

Challenges in treating liver fibrosis

Jorge L. Poo,* Linda E. Muñoz**

* Pharmacology Unit, Instituto Tecnológico de Estudios Superiores de Monterrey, Campus Ciudad de México. México.

** Liver Unit. Departamento de Medicina Interna. Hospital Universitario "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, México.

To the editor:

Once considered irreversible, there are well-documented cases of reversibility of liver cirrhosis,¹ which has stimulated evaluation of antifibrotic drugs such as pirfenidone.²

Recently, the European Medicine Agency granted authorization to commercialize pirfenidone for patients with idiopathic pulmonary fibrosis (IPF) based on evidence confirming its safety and efficacy.³ Long term pirfenidone administration (2,400 mg/day) has been evaluated in 789 patients with IPF. Median duration of exposure was 2.6 years (1 week-7.7 years). Adverse events tended to occur early, were almost always mild to moderate in severity, and rarely led to treatment discontinuation.³ In the Mexican market, a 600 mg, slow release formulation is available to reduce adverse events. Clinical trials are underway to continue evaluating this promising drug in liver disease.

There are many challenges to consider. Histopathological changes seen in cirrhosis include complex modifications in hepatocyte patterns, bile duct proliferation, stellate-cell transformation, and complex microcirculation and lymphatic abnormalities, all contributing to decreased liver function, increased intrahepatic resistance and portal hypertension. Vascular changes are also present in the splanchnic organs, heart, lungs, kidney, brain, and skin. Complete resolution of all abnormalities may require long duration treatments.

Various etiologies of liver disease should be considered, including nonalcoholic fatty liver disease (NAFLD), given its high prevalence and increasing incidence. Prior to randomized clinical trials in cirrhotic patients, a trial evaluating pirfenidone's pharmacokinetics in cirrhotics is desirable.⁴ Pirfenidone Tmax, Cmax, AUC and median half-life also should be addressed.

Control of inducers of liver damage, such as alcohol and caloric intake is necessary when evaluating therapies for NAFLD/ALD along with the wide spectrum of liver damage. Of note, pan-genotypic direct-acting antiviral drugs and host-targeted agents may, themselves, resolve fibrosis in hepatitis C patients.

Additional challenges include:

- Methods of monitoring hepatic fibrosis.
- Length of therapy.
- End-points (considering only fibrosis reduction or other clinical, biochemical, endoscopic or hemodynamic data).
- Design (double blind with random allocation is desirable).
- Active comparator medication (placebo use is recommended with appropriate standard of care to warrant official IRB approval and adherence to good clinical practices).

As always, clinicians must weigh the risks and benefits in responding to the needs of individual patients. Pirfenidone has shown a favorable benefit risk profile in IPF and promising evidence of efficacy in liver disease¹ to make it particularly deserving of additional carefully conducted research.

REFERENCES

1. Flores-Contreras L, Sandoval-Rodríguez A, Mena-Enríquez M, Lucano-Landeros S, Arellano-Olivera I, Alvarez-Alvarez A, Sánchez-Parada G, et al. Treatment with

Correspondence and reprint request: Jorge L. Poo, M.D.
Pharmacology Unit, Instituto Tecnológico de Estudios Superiores de Monterrey, Campus Ciudad de México. México.
E-mail: jpoo@itesm.mx; consultorio.jpoo@gmail.com

*Manuscript received: March 05, 2014.
Manuscript accepted: August 25, 2014.*

- pirfenidone for two years decreases fibrosis, cytokine levels and enhances CB2 gene expression in patients with chronic hepatitis C. *BMC Gastroenterology* 2014; 14: 131-41.
2. Schuppan D, Kim YO. Evolving therapies for liver fibrosis. *The Journal of Clinical Investigation* 2013; 123: 1887-901.
 3. Xaubet A, Serrano-Mollar A, Ancochea J. Pirfenidone for the treatment of idiopathic pulmonary fibrosis. *Expert opinion on pharmacotherapy* 2014: 1-7.
 4. Valeyre D, Albera C, Bradford WZ, Costabel U, King TE Jr, Leff JA, Noble PW, et al. Comprehensive assessment of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis. *Respirology* 2014; 19: 740-7.