DLCO) ≥ 30%; and patients must meet the RA diagnostic criteria according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria. The primary endpoint was determined as 10% or more decline in FVC or death during the follow-up period. The patients were randomized as a placebo and pirfenidone group at a ratio of 1:1. The study period was planned as 52 weeks, and the dose of pirfenidone as 2,403 mg day. The results of the study are eagerly awaited by those interested in the subject.

### Nintedanib therapy for RA-ILD

It has been shown in preclinical studies that nintedanib, an intracellular tyrosine kinase inhibitor, reduces the progression of lung fibrosis.[24,46] Nintedanib was first investigated in patients with SSc, and it was approved for use in Japan and the United States in 2019 in SSc-associated ILD with the SENSCIS study.[46]

In a mice-model with RA-ILD, a significant decrease in the number of myofibroblast cells, which lead to fibrosis in the lung, was found in the nintedanib group. As a result of this study, it was thought that the total effect of nintedanib on the lungs in patients with RA-ILD would be beneficial and could be used in treatment.[47]

In the INBUILD study evaluating the efficacy of nintedanib in patients with progressive fibrosing ILD (PF-ILD), the primary endpoint was a decrease in annual FVC, and the secondary endpoint was baseline scoring on the King's Brief Interstitial Lung Disease questionnaire score.[34] The change in the total score in the 52nd week was targeted. Of the total 663 patients enrolled into study, 412 (62.1%) had a fibrotic pattern similar to UIP. The most common diagnoses were chronic hypersensitivity pneumonia and autoimmune ILD. Considering the patients in the autoimmune ILD group, 89 were RA-related ILD. The annual decline in FVC was significantly lower and statistically significant in the nintedanib group (Figure 1). Considering these results, lower disease progression was found in patients enrolled in the nintedanib arm than those in the placebo arm.[34] After the INBUILD study, nintedanib was approved for use in PF-ILD in 2020. Additionally, it was found that nintedanib reduced the annual decrease in FVC in patients with IPF and SSc-ILD.[25,26,46]

The first use of nintedanib in RA was reported in a case in Japan in 2018. Initially, nintedanib treatment was started in the case diagnosed with idiopathic pulmonary fibrosis, which was followed by a diagnosis of RA with arthritis and anti-cyclic citrullinated peptide (CCP) positivity. This case is the first to show that nintedanib is effective in RA and accompanying UIP. As a result of nintedanib treatment without other immunosuppressive treatments, it was found that dry cough ceased in the 8th month, and the decrease in FVC was less.[48] The second case is a patient from Italy who was diagnosed with RA according to ACR criteria and followed by lung disease and was treated with nintedanib and sarilumumab. This is the first case in which nintedanib and disease-modifying antirheumatic drugs (DMARDs) were combined.[49]

PF-ILD is the name given to lung diseases that progress with fibrosis at a certain rate. Although there is no precise definition, certain descriptive criteria have been proposed.[50] RA is one of the conditions that causes PF-ILD. There are some questions about the use of nintedanib in connective tissue diseases. It is necessary to decide whether antifibrotic or immunosuppressive therapies should be more dominant in diseases with an inflammatory component. The effectiveness of immunosuppressive treatment has been demonstrated in patients with ILD associated with connective tissue disease and NSIP. In the future, combined use of antifibrotic and immunosuppressive treatment may be considered. Another problem is that there is no recommendation for the use of nintedanib in cases of elevated acute phase reactant (AFR) accompanying chronic fibrosing lung disease. IPF also has acute attacks with high AFR, but immunosuppressive therapy is more prominent in non-IPF ILD associated with connective tissue disease, especially during acute exacerbation. During this period, delaying nintedanib treatment may be considered until acute conditions have been controlled.

The absence of a specific definition of PF-ILD and the undefined indications for the use of antifibrotic treatment affects treatment choice. Keeping the indications wide can increase the side effects. On the other hand, keeping them tight may cause a delay in the treatment. It should be kept in mind that antifibrotic therapy must be initiated, especially before lung capacity is severely impaired. The definition of optimal criteria will be determined with further studies with larger cohorts.

## Conclusion

ILD is one of the extraarticular findings of RA and has a high mortality risk. RA-ILD may be asymptomatic in early period, and this may lead to delay in diagnosing. Early diagnosis and early treatment in symptomatic and progressed patients are very important factors that increase survival. However, the treatment method varies from patient to patient and depends on the type and degree of lung involvement. Immunosuppressive drugs and/or drugs that improve joint symptoms can be used in patients with NSIP pattern, and their positive effects can be seen. However, in fibrotic progressive disease (especially in the form of UIP), immunosuppressive drugs do not have much benefit and may even have harmful effects by increasing the risk of infection. In the treatment of fibrotic RA-ILD, antifibrotic drugs (combined with the DMARDs or not) are promising. However, further studies with large patient populations are needed to validate the safety and effectiveness of these drugs.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - C.B., O.C.İ.; Design - C.B., M.Y.M.; Supervision - C.B., O.C.İ.; Data Collection and/or Processing - C.B., G.K., M.Y.M.; Analysis and/or Interpretation - C.B., F.Y.; Literature Review - C.B., F.Y.; Writing - C.B., O.C.İ.; Critical Review - C.B., F.Y.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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