METROCHEM

A Report on Comparative Safety and Efficacy of Pirfenidone in the treatment of Idiopathic Pulmonary Fibrosis

Dr. Mohammad Younus Mohiuddin – Portfolio Management

Introduction

The interstitial lung diseases (ILDs) are a heterogeneous group of parenchymal lung diseases characterized by varying degrees of inflammation and fibrosis. Some of these may occur secondary to a known precipitant such as drugs, autoimmune connective tissue disease, hypersensitivity to inhaled organic antigens, or sarcoidosis, whilst others, the idiopathic interstitial pneumonias (IIPs), have no identifiable cause[1]. Idiopathic pulmonary fibrosis (IPF) is one of the most aggressive forms of IIP, characterized by chronic, progressive fibrosis associated with inexorable decline in lung function, progressive respiratory failure, and high mortality. Accurate diagnosis is essential to help with prognostication and optimize treatment selection.

IPF is the most common form of ILD. Reported incidence rates for IPF vary considerably depending on the method of data collection and diagnostic case definition. A systematic review of the global incidence of IPF estimated a rate of 2.8–9.3 per 100,000 per year in North America and Europe with significantly lower rates in Asia and South America. Regional variation within countries has also been observed, possibly reflecting exposure to environmental or occupational risk factors[2-6]. Evidence suggests that the incidence of IPF is rising[7]. A recent analysis of a UK-based primary care data-base calculated a rise in incidence of 78% between 2000 and 2012, as well as a doubling of prevalence, estimated at 38.8 per 100,000[5], with the consequential growing economic burden on global health care[8].

Mortality in IPF is high, with a reported median survival of 2–3 years from diagnosis, based on historical data[9]. More recent evidence shows no improvement in survival[3, 5, 10]. Mortality rates also appear to be rising, although this may partly reflect increased recognition and diagnosis[2, 11, 12]. Over the last five years, antifibrotic therapies have become increasingly available, and at present the global impact of this on survival in IPF is unclear. Early evidence from an open label extension of the Pirfenidone clinical trials reported an on-treatment median survival of 77.2 months[13]. It is well recognized that IPF is a heterogeneous disease with a variable disease course[14]. Predicting disease outcomes is difficult, particularly as baseline lung function alone is a poor predictor of mortality[15].

Pirfenidone, an orally administered pyridine, demonstrated combined anti-inflammatory, anti-oxidant and anti-fibrotic actions both in vitro and in animal models of pulmonary fibrosis, consisting in the regulation of the expression of TGF-β and inhibition of fibroblast and collagen synthesis. However, the precise mechanism of action remains unknown.

Four placebo-controlled randomized trials explored and confirmed the beneficial effect of Pirfenidone in IPF patients[16-18]. The results of a pre-specified pooled data analysis incorporating data from the phase 3 trials supported the efficacy of Pirfenidone towards the reduction of overall and IPF-related mortality, although rates of death did not differ significantly in the individual prospective trials. Overall, the use of Pirfenidone in the reported studies was associated with adverse events of generally mild to moderate intensity, such as gastrointestinal symptoms (nausea, dyspepsia), raised liver function tests and photosensitivity. The favorable safety profile and good tolerability of Pirfenidone have been confirmed by post-authorization data provided by recent interim reports from international open-label extension studies[19, 20]. Findings from several single-center European and Japanese studies have also contributed to confirm long-term tolerability and also efficacy, sometime showing a trend toward stabilization of the disease in a significant proportion of treated patients[21-24].

Nintedanib is a multiple inhibitor of tyrosine kinase receptors implicated in lung fibrosis pathogenesis, including PDGF receptors α and β, VEGF receptors 1, 2 and 3, and FGF receptors 1, 2 and 3[25], which was shown to prevent the development of lung fibrosis in the bleomycin murine model[26]. Nintedanib at a dose of 150 mg given twice daily showed efficacy in reducing in the rate of functional loss in phase 2 an 3 trials[27],prompting the approval of the drug for use in patients with mild-to-moderate IPF. Gastrointestinal side effects (diarrhea, nausea were the most common side effects in the treated groups.

Evidence from real-life experiences of Nintedanib use is very limited. Data from a German multicenter study on the compassionate use program of Nintedanib in IPF reported that after 6 months from the start of treatment with Nintedanib most patients reached clinical and functional stability, including a subgroup of patients who had progressed under previous treatment with Pirfenidone[28].

Pharmacokinetic data

Innovator	InterMune/Roche Pharmaceuticals
Regulatory Approval	USFDA – 2014, CDSCO - 2010
Patent Information (Orange Book)	Last Patent expiring in 2033, ODE expiring in 2021
Pregnancy Category	C
Dose & Dosage form	Tablet – 267mg, 801mg, Capsule – 267mg
ROA	Oral
Approved Indications	Indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)
Indications under trial	Phase III: Interstitial lung diseases Phase II: Acute lung injury; Graft-versus-host disease; Heart failure; Lung transplant rejection; Pulmonary fibrosis Phase I: Diabetic nephropathies
Bioavailability	Not determined
Time to peak	30mins – 4 hours
Protein binding	58%
Metabolism	CYP1A2 (Major)
Elimination T½	3 hours
Excretion	Urine

Comparison of Safety[22, 25]

Parameter	Pirfenidone	Nintedanib
Adverse Effects	Nausea – 36%, Rash – 30%, URTI – 27%, Diarrhea, Fatigue – 26%, Abdominal pain – 24%, Headache – 22%, Dyspepsia – 19%, Dizziness – 18%, Vomiting, Anorexia – 13%, GERD, Sinusitis – 11%, Insomnia, Decreased weight, Arthralgia – 10%, Photosensitivity reaction – 9%, Pruritus – 8%, Dysgeusia – 6%, Chest pain – 5%	Diarrhea – 62%, Nausea – 24%, Abdominal pain – 15%, Liver enzyme elevation – 14%, Vomiting – 12%, Decreased appetite – 11%, Decreased weight – 10%, Headache – 8%, Hypertension – 5%
Precautions	Caution must be exerted to be used in patients with any degree of hepatic or renal impairment.	Dosage adjustment is recommended in patients with mild hepatic impairment. Not needed in mild-moderate renal impairment.

Comparison of Efficacy[22, 25]

Outcome	Pirfenidone	Nintedanib
≥ 0% decline in FVC from Baseline at week 52	77%	70%
≥ 10% decline in FVC from Baseline at week 52	17%	29%

Conclusions

- Pirfenidone (by InterMune/Roche Pharmaceuticals) demonstrated combined anti-inflammatory, anti-oxidant and anti-fibrotic actions in Pulmonary Fibrosis, consisting in the regulation of the expression of TGF-β and inhibition of fibroblast and collagen synthesis.
- Until recently before the arrival of Pirfenidone and Nintedanib, there was only symptomatic therapy and no substantial therapy existed for Pulmonary Fibrosis.
- Upon head to head comparison of data yielded from individual clinical trials of both the drugs, Pirfenidone was found to be a little more efficacious than Nintedanib.
- Safety wise, the adverse effects reported in Nintedanib group were less than that of Pirfenidone group. Also, Nintedanib was a safer option in patients with hepatic or renal impairment.
- All in all, it can be concluded that, Pirfenidone was greater in terms of efficacy, while Nintedanib was good in terms of safety. However, as Pulmonary Fibrosis is an end stage disease, drug selection can be made solely by the clinician on case to case basis with due consideration given to the quality of life of the patient.

References

1. American Thoracic Society Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS) Am. J. Respir. Crit. Care Med. 2000;161:646–664. doi: 10.1164/ajrccm.161.2.ats3-00.
2. Navaratnam V., Fleming K.M., West J., Smith C.J., Jenkins R.G., Fogarty A., Hubbard R.B. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66:462–467. doi: 10.1136/thx.2010.148031.
3. Raghu G., Chen S.Y., Yeh W.S., Maroni B., Li Q., Lee Y.C., Collard H.R. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: Incidence, prevalence, and survival, 2001–11. Lancet Respir. Med. 2014;2:566–572. doi: 10.1016/S2213-2600(14)70101-8.
4. Hopkins R.B., Burke N., Fell C., Dion G., Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur. Respir. J. 2016;48:187–195. doi: 10.1183/13993003.01504-2015.
5. Strongman H., Kausar I., Maher T.M. Incidence, Prevalence, and Survival of Patients with Idiopathic Pulmonary Fibrosis in the UK. Adv. Ther. 2018;35:724–736. doi: 10.1007/s12325-018-0693-1.
6. Gribbin J., Hubbard R.B., le Jeune I., Smith C.J., West J., Tata L.J. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61:980–985. doi: 10.1136/thx.2006.062836.
7. Hutchinson J., Fogarty A., Hubbard R., McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: A systematic review. Eur. Respir. J. 2015;46:795–806. doi: 10.1183/09031936.00185114.
8. Diamantopoulos A., Wright E., Vlahopoulou K., Cornic L., Schoof N., Maher T.M. The Burden of Illness of Idiopathic Pulmonary Fibrosis: A Comprehensive Evidence Review. Pharmacoeconomics. 2018 doi: 10.1007/s40273-018-0631-8.
9. Raghu G., Collard H.R., Egan J.J., Martinez F.J., Behr J., Brown K.K., Colby T.V., Cordier J.F., Flaherty K.R., Lasky J.A., et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011;183:788–824. doi: 10.1164/rccm.2009-040GL.

10. Kaunisto J., Kelloniemi K., Sutinen E., Hodgson U., Piilonen A., Kaarteenaho R., Makitaro R., Purokivi M., Lappi-Blanco E., Saarelainen S., et al. Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis. BMC Pulm. Med. 2015;15:92. doi: 10.1186/s12890-015-0074-3.
11. Marshall D.C., Salciccioli J.D., Shea B.S., Akuthota P. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: An observational study of the WHO mortality database from 2001–2013. Eur. Respir. J. 2018;51 doi: 10.1183/13993003.01603-2017.
12. Algranti E., Saito C.A., Silva D., Carneiro A.P.S., Bussacos M.A. Mortality from idiopathic pulmonary fibrosis: A temporal trend analysis in Brazil, 1979–2014. J. Bras. Pneumol. 2017;43:445–450. doi: 10.1590/s1806-37562017000000035.
13. Costabel U., Albera C., Lancaster L.H., Lin C.Y., Hormel P., Hulter H.N., Noble P.W. An Open-Label Study of the Long-Term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (RECAP) Respiration. 2017;94:408–415. doi: 10.1159/000479976.
14. Ley B., Collard H.R., King T.E., Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 2011;183:431–440. doi: 10.1164/rccm.201006-0894CI.
15. King T.E., Jr., Tooze J.A., Schwarz M.I., Brown K.R., Cherniack R.M. Predicting survival in idiopathic pulmonary fibrosis: Scoring system and survival model. Am. J. Respir. Crit. Care Med. 2001;164:1171–1181. doi: 10.1164/ajrccm.164.7.2003140.
16. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–1047. doi: 10.1164/rccm.200404-571OC.
17. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–1769. doi: 10.1016/S0140-6736(11)60405-4.

18. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:821–829. doi: 10.1183/09031936.00005209.
19. Costabel U, Albera C, Bradford WZ, Hormel P, King TE, Noble PW, et al. Analysis of lung function and survival in RECAP: an open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffus Lung Dis. 2014;31:198–205.
20. Maher T, Cottin V, Skoeld M, Tomassetti S, Azuma A, Giot C, et al. S11 Pirfenidone post-authorisation safety registry (passport)-interim analysis of Ipf treatment. Thorax. 2014;69:A8–A9. doi: 10.1136/thoraxjnl-2014-206260.17.
21. Bonella F, Wessendorf TE, Costabel U. Klinische Erfahrungen mit Pirfenidon in der Therapie der idiopathischen Lungenfibrose. Dtsch Med Wochenschr. 2013;138:518–523. doi: 10.1055/s-0032-1332930.
22. Loeh B, Drakopanagiotakis F, Bandelli GP, Von Don Beck D, Tello S, Cordani E, et al. Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015;191:110–113. doi: 10.1164/rccm.201406-1106LE.
23. Okuda R, Hagiwara E, Baba T, Kitamura H, Kato T, Ogura T. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. Respir Med. 2013;107:1431–1437. doi: 10.1016/j.rmed.2013.06.011.
24. Oltmanns U, Kahn N, Palmowski K, Träger A, Wenz H, Heussel CP, et al. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a german tertiary referral center for interstitial lung diseases. Respiration. 2014;88:199–207. doi: 10.1159/000363064.
25. Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008;68:4774–4782. doi: 10.1158/0008-5472.CAN-07-6307.
26. Chaudhary NI, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J. 2007;29:976–985. doi: 10.1183/09031936.00152106.

27. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine Kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–1087. doi: 10.1056/NEJMoa1103690.
28. Bonella F, Kreuter M, Hagmeyer L, Neurohr C, Keller C, Kohlhaeufl MJ, et al. Insights from the German compassionate use program of Nintedanib for the treatment of idiopathic pulmonary fibrosis. Respiration. 2016;92:98–106. doi: 10.1159/000448288.
29. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. BRAND ESBRIET (pirfenidone). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022535s000lbl.pdf.
30. Adis Insight. Pirfenidone - Roche. Available online: https://adisinsight.springer.com/drugs/800007688.
31. USFDA. ORANGE BOOK. Available online: https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022535&Appl_type=N.
32. Drugs@CDSCO. Available online: https://cdscoonline.gov.in/CDSCO/Drugs.
33. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. BRAND OFEV (nintedanib). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205832s000lbl.pdf.