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Commentary

Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: what we already know and what we would like to know

Running title: Nintedanib in lung fibrosis

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Abstract

Interstitial lung diseases (ILDs) represent a broad category of fibrotic pulmonary diseases and are frequently present in the course of various connective tissue diseases (CTDs), especially systemic sclerosis (SSc) and rheumatoid arthritis (RA). Despite intensive research in the field, pathogenesis is incompletely understood and therapeutic options are limited to immunosuppressants and antifibrotic drugs. The current commentary focuses on a recent publication regarding the efficacy and safety of the anti-fibrotic drug nintedanib in patients with autoimmune related ILD with progressive fibrotic phenotype. We further discuss the important findings of this study and also point to what we still need to know.

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Keywords- interstitial lung disease; pulmonary fibrosis; cutaneous tissue diseases; nintedanib; progressive fibrosing phenotype

I. INTRODUCTION

Interstitial lung disease (ILD) comprises a diverse spectrum of diseases, characterized by fibrosis and/or inflammation of the lungs. ILDs represent a major health problem due to the number of affected patients, along with the incomplete knowledge of pathogenetic pathways, the absence of widely accepted predictors of disease progression and behaviour and the lack of really effective therapeutic agents.

The most common form of ILD is idiopathic pulmonary fibrosis (IPF). ILD frequently complicates connective tissue diseases (CTDs), especially Systemic Sclerosis (SSc), Rheumatoid Arthritis (RA), anti-synthetase syndrome and Mixed Connective Tissue Disease (MCTD) (1). In addition, the entity of idiopathic pneumonia with autoimmune features (IPAF) also raises significant clinical concern (2).

The involvement of the lungs in ILDs is generally described as diffuse fibrosis of the alveolar wall, with or without inflammation, that results in impairment of gas exchange. Moreover, the underlying dysfunction of the immune system in autoimmune diseases is thought to play a significant role in CTD-ILDs. However, CTD-ILDs represent a diverse group of diseases. Different CTDs manifest varying forms of ILD. Patients with SSc and MCTD most commonly present the histological pattern of nonspecific interstitial pneumonia (NSIP), while those with RA frequently have fibrosis with the histological lesions of usual interstitial pneumonia (UIP) (3).

We know from every day clinical practice, as well as from the international bibliography, that within the spectrum of ILDs a subset of patients has, despite treatment, a relentlessly progressive disorder. Those patients develop what is commonly described as a progressive fibrosing phenotype (4). Affected individuals typically present with progressive dyspnea, resulting in respiratory failure which accounts for considerable morbidity and mortality. In SSc, ILD is the first cause of mortality, whilst in all patients with autoimmune diseases represent a significant cause of disability (5).

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Although the concept of progressive fibrosing ILD was initially introduced to patients with IPF, it is now evident that progressive fibrosis can be found in patients with other ILD diagnostic categories, including those with underlying CTD (4). Therefore, the accurate diagnosis and the early identification of disease progression are of outstanding importance, and require multidisciplinary care involving pulmonologists, radiologists and rheumatologists. Corticosteroids and immunosuppressive agents are considered as the mainstay of treatment for CTD-ILDs. Immunosuppressants are currently used for the management of pulmonary fibrosis, however the emerge of antifibrotic drugs provided new hope for affected individuals.

Nintedanib is a tyrosine kinase inhibitor, initially developed as an antitumor agent. It has since been shown to have pleiotropic effects, including anti-fibrotic, anti-inflammatory, and anti-angiogenic activity through inhibition of tyrosine kinases, such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF). It binds competitively to the adenosine triphosphate (ATP)-binding pocket of these receptors and blocks the intracellular signaling, which is crucial for the proliferation, migration, transformation of fibroblasts, and collagen production (6).

In clinical trials, nintedanib has shown efficacy in the treatment of patients with idiopathic pulmonary fibrosis (IPF), thus receiving this indication in the EU and the USA. More recently it has been approved also for SSc-ILD as well as for other chronic fibrosing ILDs with a progressive phenotype. Adverse event profile is mainly characterized by gastrointestinal events.

In the SENSCIS trial, nintedanib reduced the progression of interstitial lung disease in patients with SSc-ILD, as shown by a reduction in the rate of decline in FVC over 52 weeks. In detail, the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (7). Approximately half of the patients received mycophenolate at baseline and nintedanib showed a positive effect versus placebo on the annual rate of decline in FVC regardless of MMF use at baseline; however, overall data supports the concept of combined therapy (8).

The INBUILD trial included 663 patients with chronic fibrosing ILDs and a progressive phenotype. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib versus −187.8 ml per year in the placebo group (9). Frequent ILD diagnoses were chronic hypersensitivity pneumonitis (26%) and autoimmune ILDs (25.6%), 19% idiopathic NSIP, 17% unclassifiable idiopathic interstitial pneumonia and 12% other ILDs (10). Although the trial was not designed or powered to identify differences between specific diagnostic subgroups, nintedanib reduced the rate of ILD progression, as measured by FVC decline, irrespective of the underlying ILD diagnosis (10).

Matteson et al (11) currently analyzed the efficacy and safety of nintedanib in patients with fibrosing autoimmune ILDs over 52 weeks. Despite management deemed appropriate in clinical practice, patients fulfilled inclusion criteria for ILD progression within the 24 months before screening. The subgroup of 170 patients with autoimmune disease related ILDs of the initial INBUILD study included patients with RA (89), SSc (39) MCTD (19) and other autoimmune diseases. They were randomly assigned to either nintedanib or placebo. The adjusted rate of decline in the FVC was −75.9 ml per year with nintedanib versus −178.6 ml per year in the placebo group (11). The relative reduction was consistent was previous findings observed in the overall population of the INBUILD study, in the population of patients with SSc – ILD of the SENSCIS trial, as well as with patients with IPF included in the INPILSIS trial. No heterogeneity across the different diagnostic subgroups was detected. It is noteworthy that the INBUILD study was not designed or powered to study patients with individual diseases. When patients were analyzed according to histological pattern, the effect of nintedanib versus placebo was numerically greater in subjects with a UIP fibrotic pattern on high resolution computed tomography (HRCT) compared to those with other patterns; however, no statistically significant heterogeneity was detected (11). Further analysis regarding baseline treatment with disease modifying anti-rheumatic drugs (DMARDs) and/or glucorticosteroids did not indicate significant differences. The adverse events were consistent with previous studies, with gastrointestinal events and particularly diarrhea being the more common. Regarding laboratory detection of liver enzyme elevation were more common in patients receiving nintedanib than in the placebo group, as seen in other nintedanib studies. In 17.1% and 10.2% of subjects in the nintedanib and placebo groups, respectively, adverse events led to permanent discontinuation of the trial drug (11).

II. CONCUSIONS

The current subgroup analysis is really important as it comes from a large, randomized, double-blind, placebo-controlled trial which included patients with progressive

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fibrosing autoimmune disease-related ILDs. With the INBUILD trial, the concept of progressive fibrosing ILD was introduced. Fibrosis measured with decline in FVC and/or HRCT findings and worsening of respiratory symptoms at a certain rate was considered as a progressive phenotype that required therapeutic intervention. The results of the clinical studies of nintedanib provided data on reduction of the rate of decline in FVC. The efficacy of nintedanib in slowing the rate of decline in FVC compared with placebo in all diagnostic groups has been demonstrated. The number of patients with SSc-ILD, in both the SENSCIS and the INBUILD trial, as well as those with RA-ILD included in the INBUILD trial are considered rather sufficient. However, more studies are needed to assess its efficacy in patients with other CTD-ILDs, like in those with myositis, SLE and/or Sjogren Syndrome. Moreover, the role of nintedanib in IPAF also needs to be investigated.

Another issue that needs to be assessed in future clinical studies is the treatment strategy, which will determine which treatment option should be come first, the immunosuppressants or the antifibrotic drugs, or if they should be started together. Clinical trials have provided evidence of a level of efficacy of certain immunosuppressants; however, the combination with anti-fibrotics and the appropriate time to do so, remains an unsolved issue.

Regarding safety, adverse events were in large manageable for most individuals. The need of finding promising treatments for patients with pulmonary fibrosis is clearly addressed. Timely identification and management of pulmonary fibrosis are needed to improve outcomes. Further studies that will offer data regarding quality of life, morbidity and mortality are also needed.

AUTHOR CONTRIBUTION

TS conceptualized and wrote the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. Spagnolo P, Distler O, Ryerson CJ, Tzouvelekis A, Lee JS, Bonella F, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). Ann Rheum Dis. 2021;80(2):143-50.
2. Fernandes L, Nasser M, Ahmad K, Cottin V. Interstitial Pneumonia With Autoimmune Features (IPAF). Front Med (Lausanne). 2019;6:209.
3. Hilberg O, Hoffmann-Vold AM, Smith V, Bouros D, Kilpelainen M, Guiot J, et al. Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. ERJ Open Res. 2022;8(1).
4. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev. 2019;28(151).
5. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809-15.
6. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(5):1434-45.
7. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019;380(26):2518-28.
8. Highland KB, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021;9(1):96-106.
9. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J. 2022;59(3).
10. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8(5):453-60.
11. Matteson EL, Kelly C, Distler JHW, Hoffmann-Vold AM, Seibold JR, Mittoo S, et al. Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial. Arthritis Rheumatol. 2022.