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Effectiveness and Safety of Antifibrotic Treatment in Pulmonary Fibrosis Associated with Rheumatoid Arthritis

Martyna Magdalena Martka

Karol Jonscher Municipal Medical Center, Milionowa 14, 93-113 Łódź, Poland

https://orcid.org/0009-0006-2295-5459

martyna.martka@stud.umed.lodz.pl

Marta Skorupska

Karol Jonscher Municipal Medical Center, Milionowa 14, 93-113 Łódź, Poland

https://orcid.org/0009-0001-6556-3133

mskorupska71@gmail.com

Andrzej Aleksiej

Lower Silesian Oncology Center of Pulmonology and Hematology in Wrocław, plac Hirszfelda 12, 53-413 Wrocław.

https://orcid.org/0009-0009-6408-6062

aaleksiej@gmail.com

Natalia Aleksandra Popławska

Central Clinical Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Łódź

https://orcid.org/0009-0002-6243-6603

natalia.poplawska2109@gmail.com

Justyna Śliz

Central Clinical Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Łódź

https://orcid.org/0009-0007-0242-149X

justyna-sliz@wp.pl

Magdalena Joanna Czeczotka

Karol Jonscher Municipal Medical Center, Milionowa Street 14, 93-113 Lodz

https://orcid.org/0009-0005-6306-8437

magda.czeczotka@gmail.com

Krzysztof Woźniak

Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź

https://orcid.org/0009-0004-1438-0806

wozniak.krzysztof1998@gmail.com

Abstract

Introduction and Objective.

Rheumatoid arthritis (RA) stands as a chronic, systemic autoimmune inflammatory ailment. Lung involvement is one of the most common extra-articular manifestations of RA. Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD) is a severe, progressive disease leading to pulmonary fibrosis, characterized by deterioration of lung function, exacerbation of symptoms and typical radiological features, and early mortality.

Review methods and materials

This review utilized PubMed, Mendeley by using search terms such as pulmonary fibrosis in rheumatoid arthritis nintedanib treatment, and pulmonary fibrosis in rheumatoid arthritis pirfenidone treatment. All searches were verified by humans, duplicated results and unreliable have been rejected. In addition, case reports and previously established literature reviews were excluded from the review. We used all available original studies evaluating and comparing the efficacy and safety of anti-fibrotic drugs to create this review.

Brief description of the state of knowledge

In this review, we discuss therapeutic strategies for antifibrotic treatment involving nintedanib and pirfenidone. Furthermore, we compare the efficacy of both drugs, their influence on the extension of life, their safety profiles, and associated side effects based on research findings, and discuss the molecular mechanisms of their action.

Summary

Clinical trials concerning RA-ILD showed that nintedanib and pirfenidone slow the rate of FVC decline in patients with RA-ILD. The safety profile observed in both drugs was similar

simultaneously occurring mainly gastrointestinal symptoms. Both drugs have been approved for the RA-ILD treatment program, nevertheless in the current body of knowledge, it is not feasible to definitively determine which drug therapy should be initiated first, as their characteristics are notably similar.

Keywords: rheumatoid arthritis, interstitial lung disease, antifibrotic treatment, RA-ILD, pulmonary fibrosis

INTRODUCTION

Rheumatoid arthritis:

Rheumatoid arthritis is a predominant chronic inflammatory disease that primarily affects the joints, resulting in cartilage and bone damage, and ultimately leading to disability. It mainly affects the joints, but also includes extraarticular manifestations such as rheumatoid nodules, pulmonary involvement or vasculitis, and systemic comorbidities, particularly concerning metabolism [1]. The individual burden is directly attributable to the deficits, with accompanying impairment of physical function and quality of life as well as cumulative musculoskeletal comorbidities [2]. Involvement of the respiratory system occurs in 30-40% of people with RA, making it the second most common cause of death in people with RA [3].

Interstitial lung disease in rheumatoid arthritis

Lung involvement stands as a prevalent extra-articular manifestation of rheumatoid arthritis. In the course of the disease, up to 60% of RA patients may be impacted [4]. RA is more common in females while RA-ILD is about four times more common in men [5, 6]. In clinical practice, it has been observed that RA can have a significant impact on all parts of the lung, including the parenchyma, which may manifest as interstitial lung disease or rheumatoid nodules; pleura, which may result in pleural inflammation or effusions; small and large

airways. During the first five years of illness, most respiratory manifestations occur [4]. However, this is not a rule as 10 to 20% of respiratory changes precede the onset of articular symptoms even by a few years [4]. Compared with non-ILD RA, the hazard rate ratios for death were 2 to 10 times higher in RA-ILD [7]. ILD-RA is a severe progressive condition leading to pulmonary fibrosis, which is characterized by increasing typical radiological features, decline in lung function, worsening symptoms, and early mortality [8]. Moreover, some patients with RA-ILD develop progressive pulmonary fibrosis after a prolonged period of their illness.

Risk factors of RA-ILD

Over the past few years, numerous factors have been linked to an increased risk of lung disease. In the citrullination pathway, epigenetic post-translational modifications convert arginine to citrulline. This may result in the development of a new immune response that leads to ACPA formation. Citrullination is associated with the evolution of joint destruction in RA. In addition, it can be detected in bronchoalveolar lavage fluid in patients with RA-ILD [9]. It has been shown that RAILD patients have an abundance of mutations in genes previously associated with familial pulmonary fibrosis, including TERT, RTEL1, PARN, and SFTPC [10]. The most common genetic risk factor for pulmonary fibrosis, observed in at least 50% of patients with the disease, is the MUC5B promoter variant. This variant is involved in airway clearance and bacterial host defense [11]. In addition to the previously mentioned risk factors, other factors, such as HLA variants, including HLA-B54, HLA-DQB1*0601, HLA-B40, and HLA-DR4, have been associated with the development of ILD in patients with RA [12]. Furthermore, some researchers have proposed that an elevated titer of interleukin (IL)-33 and IL-18 in patients with RA-ILD may be associated with the expansion of ILD. IL-33 is capable of mediating the immune response through the expression of T helper-2 cytokines, while IL-18 is a member of the IL-1 superfamily of cytokines that regulates immune responses [13]. Similarly, elevated levels of matrix metalloproteinase-7 (MMP-7), pulmonary and activation-regulatory chemokine (PARC), and surfactant protein-D (SPD) are closely correlated with the presence of both clinically overt and subclinical RA-ILD [14]. A substantial body of evidence indicates that cigarette smoking may be a contributing factor in the development of seropositive RA and RA-ILD [15]. It may trigger an immune response that leads to serum autoantibody production against multiple citrullinated proteins in the lungs, which in turn leads to inflammation and epithelial cell damage [12].

Clinical presentation of RA-ILD

The most common clinical manifestations of RA-ILD are exertional dyspnea and chronic dry cough. Other clinical presentations include fatigue, generalized weakness, and decreased exercise capacity. Cough and exertional dyspnea may be easily overlooked because of joint dysfunction or intensified fatigue secondary to systemic inflammation. In addition, in patients with RA-ILD, antibody titers such as rheumatoid factor RF and ACPA were increased [12].

Pulmonary function testing in RA-ILD

Pulmonary function testing (PFT) can be used as a component during early identification of lung disease. It is also a great tool for monitoring the course of the condition and detecting patients' progression. In patients with RA-ILD, PFTs frequently reveal restrictive ventilation defects with impaired gas exchange, which can be identified despite the absence of clinical symptoms [12]. Diffusing lung capacity for carbon monoxide (DL_{CO}) is the most sensitive parameter for estimating the progression and clinical exacerbation of ILD. This advanced testing method contrasts with the more routine parameters of forced vital capacity (FVC) and total lung capacity (TLC) [16].

Radiological imaging in RA-ILD

On classic chest X-rays, discrete diffuse changes in the form of reticular lesions and linear thickenings, typically located in the lower lung fields, can be seen. However, in approximately 10% of patients, there are no visible imaging changes at the onset of the disease. In the advanced stage, more pronounced fibrous alterations and reduced lung volume are seen [17]. Nowadays the standard of radiological imaging is high-resolution computer tomography (HRCT) which greatly enhances the diagnostic sensitivity and accuracy of RA-ILD compared to chest radiographs alone [18]. We were able to identify four main HRCT disease patterns, namely usual interstitial pneumonia (UIP) (37%), non-specific interstitial pneumonia (NSIP) (30%), obliterative bronchiolitis (17%), and organizing pneumonia (OP) (8%) [19]. The most prevalent radiographic pattern of UIP is characterized by subpleural, basal predominant, reticular abnormalities with honeycombing and traction bronchiectasis, with a relative deficiency of ground-glass opacities and air trapping on exhalation, and minimal or no vitreous opacity [20]. NSIP, another common pattern observed in RA-ILD, features regularity and vitreous opacity with little or no architectural distortion or

honeycombing [18]. In clinical practice, lung ultrasonography has become a widely applied diagnostic tool. The presence of multiple B lines, irregularities of the pleural line, or pleural nodules on sonographic examination may indicate the presence of lung interstitial disease [21].

Bronchoalveolar lavage fluid findings in RA-ILD

The cellular findings of bronchoalveolar lavage fluid (BALF) are commonly abnormal, although often nonspecific. Although the data is limited, it can be postulated that lymphocytosis is more commonly observed in patients with RA-ILD other than UIP, whereas an increased level of neutrophils is more widespread in patients with UIP patterns [22].

Histopathological profile in RA-ILD

Currently, it is recommended to consider lung biopsy in patients if HRCT does not detect a precise pattern of the UIP particularly when there may be an indication for this [12]. The pattern of UIP is distinguished from others by heterogeneous fibrosis components, including variation in fibrosis age, with fibroblastic foci, an area of spindle cells with plump cytoplasm, and little collagen immediately adjacent to areas of established fibrosis. One of the most important parts in establishing the diagnosis of UIP is the pattern of fibrotic lesions and honeycombing. In the meantime, in NSIP, fibrosis, and inflammation were either patchy or more often diffuse, but the pattern of lung injury remained temporally uniform [19].

MATERIAL AND METHODS

In accordance with the latest American College of Rheumatology (ACR) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease, antifibrotic drugs such as nintedanib and pirfenidone are considered as a treatment option for RA-ILD progression. In view of the above, this review utilized PubMed, Mendeley by using search terms such as pulmonary fibrosis in rheumatoid arthritis nintedanib treatment, pulmonary fibrosis in RA nintedanib, pulmonary fibrosis in rheumatoid arthritis pirfenidone treatment, pulmonary fibrosis in RA nintedanib. All searches were verified by humans, duplicated results and unreliable have been rejected. In addition, case reports and previously established literature reviews were excluded from the review. We used all available original studies evaluating and comparing the efficacy and safety of anti-fibrotic drugs to create this review.

STATE OF KNOWLEDGE

Treatment of pulmonary fibrosis associated with RA-ILD

According to "2023 American College of Rheumatology (ACR) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease", the preferred first-line therapy in interstitial lung disease in rheumatoid arthritis is mycophenolate. Other first-line treatment options include azathioprine and rituximab. Additionally, cyclophosphamide is an alternative option, and short-term glucocorticosteroids may be added if warranted. For individuals with RA-ILD, the panel of experts was not able to reach a consensus on whether to recommend nintedanib as a first-line ILD treatment option. For those with the progression of interstitial lung disease while on first-line therapy, it is recommended that another drug be added or that therapy be changed to drugs such as mycophenolate or rituximab if they have not been used previously, or that tocilizumab, nintedanib, and pirfenidone be included. For people with RA-ILD progression despite initial ILD treatment, the expert team conditionally recommends the addition of pirfenidone as a treatment option. Long-term use of glucocorticosteroids is not recommended. It is advised that patients be referred for lung transplant evaluation at the appropriate time of disease progression [23].

Nintedanib

Nintedanib is a small molecule tyrosine kinase inhibitor that targets platelet-derived growth factor receptor (PDGFR) α and β, vascular endothelial growth factor receptor (VEGFR) 1-3, and fibroblast growth factor receptor (FGFR) 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors, thereby blocking intracellular signaling. Nintedanib also inhibits the Src family kinase Lck (lymphocyte-specific protein tyrosine kinase), CSF1R (colony-stimulating factor 1 receptor), and 20 other kinases with IC50 values below 100 nM. The potential impact of enzymatic inhibition on the cellular functions of most of these kinases remains unexplored. Preclinical studies have demonstrated that nintedanib exerts antifibrotic and anti-inflammatory effects, which serve to decelerate the progression of pulmonary fibrosis. These effects include the inhibition of the release of profibrotic and proinflammatory mediators, the migration and differentiation of fibroblasts, and the in vivo deposition of extracellular matrix [24]. The most frequently reported side effects associated with the use of nintedanib included gastrointestinal symptoms, most commonly diarrhea, nausea, and vomiting. The effectiveness of nintedanib in reducing

the rate of FVC decline in RA-ILD over time has been demonstrated in various studies. The INBUILD trial Matteson et al. [8] study included a subgroup of 89 patients, with a mean age of 66.9 years. In this cohort of patients, 39.3% were female, and 86.5% exhibited a fibropathic profile comparable to the UIP pattern observed on HRCT. The baseline mean (standard deviation) FVC was 71.5 (16.2) % predicted, while the SD DL_{CO} was 47.7 (15.6) % predicted. In both groups, the mean duration of exposure to trial drugs during the whole study was 17.4 months. In this assessment of patients with RA-ILD, the adjusted annualized rate of reduction in FVC over 52 weeks was -82.6 mL/year in the nintedanib group vs -199.3 mL/year in the placebo group (difference 116.7 mL/year [95% CI (confidence interval) 7.4, 226.1]; nominal p = 0.037). A distinction between treatment groups has been observed from the 24th week of baseline changes in FVC. At 52 weeks, absolute and relative reductions in FVC % predicted to be greater than 10% were observed in a smaller proportion of patients in the nintedanib group compared to the placebo group. Eight patients (19.0%) in the nintedanib group and 15 patients (31.9%) in the placebo group suffered from an acute exacerbation of interstitial lung disease or death. The hazard ratio (HR) was 0.54 [95% CI 0.3, 1.28], with a nominal p-value of 0.16. A total of 18 patients (42.9%) in the nintedanib group and 22 patients (46.8%) in the placebo group experienced respiratory-related admissions to hospital or death (HR 0.87 [95% CI 0.46, 1.62]; nominal p = 0.65). The proportion of patients who experienced disease progression or death was 45.2% in the nintedanib group and 61.7% in the placebo group. A total of seven patients (16.7%) in the nintedanib group died (HR 0.63 [95% CI 0.35, 1.13]) compared to nine patients (19.2%) in the placebo group (HR 0.86 [95% CI 0.32, 2.31]). The p-value for the nintedanib group was 0.12 while the p-value for the placebo group was 0.76. The most common adverse reaction observed in patients with both rheumatoid arthritis-associated interstitial lung disease and nintedanib treatment was diarrhea, which was reported in 61.9% of patients receiving nintedanib. Additionally, nausea was reported as an adverse reaction in 21.4% of the nintedanib group. Manfredi et al. [25] conducted a retrospective study that enrolled all RA patients with ILD confirmed by HRCT and a minimum of 24 months of follow-up. Patients were defined as having progressive fibrotic ILD if there was a relative decrease in FVC ≥10% of predicted and/or an increased extent of fibrotic changes on chest imaging at 24 months, following the current indications for nintedanib. To reduce the potential for bias resulting from retrospective interpretation of cough and dyspnea, respiratory symptoms were excluded from the study. A total of 134 patients with RA-ILD (59.7% were females, with a mean age of 72 ± 9.5 years and a mean duration of RA and ILD of 13.1± 9.5 and 4.6 ± 4.1 years) were included in the study. Radiological features were used to classify

ILD as probable or definite UIP in 50.7% of patients, NSIP in 19.4%, and other patterns in 29.8%. A fibrosis pattern was noted in 73.9% of cases. During the follow-up period, a relative decrease in FVC of 6.8% was observed, with no significant difference between ILD with and without fibrosis (6.3% ± 13.8 vs. 5.9% ± 21.3). A decrease in FVC ≥ 10% and/or progression of radiographic fibrosis was observed in 38 patients. In a retrospective cohort study conducted by Serra Gaspar Silva et al. [26], medical records of patients diagnosed with interstitial lung disease in inflammatory rheumatic diseases (IRD-ILD) and treated with nintedanib were reviewed. The frequency and the mean values of both linear and constant variables were presented. The results showed that a total of 64 patients, 70% female, have been identified. RA was the second most common underlying IRD in this study, accounting for 28%. The frequency and mean values of linear and constant variables were presented. The results indicated that a total of 64 patients were identified, with 70% of them being female. The second most prevalent underlying IRD in the study was rheumatoid arthritis, which constituted 28% of cases. The average period of nintedanib administration was 18.5 ± 15.9 months, with 17 patients receiving treatment for more than 24 months. Following a six-month period, there was a statistically significant improvement in $DL_{CO}c$ SB ($p = 0.041$) and $DL_{CO}c$/VA ($p = 0.029$) in comparison to the baseline. This improvement was not observed at 12 or 24 months ($p > 0.05$). However, the FVC and $DL_{CO}c$ SB values were found to be 0.173 and 0.199, respectively, in comparison to the UIP values. This indicated a trend towards a reduced overall benefit in the initial 12 months of NSIP therapy. In patients with less than three years of ILD duration (n=20 [8 NSIP; 12 UIP]), a 24-month analysis revealed a significant improvement in $DL_{CO}c$ SB and $DL_{CO}c$/VA ($p=0.003$ and $p=0.017$). 60 patients were included in this study. Of those patients, 38 (62%) were able to maintain a daily dose of 150 mg twice daily. Twenty-four (40%) required a dose reduction to 100 mg due to gastrointestinal symptoms. Two patients (3%) discontinued treatment. Redente et al. [27] extracted data from 11 patients who were treated with nintedanib. Subsequently, the subjects were divided into two groups: the RA group, 6 patients (50% were females), and the non-RA group, 5 patients (60% were females). The mean age at the time of nintedanib administration was 70.8 in the RA group and 59.0 years in the non-RA group ($P = 0.035$). At the time part of patients received additional oral glucocorticosteroids and immunosuppressants. After six months of nintedanib treatment, the change in FVC was -18.3 ± 103.5 ml and -24.0 ± 101.5 ml. The change in percentage of FVC was 0.75 ± 5.03% and -2.4 ± 1.91%, and the change in percentage of DLco was 0.375 ± 4.02% and -7.27 ± 6.54% ($P = 0.52$, 0.20, and 0.28, respectively). The incidence of adverse events was 50% in the RA group and 40% in the non-

RA group. Dixon et al. [28] conducted a national service evaluation involving 24 centers in the United Kingdom. Data regarding underlying diagnoses, PFTs, diagnostic criteria, HRCT, concurrent immunosuppressive therapies, and drug tolerability were collected via an electronic survey. Of the 1120 patients who received a multidisciplinary team recommendation to commence nintedanib for the progressive fibrosing phenotype of interstitial lung disease (PF-ILD), 180 (16%) of them had rheumatoid arthritis-associated ILD. The most frequent reason for diagnosing PF-ILD was the progression of ILD coupled with deteriorating respiratory symptoms. The use of nintedanib in the treatment of PF-ILD has been demonstrated in a wide range of underlying diseases.

Pirfenidone

Pirfenidone (PFD) is an orally bioavailable synthetic compound. The active ingredient is a pyridone derivative with a widespread anti-fibrotic, anti-inflammatory, and antioxidant activity. It modulates a range of cytokines, such as transforming growth factor-b1, interleukin (IL)-1, IL-4, IL-6, IL-8, IL-13, and tumor necrosis factor-a. It has already been approved for worldwide use for the treatment of idiopathic pulmonary fibrosis (IPF) based on its ability to slow the decline in lung function and disease progression, as demonstrated in phase III clinical trials [29]. As evidenced by alterations in FVC, a walking distance of a six-minute walk test, and progression-free survival, it can be concluded that pirfenidone is an efficacious agent in slowing of disease progression. During the trial, it was observed that the early and increasing impact of treatment on FVC resulted in a halving of the rate of decline at one year [30]. In IPF, the recommended dose of pirfenidone is 2403 mg per day in 3 divided doses taken with food which are proven to be effective [31]. In line with previous studies, treatment with pirfenidone was shown to be generally safe with an acceptable adverse event profile [32]. Gastrointestinal and skin-related adverse events were prevalent among patients receiving pirfenidone treatment. In 2.2% and 2.9% of patients treated with pirfenidone and 1.1% and 0.4% of patients treated with placebo, these events were generally mild to moderate in severity and led to discontinuation of treatment. The group administered with pirfenidone demonstrated a reduction in both the occurrence and severity of adverse events and deaths when compared to the placebo group. Aminotransferase levels exhibited a greater tendency to increase to a clinically significant degree in the pirfenidone group. However, these elevations were observed in less than 3% of patients, were reversible, and did not result in clinically significant consequences [31]. The patients participating in the TRAIL1 trial, as reported by

Solomon et al. [32, 33], were randomly assigned to receive either 2403 mg of oral pirfenidone per day or a placebo. The primary objective was to determine the incidence of the composite endpoint of either a decline from baseline in percent predicted FVC of 10% or more or death during the 52-week treatment period. The results were assessed in the population of individuals who were treated in accordance with the study protocol, which is referred to as the intention-to-treat population. The change in absolute and FVC% over 52 weeks, the proportion of patients with a decrease in FVC% of 10% or more, and the frequency of progression in the intention to treat population were key secondary endpoints. A total of 231 patients were included in the study, of whom 123 were randomly assigned to receive either pirfenidone (63 patients) or a placebo (60 patients). There was no statistically significant difference in the proportion of patients in the pirfenidone and placebo groups who met the composite primary endpoint, with 7 patients in the former group (11% of the total number of patients) and 9 patients in the latter group (15% of the total number of patients) respectively. This was represented by an odds ratio (OR) of 0.67 (95% confidence interval [CI] 0.22 to 2.03), with a statistical significance level of p = 0.48. The results indicated that patients in the pirfenidone group exhibited a slower decline in lung function compared to the placebo group. The estimated annual change in FVC was -66 vs -146 for pirfenidone vs placebo, respectively (p=0.0082), while the change in FVC% was -1.02 vs -3.21, respectively (p=0.0028). The decline in FVC% was found to be comparable between the two groups, with 5% (n = 8) of participants in the pirfenidone group exhibiting a decline in FVC% of at least 10% compared to 7% (n = 12) of participants in the placebo group (p = 0.32). Furthermore, there was no statistically significant difference between the two groups in the frequency of progression (25% in the pirfenidone group vs. 32% in the placebo group, n = 60). The proportion of patients who exhibited a decline in FVC of 10% or more was comparable between the two groups (5 [8%] in the pirfenidone group versus 7 [12%] in the placebo group; OR 0.52 [95% CI 0.14-1.90]; p = 0.32). Additionally, the frequency of disease progression was comparable between the two groups, with 16 individuals (25%) in the pirfenidone group experiencing progression, in line with 19 individuals (32%) in the placebo group. The rate of treatment-emergent serious adverse events was similar in both groups, and there were no treatment-related deaths. In patients with IPF, treatment with pirfenidone has been shown to result in a slowing of the rate of decline in the forced vital capacity (FVC) over time. In both RA and IPF, there are established measures of disease severity and patient-reported outcomes (PROs) that assess health-related quality of life (HRQL). In IPF, the use of established PROs is associated with a correlation with the severity of lung disease. The correlation between

established indices and measures of disease severity in patients with RA-associated ILD and PROs in ILD patients remains unknown. Similarly, it is unclear if the established PROs in IPF correlate with the severity of ILD in patients with RA. Dellaripa et al. [34] aimed to identify any a priori relationships between PROs, measures of RA disease severity, and severity of ILD, as well as correlations between PROs used in RA and IPF, using baseline data collected in the TRAIL1 trial. The study was conducted based on baseline data from 123 subjects who were randomly selected to participate in TRAIL1, as outlined in the study protocol. All study participants were required to complete the PROs and the DAS28, which is the Disease Activity Score, at the time of their initial enrolment in the study. The following PROs were examined: the RAPID3 in RA, the St. George's Respiratory Questionnaire (SGRQ), and Dyspnea-12 for ILD. The baseline PROs showed mild activity in RA, while dyspnoea and pulmonary-specific HRQL reported by SGRQ were shown to be less impaired than that seen with IPF. There was no association of DAS28 and PROs with the severity of ILD disease. There was a strong correlation between the RAPID3 and the ILD-specific PROs (SQRQ and Dyspnea-12). As measured by PFTs and the extent of fibrosis on HRCT, no correlation between joint disease activity and RAILD severity has been observed. Furthermore, no correlations were evident between ILD-specific PROs and the severity of lung disease in RA-ILD, as is observed in IPF. The results suggest that RA-ILD has distinct characteristics from IPF, although the sample size was comparatively small. The systemic nature of RA and the multicompartment lung involvement that can be seen in RA may have an impact on this. In patients with RAILD, these differences may lead to the development of specific PROs that are more precise in predicting lung function. Wang et al. [29] carried out a survey of 111 patients with connective tissue disease-related interstitial lung disease (CTD-ILD), one group of which was RA (17, 15.32%). Glucocorticosteroids (GS) and/ or immunosuppressants (IS) have been administered to patients with relatively stable doses since their initial screening. After assessment of HRCT, lung function (FVC% and DL_{CO}%), and baseline disease severity, pirfenidone was added or not and patients were followed up regularly for 24 weeks. At an initial visit, DL_{CO}% in the other CTDs was reduced compared to systemic scleroderma (SSc), idiopathic inflammatory myositis (IIM), and RA patients (54.58 vs 65.55, 68.71, 66.89, p=0.036), while there were no meaningful differences in baseline FVC% between these diseases. After 24 weeks of exposure, RA-pirfenidone increased DL_{CO}% by 7.40% compared to a 5.50% decrease from baseline in RA-no-pirfenidone (p=0.002). Moreover, DL_{CO}% improved significantly in the subgroup of RA-irfenidone-non-UIP patients, compared with RA-irfenidone-UIP patients (10.40 vs. -4.45, p=0.017). In the RA-pirfenidone pts, DL_{CO}%

demonstrated a greater improvement in the baseline DL_{CO}% less than 70% subgroup versus RA-no-pirfenidone (7.40% vs. -6.60%, p=0.011). Baseline IS were comparable between pirfenidone and non-pirfenidone groups during the trial and no differences in baseline and follow-up GS and IS doses were observed in any subgroup. Baseline FVC%<70% (HR=4.56,6.81) and pirfenidone prescription (HR=4.56,4.37) may positively influence changes in FVC% and DL_{CO}% (all p<0.05) according to multiple linear regression analysis.

Comparison of the effectiveness of antifibrotic drugs

Furthermore, additional studies have been conducted to compare the effectiveness of the two drugs. Juge et al. [35] performed a retrospective analysis of 74 patients with RA-ILD who were started on antifibrotics (mean age 67.8 years, 47% were women). Nintedanib and pirfenidone were used in 40 and 34 of these patients, respectively. The median follow-up was 89 weeks, with a minimum of 4 weeks and a maximum of 387 weeks. There was a significant improvement in the estimated slope of FVCpp after starting antifibrotics, with a reduction of -0.3% per year after starting antifibrotics compared with -6.2% per year before starting antifibrotics (p = 0.03). The trajectory of FVCpp was similar for both nintedanib and pirfenidone. Throughout a follow-up period, 26 patients (35%) died and 4 (5%) received a lung transplant. Adverse events (AEs) were reported in 41 (55%) of the patients, with gastrointestinal AEs being the most common (n = 30). The first-line antifibrotic agent was discontinued in 34 (46%) patients, the majority of which were due to GI AEs (n = 19). There was no significant difference between nintedanib and pirfenidone (p = 0.68) with a median duration of 142 weeks (95% CI 56, 262).

Results

Clinical trials concerning RA-ILD showed that nintedanib slows the rate of FVC decline in patients with progressive pulmonary fibrosis, moreover, the efficacy and safety of that treatment were consistent with those observed in the general trial population. The safety profile observed in the pirfenidone trials was similar to nintedanib in patients with RA-ILD simultaneously the side effects of pirfenidone and nintedanib occur with similar frequency, and these were mainly gastrointestinal symptoms. It has been shown that approximately one-third of patients with RA-ILD show a progressive pattern of ILD fibrosis and may benefit from antifibrotic treatment, alone or in combination with antirheumatic drugs. Clinical studies have demonstrated significant improvement in DLCO among patients taking nintedanib or

pirfenidone with no decreases in FVC and DLCO parameters, which suggests that early treatment may significantly slow down the progression of ILD. Stability of the disease or improvement in the severity of shortness of breath was observed in both patients taking nintedanib or pirfenidone. There is limited evidence confirming the effectiveness of nintedanib and pirfenidone; however, both drugs have been approved for the RA-ILD treatment program, nevertheless in the current body of knowledge, it is not feasible to definitively determine which drug therapy should be initiated first, as their characteristics are notably similar.

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