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Role and New Insights of Pirfenidone in Pulmonary Fibrotic Diseases

[1]Dr. Satyendra Kumar Singh, [2]Dr. Gregory Minj
[1](Department of Medicine/Associate Professor/R.I.M.S/Ranchi University/India)
[2](Department of Medicine/Associate Professor/R.I.M.S/Ranchi University/India)

Abstract: *Pirfenidone (PFD) is a non-peptide synthetic molecule issued as a broad-spectrum anti-fibrotic drug with the ability to decrease TGF-β1, TNF-α, PDGF and COL1A1 expression, which is highly related to prevent or remove excessive deposition of scar tissue in several organs. Basic and clinical evidence suggests that PFD may safely slow or inhibit the progressive fibrosis swelling after tissue injuries. Furthermore, a number of evidence suggests that this molecule will have positive effects in the treatment of other inflammatory diseases. This review contains current research in which PFD has been used as the treatment of several diseases, and focus mainly in the outcomes related to improve inflammation and fibrogenesis. Therefore, the main goal of this review is to focus on the novel findings of PFD efficacy rather than deepen in the chemical aspects of the molecule.*

I. Introduction

This review intends to draw the attention of the reader on the updated and current knowledge of the use of Pirfenidone (PFD) in the treatment of several fibrotic diseases. It is structured in such a way that the reader will be able to grasp easily the actual concept on PFD action on different organs. Each section is divided in the basic preclinical studies, followed by the most recent findings in the clinical scenario. PFD is being investigated for therapeutic profits to patients suffering from fibrosis conditions such as idiopathic pulmonary fibrosis (IPF). PFD has also been studied to analyze pharmacologic effects in preventing, or even stopping, scarring process found in fibrosis in injured tissues including those of lungs, skin, joints, kidneys, prostate glands and liver.[1] Research suggests that PFD may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new lesions following tissue injuries. PFD is provided for oral administration in capsules or tablets. Different formulations have been tested and implemented in clinical trials, additional research and experiments. There are a number of reviews available regarding the action and pharmacokinetics of PFD.[2-5] The main goal of this review is to focus on the novel findings of PFD efficacy rather than deepen in the chemical aspects of this molecule.

Role Of Pirfenidone In Regulation Of Fibrosis

Fibrosis is the state resulting from excessive accumulation of extracellular matrix components such as collagen and fibronectin secreted by myofibroblasts in response to cellular damage. Parenchyma replacement by extracellular matrix excess during chronic fibrosis damage eventually leads to organ failure[2-5]. In addition, fibrosis is a condition arising from chronic state of various diseases such as scleroderma, rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus and idiopathic pulmonary fibrosis (IPF). These events fall into three main mechanisms: cell damage, inflammation and eventually fibrosis. These pathologies cause organ dysfunction, through permanent scar tissue accumulation, and many even lead to death[6,7]. PFD has been tested as an anti-fibrotic drug in lung, liver, kidney and myocardium. It has also been shown that PFD reduces keloid formation in an animal model.

Effect Of Pirfenidone In Interstitial Lung Disease

The use of PFD in lung tissue has been extensively studied, which has led to describe several therapeutic targets, especially those related to anti-inflammatory and anti-fibrogenic actions directing attention to research development in conditions that compromise pulmonary tissue architecture, mainly in IPF. This chronic and progressive disease is characterized by a progressive decline in lung function. The prevalence of IPF is estimated at 20/100,000 for males and 13/100,000 for females with a greater incidence in individuals aged over 50 years; approximately two-thirds are over the age of 60 years old at the time of disease beginning[8,9]. The etiology of IPF remains unclear and the only risk factors associated with the disease onset are smoking, exposure to toxic gases, genetics and environmental factors IPF pathophysiology has not been fully defined but is attributed to organ damage, specifically, epithelial damage with consequent activation of alveolar cells that secrete a cascade of pro-inflammatory molecules activating fibroblast proliferation and myofibroblast differentiation with a reduced apoptosis rate. Therefore, the main therapeutic target for IPF is the decrease of

extracellular matrix accumulation[10,11]. IPF is characterized by irregular scattered fibrotic areas, fibroblast proliferation and epithelial to mesenchymal transition, where cells in turn are the major source of profibrogenic mediators such as platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and TGF-β1, which has been shown to increase mRNA expression of collagen type I and heat shock protein 47 (HSP47), a collagen-specific chaperone, located in the endoplasmic reticulum which is engaged in processing, assembly and secretion of procollagen during fibrotic processes.

It has also been demonstrated that PFD inhibits TGF-β1-induced over-expression of collagen type I, and heat shock protein 47 in A549 cells. These mechanisms are summarized in figure 1. PFD has been tested in experimental and clinical models of IPF with favorable results. In phase II and III clinical trials, PFD has shown to improve the decrease of functional vital capacity (FVC) of patients at 32 and 52 weeks respectively up to 44% compared to placebo, improving survival (p=0.0280) rate. This phase III trial, has shown that basal FVC ≥ 70 % and oxygen saturation < 90 % (measured by pulse oximetry (SpO2)) during the 6MET, low doses of PFD (1800 and 1200 mg/day) provide more benefits to patients in terms of FVC and progression- free survival (PFS) changes, but also in subjective symptoms such as cough and dyspnea compared to placebo patients[9]. Studies as Capacity 004 and 006 have also shown reduction in FVC decline at 72th week of treatment, improving parameters in the test results of 6-minute walk test (6MWT) at the standard dose of 2403 mg/day[13].

In other multicenter phase III trial, the efficacy of PFD was analyzed in patients with IPF and results shown in this trial suggested that, when 5 % change in VC was used as an index instead of the 10 % change, the efficacy of PFD could be evaluated with higher sensitivity and robustness over the 12-month study. It was also suggested that 5 % change in FVC at month 3 is clinically useful and a significant promising prognostic factor of IPF. Systematic reviews has been conducted in order to investigate effectiveness of available IPF treatments, Loveman E (2015) analyzed fourteen studies of clinical effectiveness, one evaluated azathioprine, three N-acetylcysteine (NAC) (alone or in combination), four pirfenidone, one BIBF 1120, one sildenafil, one thalidomide, two pulmonary rehabilitation, and one a disease management program. Authors observed that these studies were generally good, with low risk of bias, and that some treatments appear to be clinically effective. The model base-case results showed increased survival for five pharmacological treatments, but general recommendations cannot be made due to cost-effectiveness and to limitations in the evidence base. Also, a phase II study (WJOG 6711L) has been developed to validate effectiveness and the safety of perioperative administration of PFD to lung cancer patients with IPF, trying to analyse whether PFD reduces lung injury after lung resection[16].

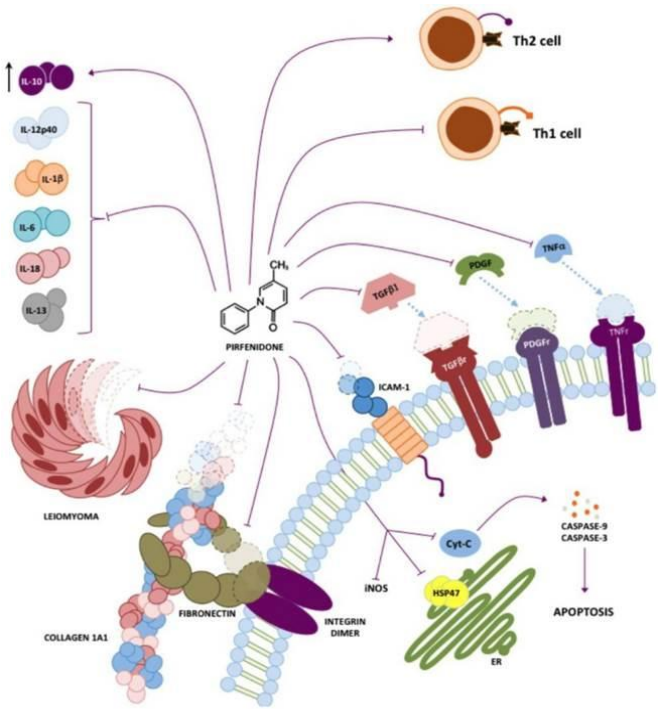

Figure 1: Pirfenidone targets. Different targets in vivo and in vitro for PFD have been described, the most prominent being inhibition of TGF-β1 and TNF-α. However, it has also been shown that PFD has either direct or indirect action on other molecules such as collagen I, PDGF, IL-6, IL-1β, IL-13, IL-12p40, fibronectin, HSP47 and ICAM-1.

Other drugs for IPF treatment

Some therapies have been developed to treat IPF, such as corticosteroids, azathioprine, azathioprine and prednisolone, cyclophosphamide, everolimus, anticoagulants, endothelin inhibitors I (ET), Sildenafil, Interferon, Etanercept, Imatinib, CC-930, N-acetylcysteine (NAC), monoclonal antibodies, angiotensin receptor blockers as losartan A1, somatostatin analogues such as Octreotide, etc. [17-20]. However some of these strategies did not produce significant benefits, or even were more harmful for disease treatment. Besides the side effects of different therapies, correct stratification of patients according to degree of pulmonary function is a limitation that reduce the application of specific dose of many drugs, for example the triple therapy with NAC, azathioprine and prednisone, which unfortunately have shown an increased death rate and hospitalization compared with placebo[17]. However other therapies such tyrosine kinase inhibitors as BIBF 1120 (Nintedanib) have been approved for application in patients with IPF in January 2015 based on results from the replicate Phase III INPULSIS trials. This therapy slowed disease progression by reducing the annual rate of decline in lung function by 50% in a broad range of IPF patients. Regardless of the armamentarium available as potential candidates to be used to treat this life-threatening disease, the relatively positive results in various tests of lung function enabled PFD as one of the main approved drug to treat mild to moderate IPF in Japan, China and India in 2008[16] and in February 2011 it was also approved by the European Commission for the treatment of the same lung condition.

The ASCEND clinical trial (PIPF-016) was a randomized, double-blind, placebo controlled, phase 3 study of the efficacy and safety of PFD in patients with IPF aiming to confirm the PFD-treatment effect on change in predicted forced vital capacity (%FVC), and to confirm the safety of PFD treatment. This clinical trial enrolled 555 patients from 127 sites in 9 countries, mostly in the U.S., 278 were assigned to receive PFD, and 277 were assigned to receive placebo. Subjects had clinical-radiographic or biopsy-confirmed IPF, and mild to moderate restrictive lung disease (FVC, forced vital capacity 50-90% predicted) with diffusion impairment on pulmonary function testing, and were randomized 1:1 to PFD or placebo one-year treatment. After 52 weeks, patients receiving PFD had a significant decline in FVC (≥10% predicted) compared to placebo patients (16.5% vs. 31.8%), which emerged early and increased during the course of the trial. Also, the 6-minute walk distance test increased 27 m (Relative difference 44.2%; P=0.04) in subjects taking PFD. The highly significant finding was supported by the encouraging effect on rates of death from any cause (4.0% vs. 7.2%) and from IPF (1.1% vs. 2.5%), since progression-free survival (PFS) was reduced with PFD (HR 0.57; 95% CI 0.43-0.77; P<0.001). As mentioned before in many clinical trials, it is difficult to reconcile results obtained from tested groups with all established stages in a disease, since these observations were obtained from enrolled patients with mild-to-moderate physiological impairment, results from population of patients with advanced disease are therefore uncertain. Based on this evidence authors conclude that PFD as compared with placebo reduced disease progression in patients with IPF, treatment was generally safe with an acceptable side-effect profile, and was associated with fewer deaths by slowing the rate of IPF worsening. Therefore, evidence shown in this research is positive for patients with IPF who have a very poor prognosis[13]. Based in this evidence, PFD was approved by FDA for use in IPF[21].

Adverse effects of pirfenidone

In the vast majority of the clinical protocols carried out to date, the most common adverse effects of PFD have been shown to be photosensitivity and rash as dermatological issues; gastrointestinal: nausea, diarrhea, and dyspepsia; neurological: fatigue, insomnia and dizziness.It is important to notice the efforts of Onoue et al. in the sense to device an alternative delivery of PFD as an inhalable powder. By using this pharmaceutical preparation they reduced phototoxicity in an experimental model with favorable results. This kind of findings calls for the design of new forms of PFD delivery to reduce sensitivity and dosing required achieving therapeutic levels increasing bioavailability in nasal mucosa. Eventually, this type of strategy will have to be assayed in human beings under the scrutiny of controlled clinical trials. However, more studies should be carried out since treatment effectiveness is related to the time and concentration of the drug at the site of damage. In the case of IPF, PFD would have to be not only in the nasal mucosa but reach the alveoli for better diffusion in the lung tissue.

Another trial named CAPACITY, rendered data that only 1% of patients discontinued treatment due to nausea and another 1% due to rash[9,10]. The extension phase of the study CAPACITY named RECAP, evaluated the safety of PFD after phase III studies to confirm the tolerability of PFD in patients who were treated for a mean of 2.9 years[11] though safety and tolerability of PFD treatment has been questioned by other authors. On the other hand, a prospective, double-blind, randomized, placebo-controlled trial that included 35 patients with type 1 Hermansky-Pudlak syndrome (HPS-1), investigated the safety and efficacy of PFD in mild to moderate HPS-1 (NHGRI protocol 97-HG-0085). During the trial there were 10 severe adverse events (SAE) and several non-serious adverse events including 3 deaths, considered to be part of the natural course of the lung disease, chest pain (2 subjects), elevated CPK (2 subjects), deep vein thrombosis, hematochezia and otitis with vertigo

on one subject each one. Furthermore, the most commonly reported non-serious adverse events include dyspepsia and heartburn in approximately 50% of the subjects in placebo and PFD groups, and almost all patients required anti-acid therapy. Other adverse events included photosensitivity rash. There was no evidence of bone marrow (hemoglobin, total leucocyte count), renal (serum creatinine), hepatic toxicity (alanine aminotransferase) or cardiac toxicity[23,24].

Among the broad spectrum of PFD actions, it has been suggested the use of this molecule to treat pulmonary fibrosis in patients previously poisoned by mustard gas, since the intermediate products originated by this molecule tend to permanently alkylate guanine from DNA, preventing cellular division and inducing cell death. Tissues exposed to this agent could present side effects even years after gas exposure, developing for example abnormal skin pigmentation, eye problems, cancer and pulmonary fibrosis. Therefore, the use of PDF could be helpful to treat exposed soldiers or workers to this hazardous material in the attempt to reduce signs and symptoms of pulmonary fibrosis[25].

II. Conclusion

There have been several studies in animal models of fibrosis where PFD immune modulation activities of have been evaluated. Macrophages are effector cells of innate response they are involved in the initiation and regulation of adaptive responses. Research has been conducted to analyse the effect of PFD in macrophages infiltration, where PFD has shown protective effects. Nephrectomised rats showed an increase in various molecules such as TNF-α, IL-6, and nitric synthase-2 oxide (expressed by macrophages M1), which decreased significantly their expression after PFD treatment. But several questions relating PFD effects on the control of transcription factors and cytokine network remain unanswered. The knowledge of these complex processes and its regulatory pathway are essential in order to develop safe and effective anti-inflammatory therapies against pathologies where inflammation induced damaged is relevant. Currently, a phase II clinical trial is on-going in order to analyse PFD effects on Systemic Sclerosis-Related Interstitial Lung Disease (NCT01933334) [26]. Thus, this type of studies will provide solid evidence for a better understanding of mechanisms involved in the effects of anti-inflammatory and anti-fibrotic drugs.

References

[1]. Huang NY, Ding L, Wang J, Zhang QY, Liu X, Lin HD, Hua WY. **Pharmacokinetics, safety and tolerability of pirfenidone and** its major metabolite after single and multiple oral doses in healthy Chinese subjects under fed conditions. Drug Res. 2013;63:388-95

[2]. Macias-Barragan J, Sandoval-Rodríguez AS, Navarro-Partida J, Armendariz-Borunda J. The multifaceted role of pirfenidone and its novel targets.Fibrogenesis Tissue Repair. 2010;3:16

[3]. Paz Z, Shoenfeld Y; Antifibrosis. To reverse the irreversible. Clinic Rev Allerg Immunol. 2010;38:276-86

[4]. Zamara E, Novo E, Parola M. Oxidative stress and liver fibrosis: from liver injury to the modulation of cell signaling and response. Ali S, Mann DA, Friedman SL, eds. Liver Diseases: Biochemical Mechanisms and New Therapeutic Insights Enfield, NH, USA: Science Publishers 2004:93-114

[5]. Salazar-Montes A, Ruiz-Corro L, López-Reyes A, Castrejón-Gómez E, Armendáriz-Borunda J. Potent antioxidant role of pirfenidone in experimental cirrhosis. Eur J Pharmacol. 2008;24:69-77

[6]. Seki E, Brenner DA. Recent advancement of molecular mechanisms of liver fibrosis. J Hepatobiliary Pancreat Sci. 2015

[7]. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2012;18:1028-1040

[8]. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824

[9]. Azuma A, Taguchi Y, Ogura T, Ebina M, Taniguchi H, Kondoh Y, Suga M, Takahashi H, Nakata K, Sato A, Kudoh S, Nukiwa T; Pirfenidone clinical study group in Japan. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. Respiratory Research. 2011;12:143

[10]. Cottin V. The role of pirfenidone in the treatment of idiopathic pulmonary fibrosis. Respiratory Research. 2013;14(Suppl 1):S5

[11]. Albera C, Ferrero C, Rindone E, Zanotto S, Rizza E. Where do we stand with IPF treatment?. Respiratory Research. 2013;14(Suppl 1):S7

[12]. Hisatomi K, Mukae H, Sakamoto N, Ishimatsu Y, Kakugawa T, Hara S, Fujita H, Nakamichi S, Oku H, Urata Y, Kubota H, Nagata K, Kohno S.Pirfenidone inhibits TGF-β1-induced over-expression of collagen type I and heat shock protein 47 in A549 cells. BMC Pulmonary Medicine.2012;12:24

[13]. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083-92

[14]. Taniguchi H, Kondoh Y, Ebina M, Azuma A, Ogura T, Taguchi Y, Suga M, Takahashi H, Nakata K, Sato A, Sugiyama Y, Kudoh S, Nukiwa T; Pirfenidone Clinical Study Group in Japan. The clinical significance of 5% change in vital capacity in patients with idiopathic pulmonary fibrosis: extended analysis of the pirfenidone trial. Respir Res. 2011;12:93

[15]. Loveman E, Copley VR, Colquitt J, Scott DA, Clegg A, Jones J, O'Reilly KM, Singh S, Bausewein C, Wells A. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. Health Technol Assess.2015;19(20):1-336

[16]. Kometani T, Okamoto T, Yoshida S, Yoshino I. Acute respiratory distress syndrome after pulmonary resection. Gen Thorac Cardiovasc Surg. 2013;61:504-12

[17]. Rafii R, Juarez MM, Albertson TE, Chan AL. A review of current and novel therapies for idiopathic pulmonary fibrosis. J Thorac Dis. 2013;5:48-73
[18]. Richeldi L, Yasothan U, Kirkpatrick P. Pirfenidone. Nature Reviews Drug Discovery. 2011;10:489-90
[19]. Couluris M. Treatment of idiopathic pulmonary fibrosis with losartan: a pilot project. Lung. 2012;190:523-527
[20]. Gan Y, Herzog EL, Gomer RH. Pirfenidone treatment of idiopathic pulmonary fibrosis. Therapeutics and Clinical Risk Management 2011.2014;7:39-47
[21]. FDA.gov: Silver Spring (MD). FDA News Release: FDA approves Esbriet to treat idiopathic pulmonary fibrosis. Revised 24 Mar 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418991.htm
[22]. Jiang C, Huang H, Liu J, Wang Y, Lu Z, Xu Z. Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials. PLoS One. 2012;7:47024
[23]. O'Brien K, Troendle J, Gochuico BR, Markello TC, Salas J, Cardona H, Yao J, Bernardini I, Hess R, Gahl WA. Pirfenidone for the treatment of Hermansky-Pudlak Syndrome pulmonary fibrosis. Mol Genet Metab. 2011;103:128-134
[24]. Thielen N, Huizing M, Krabbe JG, White JG, Jansen TJ, Merle PA, Gahl WA, Zweegman S. Hermansky-Pudlak syndrome: the importance of molecular subtyping. J Thromb Haemost. 2010;8:1643-1645
[25]. Zamani N. Pirfenidone; can it be a new horizon for the treatment of pulmonary fibrosis in mustard gas-intoxicated patients?. DARU Journal of Pharmaceutical Sciences. 2013;21:13
[26]. Clinica lTrials. gov: Bethesda (MD). Safety and to lerability of pirfenidone in patients with systemic sclerosis- related interstitial lung disease (SSc-ILD) (LOTUSS). Identifier: NCT01933334. Revised 2 Oct 2014. http://clinicaltrials.gov/ct2/show/ study/ NCT01933334