

ŻUBER, Michał, DĄBROWSKA, Paulina and DACKA, Michał. The role of nintedanib and pirfenidone in the treatment of idiopathic pulmonary fibrosis and review of recent clinical trials of IPF therapy. Quality in Sport. 2024;20:51395. eISSN 2450-3118. <https://dx.doi.org/10.12775/QS.2024.20.51395> <https://apcz.umk.pl/QS/article/view/51395>

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 16.05.2024. Revised: 25.05.2024. Accepted: 29.05.2024. Published: 05.06.2024.

The role of nintedanib and pirfenidone in the treatment of idiopathic pulmonary fibrosis and review of recent clinical trials of IPF therapy

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, rare disease characterized by continuous fibrosis of the lung parenchyma. It mainly affects the elderly; however, it is increasingly being diagnosed in younger patients as well. Risk factors include smoking, occupational dust exposure and genetic factors. Symptoms of IPF include shortness of breath, dry cough and reduced exercise tolerance, leading to a reduced quality of life for patients. Diagnosis is based on imaging, mainly high-resolution CT scans, and the exclusion of other causes of interstitial lung disease. Two antifibrotic drugs, nintedanib and pirfenidone, are now approved to slow disease progression. Nintedanib acts as a tyrosine kinase inhibitor, blocking the signaling pathways of lung fibroblasts. Pirfenidone, on the other hand, has anti-inflammatory and anti-fibrotic effects by inhibiting TGF- β signaling pathways. Clinical trials have confirmed their efficacy in reducing the decline in increased vital capacity and the risk of disease progression. In Poland, patients with IPF can benefit from nintedanib and pirfenidone therapy under the drug program. Despite advances in treatment, more research is needed on new IPF therapies. Clinical trials of zinpentraxin, ziritaxestat and pambrevalumab have not confirmed their efficacy in treating IPF. Results from initial studies of bexotegrast show promise, but further studies are needed and are ongoing. Despite advances in the treatment of IPF, further research into new therapies is needed to improve therapeutic outcomes and patient quality of life.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease of unknown cause characterized by continuous fibrosis of the lung parenchyma, with the histological and/or radiological picture of usual interstitial pneumonia [1]. IPF is a rare disease. Estimates of incidence and prevalence range from 0.09-1.30 and 0.33-4.51 per 10,000 people, depending on latitude [2]. The average age of a patient's incidence is in the 6th or 7th decade of life, but there are cases in younger age groups. With the aging population, the number of cases is projected to increase in the future [1]. IPF affects men more often. In addition, people who smoke tobacco and are exposed to metal and wood dust inhalation are at higher risk. It is also suspected that genetic factors may be behind the increased susceptibility to the disease [3]. Typical of the course of IPF is the increase in disease symptoms with the duration of the disease. Characteristically, patients experience shortness of breath, the occurrence of a dry, non-productive cough and reduced exercise tolerance. Physical examination usually reveals

symmetrical butters crackles. As the disease progresses, crackles may begin to be heard in the higher parts of the lungs. Shallow breathing and tachypnoea are also often observed in patients. In the advanced stage of the disease, clubbing fingers and complications such as cyanosis resulting from respiratory failure and signs of heart failure as a consequence of pulmonary hypertension can be observed [4]. Pulmonary function tests show reduced enhanced lung capacity (FVC) and reduced enhanced first-second expiratory volume (FEV1). A reduced lung gas exchange capacity estimated by DLco testing is also found. The treatment providing the best long-term results is lung transplantation. Currently, there is no pharmacological treatment available to completely cure IPF, and the probability of 5-year survival from diagnosis is 20% to 40% [5]. Two antifibrotic drugs, nintedanib and pirfenidone, are approved for the treatment of IPF, both of which slow the progression of the disease. The purpose of this work is to discuss the efficacy of nintedanib and pirfenidone therapy in slowing the progression of IPF and to review work on potentially new therapies for IPF.

2. Materials and methods

In this review paper, we discuss the efficacy of nintedanib and pirfenidone therapy in slowing the progression of idiopathic pulmonary fibrosis and briefly review recent studies of new IPF therapies. Scientific articles were reviewed within the databases: PubMed, Google Scholar and Web of Science using the following keywords: idiopathic pulmonary fibrosis, nintedanib, pirfenidone, treatment, IPF pathogenesis

3. Pathophysiology

A good understanding of the pathophysiological mechanisms that cause IPF will allow a proper understanding of the mechanisms of action of drugs used to treat IPF. The pathomechanism of idiopathic pulmonary fibrosis is very complex and involves a large number of cells and signaling pathways. The pathogenesis of IPF is associated with several factors. Prominent among them are smoking, chronic infections, exposure to environmental factors and genetic predisposition. It is believed that people with a genetic predisposition are particularly susceptible to developing IPF, that is, carriers of telomerase gene mutations, in which there is telomere shortening of alveolar epithelial cells. This leads to ongoing damage to alveolar cells [6, 7]. In response to factors that provoke cell damage and inflammation, a cellular response is induced in the lung parenchymal tissue, characterized by the onset of fibrosis. During the initial phase of the inflammatory response, inflammatory cells such as neutrophils and macrophages release many pro-inflammatory and profibrogenic cytokines. These include substances such as

transforming growth factor beta (TGF- β), platelet-derived growth factor (PDGF) and tumor necrosis factor (TNF- α). Of all these substances, transforming growth factor- β (TGF- β) seems to have the greatest role [8]. This factor is involved in apoptosis and damage of alveolar epithelial cells and activation of myofibroblasts and fibroblasts. Membrane receptors - serine/threonine kinases - are involved in signal transduction involving TGF- β . SMAD proteins are responsible for transmitting the signal to the cell nucleus, affecting various transcription factors in the cell nucleus to promote the expression of various genes [9]. Released TGF- β factor combining on the cell membrane with a specific type II receptor (T β RII) leads to its phosphorylation and activation of the type I receptor (T β RI). The complex thus formed triggers a cascade of events leading to the phosphorylation of SMAD-type proteins. The complex formed from the combination of SMAD2, SMAD3 and SMAD4 proteins is transported to the cell nucleus where it induces transcription of genes responsible for the production of extracellular matrix proteins and collagen [10]. Increased production of matrix proteins and collagen results in increased fibrosis of lung parenchymal tissue. The fibrosis processes do not occur simultaneously in the lung tissue and may be more or less expressed in different segments of the lung. This heterogeneous picture of fibrosis corresponds morphologically to typical lobular pneumonia [11].

4. Diagnostic

The clinical symptoms presented by patients with idiopathic pulmonary fibrosis are nonspecific and require expanded diagnosis. The disease should be suspected in all adults who present with chronic exertional dyspnea unrelated to another diagnosed condition, chronic cough, crackles at the base of the lungs or characteristic clubbing fingers with no other identifiable cause [11, 12]. In February 2022, guidelines for the diagnosis and treatment of IPF were published. These guidelines are the result of the work of experts from the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Asociacion Latinoamericana de Torax. Idiopathic pulmonary fibrosis can be identified on the basis of a characteristic radiographic and/or histologic picture, which is the typical picture of usual interstitial pneumonia [11]. Definitive diagnosis requires exclusion of other causes that may cause interstitial lung disease. We are talking about such factors as connective tissue diseases, occupational diseases, exposure to harmful agents and toxic effects of drugs. Laboratory tests can be helpful in ruling out these causes, but do not play a significant role in making the diagnosis of IPF [11, 13]. High-resolution computed tomography (CTWR) plays a dominant role in the diagnosis of IPF. IPF is characterized by a radiological pattern of interstitial

pneumonia (UIP). This pattern can be diagnosed if there are radiological features of fibrosis, i.e. dilatation of peripheral bronchi and bronchioles with pulling, and the occurrence of so-called honeycombing - a cluster of cysts 3-10 mm in diameter with clearly visible walls [14]. If a typical radiological pattern is found on CTWR, a lung biopsy is usually not necessary to confirm the diagnosis. If the "honeycomb" is not visualized on CTWR, or other features atypical of IPF are found, further histological diagnosis is indicated. Transbronchial lung cryobiopsy, which can be considered an equivalent technique to surgical lung biopsy, can be performed in patients with an uncertain diagnosis [4, 11]. As with CBCT, typical patterns of disease that correspond to interstitial pneumonia are needed to make a confident diagnosis in the biopsy. These areas are characterized by spatial heterogeneity with areas of marked fibrosis adjacent to normal-appearing tissue, distorted architecture, "honeycombing," and scattered fibroblastic foci, which are thought to be sites of active fibrogenesis [15, 16]. If typical lesions are not visualized in the biopsy or atypical lesions are visualized, a multidisciplinary discussion between pulmonologists, radiologists and pathomorphologists may be necessary to make a definitive diagnosis based on the clinical picture, CTWR examination and evaluation of the biopsy material [11].

5. Treatment

Until 2014, the standard treatment for IPF was combination therapy with prednisone, azathioprine and n-acetylcysteine. A study conducted and results published in 2012 showed that patients on this therapy, compared to patients who took placebo, were hospitalized more often for disease exacerbations, and the death rate was also higher than in the group taking placebo [17]. Due to the ineffectiveness of the therapy at the time, two drugs with antifibrotic effects - nintedanib and pirfenidone - were approved for the treatment of IPF [18]. To evaluate the effect of nintedanib on IPF progression, clinical trials called INPULSIS-1 and INPULSIS-2 were conducted. These were phase III clinical trials using a double-blind, randomized design. The studies included 1,066 patients. The studies were undertaken to examine the effect of nintedanib therapy at a dose of 150mg twice daily on the progression of IPF. It was shown that the annual rate of decline in enhanced vital capacity (FVC) was significantly lower in patients receiving nintedanib compared to those receiving placebo. In the INPULSIS-1 trial, the annual decline in FVC was 125.3 mL less compared to patients taking placebo, while in the INPULSIS-2 trial, the difference was 93.7 mL in favor of nintedanib. In addition, the results of the study indicate a lower risk of disease exacerbation in patients taking nintedanib. Both studies show that the risk of progression was significantly reduced for patients treated with nintedanib compared to

placebo, indicating a 40% reduction in the risk of progression compared to placebo. The analysis also provides results on patient mortality during 52 weeks of follow-up. Mortality in the group of patients taking nintedanib was lower at 5.5% of patients, compared to 7.8% of patients in the placebo group [19,20]. Three large, multicenter clinical trials have been conducted to evaluate the efficacy of pirfenidone in the treatment of idiopathic pulmonary fibrosis [21]. Two studies compared treatment with pirfenidone at a daily dose of 2403 mg with placebo, while in the third study the dose of pirfenidone was 1800 mg/day (Japanese population). The drug was administered three times daily. After 72 weeks, FVC values were assessed. It was shown that among patients taking pirfenidone, there was a significant reduction in the decline in FVC values from baseline, compared to patients receiving placebo, in whom the decline was greater. Moreover, a decrease from baseline in the percentage of FVC values \geq 10% was observed in 20% of patients receiving pirfenidone compared to 35% of patients in the placebo group. In both studies, the mortality rate in the group taking pirfenidone was lower than in the group taking placebo by about 2% [21, 22]. Nonpharmacologic treatments for patients with IPF include oxygen therapy especially indicated in patients with significant hypoxemia at rest or during exercise. It is also advisable to conduct pulmonary rehabilitation programs in patients aimed at maintaining or improving previous exercise tolerance [18]. The indications for lung transplantation should be considered early in each patient. The main advantage over other treatments is that lung transplantation can significantly alleviate disease symptoms as well as increase estimated survival time [23, 24]. Among the criteria for placing a patient on the transplant waiting list are a rapid decline in FVC, hypoxemia, a decrease in distance covered during the 6-minute walk test, pulmonary hypertension, hospitalization for respiratory failure or pneumothorax [5]. The value of 5-year survival after lung transplantation oscillates around 50% of patients [25].

6. Nintedanib

Nintedanib is a small-molecule inhibitor of tyrosine kinases, including platelet-derived growth factor receptors (PDGFR) α and β , and receptors for fibroblast growth factor (FGFR) and vascular endothelial growth factor (VEGRF) [26]. Nintedanib blocks TGF- β -induced activation of the FGFR and PDGFR signaling pathways, which play a key role in the processes of proliferation, migration and differentiation of lung fibroblasts and myofibroblasts. In addition, nintedanib reduces the amount of collagen produced in response to TGF- β , and increases the secretion of metalloproteinase two, which plays a positive role in the breakdown of extracellular matrix components [27]. In addition, the beneficial anti-inflammatory effects of nintedanib may

be suggested by results obtained from bronchoalveolar lavage fluid from animal models, which showed reduced numbers of neutrophils and lymphocytes compared to models without nintedanib therapy [28]. Maximum plasma concentration of nintedanib is reached within 2-4 hours after oral intake. It binds mainly to serum albumin, and is metabolized mainly by hydrolytic cleavage by esterases. The involvement of CYP enzymes in its metabolism is minor. It is excreted mainly in bile and stool, and complete elimination of the drug from the body occurs within 4 days after administration [20]. The most common side effects associated with the use of nintedanib are diarrhea and nausea, which in most cases are mild. Increased liver enzymes are also common. However, it is mild and reversible in nature, not coexisting with clinical signs of liver failure [19].

7. Pirfenidon

Pirfenidone is an oral drug with antifibrotic and anti-inflammatory effects [29]. The exact mechanism of action of pirfenidone remains unclear; however, it has been suggested that it inhibits TGF- β -activated signaling pathways, including SMAD protein-dependent signaling pathways [30]. The consequence of this action is a reduction in pulmonary fibroblast proliferation and differentiation into myofibroblasts and extracellular matrix accumulation [21,31]. Studies in animal models where lung fibrosis was induced with bleomycin demonstrate the beneficial effects of pirfenidone on reducing fibroblasts, myofibroblasts and inflammatory cell accumulation in lung tissue [31, 32]. Pirfenidone in the human body binds mainly to plasma albumin. It is metabolized by CYP isoenzymes, mainly by the CYP1A2 isoenzyme. Concomitant use of pirfenidone and potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin may result in the need to reduce the daily dose of pirfenidone [21]. Smoking, which is a CYP1A2 inducer, may decrease plasma concentrations of pirfenidone [21]. Approximately 80% of an orally administered dose of pirfenidone is excreted in the urine within 24 hours after intake. The most common reported side effects of pirfenidone are nausea, rash, fatigue, diarrhea, indigestion and photosensitivity [33].

8. Drug program "treatment of idiopathic pulmonary fibrosis with pirfenidone" and "treatment of idiopathic pulmonary fibrosis with nintedanib" (Program B.87.).

In Poland, patients with idiopathic pulmonary fibrosis have the opportunity to participate in drug therapy with nintedanib and pirfenidone under drug program B.87. "treatment of idiopathic pulmonary fibrosis." Patients who have reached the age of 18 are eligible for the drug program. Inclusion in the program requires a diagnosis of IPF on the basis of a high-resolution computed tomography scan (CTWR), after a pulmonology specialist has ruled

out known causes of pulmonary fibrosis. In a situation where the CT scan has failed to make a confident diagnosis, evaluation of biopsy material taken from lung tissue is required before inclusion in the program. In addition, another criterion for inclusion in the program is that the patient obtains an FVC value above 50% of the normal value on spirometry and a DLco above 30%. Contraindications for inclusion in the drug program include severe liver dysfunction, chronic renal failure with creatinine clearance below 30 ml/min, pregnancy and breastfeeding, and the presence of other severe chronic diseases such as cancer or severe heart failure. Patients in the drug program are subject to continuous monitoring aimed at assessing disease progression. Tests to assess respiratory function such as spirometry, DLco and blood gasometry should be performed every 6 months. The imaging test used for monitoring is a high-resolution CT scan (of the chest), which should be performed every 12 months. In addition, ALT and AspAT activity should be monitored once a month for the first six months of treatment, after which time the test should be performed once every three months. Blood counts should be performed every six months. Exclusion of a patient from the drug program occurs as a result of the treatment team's assessment of treatment failure. For this, it is necessary to find a reduction in FVC of at least 10% during the first 12 months of treatment and every 6 months thereafter, confirmed by two spirometry tests performed 2-4 weeks apart measured every 6 months of treatment [34].

9. Latest clinical trials

Idiopathic pulmonary fibrosis is still a disease whose pathogenesis has not been fully elucidated. Clinical trials are constantly being conducted to understand the mechanisms of the disease and develop new therapies [7]. Considerable hopes were pinned on a multicenter, randomized phase II clinical trial testing a recombinant human protein, Pentraxin-2 (zinpentraxin) which inhibits the differentiation of monocytes into profibrotic macrophages and fibrocytes. After a promising Phase II clinical trial in which patients treated with zinpentraxin showed a smaller decrease in FVC values, Phase III clinical trials were initiated. Unfortunately, the Phase III clinical trial involving 665 participants failed to confirm the efficacy of zinpentraxin in patients with IPF and was prematurely terminated in 2023 [7,35]. Clinical trials of ziritaxestat, an inhibitor of the enzyme autotaxin, ended with similar results. Autotaxin is an enzyme that catalyzes the hydrolysis of lysophospholipids to lysophosphatidic acid, elevated levels of which are found in IPF. Ongoing phase II clinical trials have shown increased FVC values in IPF patients using ziritaxestat compared to the placebo group. A large multicenter randomized phase III study failed to confirm the drug's efficacy in slowing FVC decline and observed an increased mortality rate in the ziritaxestat-treated group compared to the placebo group. The study was terminated early in 2023 [36]. Pambrevalumab, a monoclonal antibody against connective tissue growth factor (CTGF), has also become an object of research in the context of IPF. Excessive CTGF activation in IPF leads to excessive collagen accumulation in lung tissue. The potential inhibitory effect of pambrevalumab on CTGF has raised hopes for its use in IPF therapy. In a phase II clinical trial involving 103 subjects, the decline in FVC from baseline after 48 weeks of pambrevalumab was 4.3% lower than in the placebo group [37]. Despite promising phase II studies, the phase III study that was initiated was terminated due to failure to meet the study's main objectives, which were to significantly delay disease progression and reduce the risk of death [38]. An open-label, randomized, double-blind phase IIa study of the integrin inhibitor av β 6 and av β 1 ended with promising results. av β integrins are key regulators of transforming growth factor TGF- β activation. They have also been shown to be expressed in fibroblasts and fibrosis-affected lung tissue [39]. In a

study called INTEGRIS-IPF, which tested an integrin inhibitor called bexotegrast (PLN-74809), patients received the inhibitor at a varying dose (40-320mg). Preliminary results of the study are promising and indicate that the average decrease in FVC in patients in the group receiving 320mg of bexotegrast was 15.1ml, compared to the group of patients taking placebo, where the decrease in FVC was 74.1ml [40]. Currently underway is a multicenter, randomized, double-blind phase IIb study called BEACON-IPF. The study involves 270 patients with IPF. The study is evaluating the effect of bexotegrast at doses of 160 mg or 320 mg on FVC at week 52 of therapy relative to baseline FVC. Other factors to be evaluated in the study will be the frequency of IPF exacerbations during therapy, the effect on mortality rates, the frequency and type of adverse symptoms experienced, and the drug's effect on the patient's overall health [41].

10. Summary

Idiopathic pulmonary fibrosis is a severe chronic disease affecting more and more patients worldwide. It mainly affects people in their 6th and 7th decades of life. It is characterized by increased fibrosis of lung tissue, likely influenced by genetic factors such as telomere shortening of alveolar epithelial cells, and environmental factors such as smoking and exposure to toxic substances. The disease leads to impaired gas exchange and manifests as shortness of breath, dry cough, crackles at the base of the lungs and impaired exercise tolerance, among other symptoms. The pathogenesis of the disease is not yet precisely elucidated, but with high probability a large role is attributed to pro-inflammatory cytokines and factors such as TNF- α , or TGF- β , which induce fibrotic processes in lung tissue in response to cellular damage. Making a diagnosis of IPF requires detecting a pattern of typical interstitial pneumonia on a high-resolution CT scan and/or in a biopsy specimen taken from a lung biopsy. As of today, two antifibrotic drugs - nintedanib and pirfenidone - are approved for pharmacological treatment and form the basis of IPF drug therapy. The former is used at a dose of 150mg twice daily, while the latter is used at a dose of 801mg three times daily. Numerous large randomized clinical trials have demonstrated the effectiveness of these drugs in slowing disease progression. In Poland, both of these drugs are reimbursed to patients under drug program B.87. In parallel with pharmacotherapy, pulmonary rehabilitation and oxygen therapy should be used in patients who require it. An early decision should also be made to include the patient in the waiting list for lung transplantation, since at the moment this is the only treatment that significantly reduces patient mortality in the long term. Since IPF is a disease affecting an increasing number of people, and no pharmacotherapy has been developed to date to ensure a permanent cure for the disease, it is important to continue research into new therapies and the search for predictive biomarkers responsible for the pathogenesis of IPF, which will enable a better understanding of the disease and the development of new treatments.

11. Disclosure

Authors contribution:

Conceptualization: Michał Żuber, Paulina Dąbrowska, Michał Dacka

Methodology: Michał Żuber, Paulina Dąbrowska, Michał Dacka

Formal analysis: Michał Żuber, Paulina Dąbrowska

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Writing – review and editing: Paulina Dąbrowska, Michał Żuber, Michał Dacka

Visualization: Michał Żuber, Michał Dacka

All authors have read and agreed with the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Funding statement: No external funding was received to perform this review.

Board statement: Not applicable – this review included analysis of the available literature.

Statement of informed consent: not applicable.

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