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Pirfenidone

Updated: July 31, 2015.

OVERVIEW

Introduction

Pirfenidone is an orally available pyridinone derivative that inhibits collagen formation and is used to treat idiopathic pulmonary fibrosis. Elevations in serum enzyme levels during pirfenidone therapy are not uncommon, but it has yet to be implicated in cases of clinically apparent liver injury with jaundice.

Background

Pirfenidone (pir fen' i done) is an orally available, antiinflammatory and antifibrotic agent that is used to treat idiopathic pulmonary fibrosis. It is a small molecular weight phenyl substituted pyridinone that has antifibrotic activity both in vitro and in vivo. In animal models, pirfenidone decreases fibroblast proliferation and reduces transforming growth factor-beta (TGF-β) synthesis and activation of fibrogenic pathways. In several prospective, placebo controlled trials, pirfenidone was found to reduce the progression of fibrosis and worsening of lung function in patients with idiopathic pulmonary fibrosis. Pirfenidone was approved for use in the United States in 2014, but has been available in other countries for much longer. It is available as capsules of 267 mg under the brand name Esbriet. The typical initial dose in adults is one capsule (267 mg) orally three times daily, which can be increased to 3 capsules three times daily based upon tolerance. Side effects are not uncommon, but are generally mild and can include photosensitivity, rash and gastrointestinal upset with nausea, diarrhea, dyspepsia, reflux and abdominal pain.

Hepatotoxicity

In large randomized controlled trials, serum aminotransferase elevations more than 3 times the upper limit of normal (ULN) occurred in 4% of pirfenidone- compared to less than 1% of placebo-treated patients. The elevations were generally asymptomatic and short lived, resolving with or without dose modification and requiring drug discontinuation in approximately 1% of patients. Despite the frequency of serum enzyme elevations during therapy, clinically apparent liver injury was not reported in preregistration studies. Furthermore, since the general availability of pirfenidone in the United States and during years of clinical use elsewhere, it has not been linked to clinically significant liver injury in the published literature and no mention of jaundice or hepatitis occurs in the product label. Thus, pirfenidone has yet to be shown to cause clinically apparent liver injury but is, nevertheless, likely to be hepatotoxic, although clinically significant injury may be avoided by careful monitoring and early discontinuation for significant serum enzyme elevations before the onset of jaundice.

Mechanism of Injury

The mechanism by which pirfenidone might cause liver injury is not known. It is metabolized in the liver largely via the cytochrome P450 system, predominantly CYP 1A2, and liver injury may be due to production of a toxic or immunogenic metabolite. Pirfenidone is also susceptible to drug-drug interactions with strong inducers or inhibitors of CYP 1A2 (such as fluvoxamine).

Outcome and Management

While chronic therapy with pirfenidone can be associated with mild-to-moderate serum aminotransferase elevations, it has not been convincingly linked to cases of clinically apparent liver injury. Nevertheless, monitoring of serum aminotransferase levels monthly during the first 6 months and every 3 months thereafter is recommended. Patients who develop aminotransferase elevations on therapy should be monitored more carefully, and pirfenidone should be permanently discontinued if jaundice or symptoms of liver injury arise or if serum ALT or AST levels rise above 5 times the ULN.

Drug Class: Pulmonary Fibrosis Agents

Other Drugs in the Class: Nintedanib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pirfenidone – Esbriet®

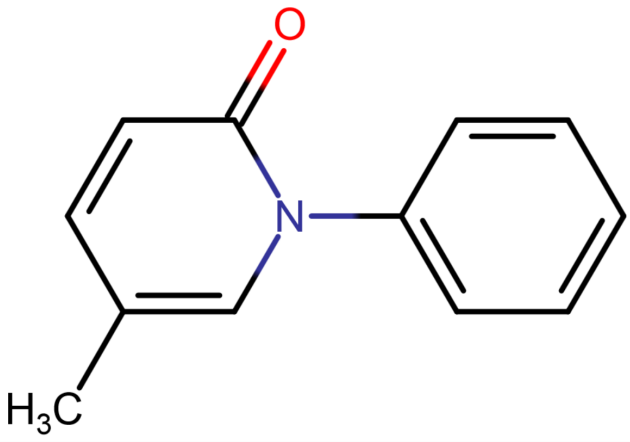
DRUG CLASS

Pulmonary Fibrosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pirfenidone	53179-13-8	C12-H11-N-O	

ANNOTATED BIBLIOGRAPHY

References updated: 31 July 2015

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013; does not discuss pirfenidone).

Angulo P, MacCarty RL, Sylvestre PB, Jorgensen RA, Wiesner RH, LaRusso NA, Lindor KD. Pirfenidone in the treatment of primary sclerosing cholangitis. Dig Dis Sci 2002; 47: 157-61. PubMed PMID: 11837718.

(Among 24 patients with primary sclerosing cholangitis treated with pirfenidone [2400 mg daily] for 1 year, AST and Alk P levels, histology and cholangiography findings did not change significantly, while adverse events were frequent and 1 patient had worsening of liver disease after 6 months of therapy leading to referral for liver transplantation).

Gahl WA, Brantly M, Troendle J, Avila NA, Padua A, Montalvo C, Cardona H, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab 2002; 76: 234-42. PubMed PMID: 12126938.

(Among 21 adults with Hermansky-Pudlak syndrome and progressive pulmonary fibrosis treated with pirfenidone or placebo for up to 3 years, serum ALT levels did not change and there were no serious hepatic adverse events).

Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171: 1040-7. PubMed PMID: 15665326.

(Among 107 patients with idiopathic pulmonary fibrosis treated with pirfenidone or placebo for 6 months, one patient discontinued therapy because of abnormal liver tests and one developed a liver cancer, both of whom were on pirfenidone).

Armendáriz-Borunda J, Islas-Carbajal MC, Meza-García E, Rincón AR, Lucano S, Sandoval AS, Salazar A, et al. A pilot study in patients with established advanced liver fibrosis using pirfenidone. Gut 2006; 55: 1663-5. PubMed PMID: 17047115.

(Among 15 patients with chronic hepatitis C treated with pirfenidone for 12 months [1200 mg daily], ALT levels declined and paired liver biopsies showed improvements in fibrosis scores in 5 and stable scores in 10 patients).

Rockey DC. Current and future anti-fibrotic therapies for chronic liver disease. Clin Liver Dis 2008; 12: 939-62. PubMed PMID: 18984475.

(Review of the pathogenesis and cellular pathways of fibrosis in patients with chronic liver disease, and the status of antifibrotic agents, none of which have been shown to be effective in treating or preventing hepatic fibrosis).

Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, et al.; Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821-9. PubMed PMID: 19996196.

(Among 275 patients with idiopathic pulmonary fibrosis treated with pirfenidone [1200 or 1800 mg daily] or placebo for 12 months, the decline in lung vital capacity was less with pirfenidone [-0.08 and -0.09] than placebo [-0.16]; photosensitivity occurred in 51-52% on pirfenidone and GGT elevations in 22-23%; no mention of clinically apparent liver injury).

O'Brien K, Troendle J, Gochuico BR, Markello TC, Salas J, Cardona H, Yao J, et al. Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. Mol Genet Metab 2011; 103: 128-34. PubMed PMID: 21420888.

(Among 35 patients with Hermansky-Pudlak syndrome and pulmonary fibrosis who were treated with pirfenidone [n=23] or placebo [n-12] for 1-3 years, mean serum ALT levels did not change and "there was no evidence of ... hepatic toxicity").

Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, et al.; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377 (9779): 1760-9. PubMed PMID: 21571362.

(Among 779 patients with pulmonary fibrosis treated in two studies with pirfenidone [1197 or 2403 mg daily] or placebo, side effects included nausea [36%], dyspepsia [19%], anorexia [11%], photosensitivity [12%], rash [32%] and ALT elevations above 3 times ULN [4% vs <1% in controls]).

Two new drugs for idiopathic pulmonary fibrosis. Med Lett Drugs Ther 2014; 56 (1457): 123-4. PubMed PMID: 25461229.

(Concise review of the mechanism of action, efficacy and safety of pirfenidone and nintedanib for idiopathic pulmonary fibrosis mentions that both agents can increase hepatic enzyme levels and dose adjustment may be required).

King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, et al.; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2083-92. PubMed PMID: 24836312.

(Among 555 patients with idiopathic pulmonary fibrosis treated with pirfenidone [2403 mg/day] or placebo for 52 weeks, pirfenidone led to a lower rate of disease progression, but a higher rate of adverse events including ALT elevations above 3 times ULN in 2.9% [vs 0.7% in placebo controls], but all elevations "were reversible and without clinically significant consequences").

Valeyre D, Albera C, Bradford WZ, Costabel U, King TE Jr, Leff JA, Noble PW, Sahn SA, et al. Comprehensive assessment of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis. Respirology 2014; 19: 740-7. PubMed PMID: 24836849.

(Among 789 patients with idiopathic pulmonary fibrosis being monitored for safety for an average of 2.6 years, elevated ALT or AST values [above 3 times ULN] occurred in 2.7% on pirfenidone, but none developed clinically apparent liver injury, although 1% required drug discontinuation for the enzyme elevations).

Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment of idiopathic pulmonary fibrosis. Eur Respir Rev 2015; 24: 58-64. PubMed PMID: 25726556.

(Analysis of long term, postmarketing monitoring of pirfenidone therapy of idiopathic pulmonary fibrosis focused on the frequency of common adverse events, including nausea [32%], diarrhea [19%], photosensitivity [9%] and rash [26%]).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to pirfenidone or other agents for pulmonary fibrosis).