Commentary: Antifibrotic agents in the postoperative period: Friends or foes?

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Pirfenidone is a Food and Drug Administration–approved drug for idiopathic pulmonary fibrosis (IPF) and can delay the progression of lung disease over time. The underlying mechanism of pirfenidone is not completely understood, but it displays both anti-inflammatory and antifibrotic effects.¹ Thus, pirfenidone's mechanism of action has been postulated to involve the inhibition of production and activation of transforming growth factor (TGF)- β . Amelioration of TGF- β is thought to inhibit collagen deposition and fibrosis. However, recent data in both animals and humans demonstrate clinically important anti-inflammatory effects of pirfenidone as well, including the decrease in acute exacerbations of IPF, as outlined in the accompanying article in this issue of the *Journal*.^{2,3}

IPF is the leading indication for lung transplantation in the United States. With the development and clinical use of 2 Food and Drug Administration–approved antifibrotic agents, pirfenidone and nintedanib, the pretransplant management of IPF has changed dramatically. Little is known about the antifibrotic effects of these drugs in the immediate postoperative period. Saito and colleagues,² from Kyoto University in Japan, key in on the anti-inflammatory effects of pirfenidone using an acute lung transplantation rat model. They hypothesize that pirfenidone may offer a unique preventative treatment option for ischemia–reperfusion injury (IRI) and primary graft dysfunction (PGD).² Because PGD is the leading cause of early post-lung transplant mortality and increases the risk of chronic allograft dysfunction in lung transplant recipients, any methods to ameliorate this condition would be a welcome addition to current perioperative management.⁴ In their novel article, Saito and colleagues² clearly show promising results in an IRI model treated with pirfenidone, including an increase in lung compliance, a decrease in the mean airway pressures, an improvement in oxygenation, and a

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Central Message

Despite the canonical dogma that antifibrotic agents are contraindicated after lung transplantation, their use may have clinical benefits for PGD in the absence of detrimental wound healing problems.

See Article page 289.

decrease in lung edema. They also demonstrate an improvement in other parameters of lung injury, including perivascular edema and neutrophil infiltration.²

Although it is clear that TGF- β is a profibrogenic cytokine, with the deleterious side effect of pulmonary fibrosis, it also plays a major role in wound healing.⁵ Thus, its inhibition in the perioperative period is a topic of major controversy. Sternal wound and airway complications, including anastomotic dehiscence, have been reported in up to 35% of patients after lung transplantation resulting in serious morbidity as well as death.⁶ For these reasons, the standard surgical dogma has been to hold antifibrotic agents at the time of listing to prevent such complications. This assumption was primarily based on the mechanistic understanding of pirfenidone's and nintedanib's mechanism of action but not on data-driven clinical science. In the past several years, small retrospective reports have been published arguing against such theoretic complications of the antifibrotic agents continued in the perioperative period. Delanote and colleagues,⁷ from the University Hospitals Leuven, Belgium, reported on 7 patients treated with pirfenidone at the time of transplantation and describe a 43% incidence of airway anastomotic complications. However complications were minor and occurred at a delayed time point in the perioperative course.⁷ Additionally, there

were no differences in the incidence of airway complications compared with historical controls. Leuschner and colleagues,⁸ from the University of Munich, Germany, evaluated 23 patients treated with pirfenidone, along with 7 patients on nintedanib, at the time of transplantation compared with 32 control patients. Approximately one third of patients required postoperative intervention for bleeding or impaired wound healing, but there were no differences in complications between the experimental and control groups. There were also no differences in bronchial anastomotic complication rate between the 2 groups.⁸ Finally, Mortensen and colleagues⁶ described 18 patients prescribed pirfenidone before lung transplantation, with 13 taking the medicine up until the time of transplant. Only 1 of the patients developed a sternal wound complication, thought not to be related to pirfenidone, and there were no reported airway complications.⁶ Cumulatively, such retrospective evidence suggests that pirfenidone may not truly interfere with wound or airway healing post-transplant.

Saito and colleagues' experimental data² definitely open the door to the idea of using pirfenidone for its anti-inflammatory effects on IRI and PGD. Because the half-life of the drug is only 3 hours, it could be inferred that cessation of the drug after organ reperfusion or in the immediate postoperative period might be used to ameliorate IRI without any interference in the wound healing response. It

is also exciting to have experimental evidence that pirfenidone may play a role in the post-transplant population, both in the acute and chronic phases of disease, as mentioned by the review of the literature in the "Discussion" section of Saito and colleagues' article.² However, without rigorous prospective trials, the question still remains whether antifibrotic agents in the post-transplantation period are friends or foes?

References

1. Cho ME, Kopp JB. Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. *Expert Opin Investig Drugs*. 2010;19:275-83.
2. Saito M, Chen-Yoshikawa TF, Suetsugu K, Okabe R, Takahagi A, Masuda S, et al. Pirfenidone alleviates lung ischemia-reperfusion injury in a rat model. *J Thorac Cardiovasc Surg*. 2019;158:289-96.
3. 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;171:1040-7.
4. Lee JC, Christie JD. Primary graft dysfunction. *Proc Am Thorac Soc*. 2009;6:39-46.
5. Finnson KW, McLean S, Di Guglielmo GM, Philip A. Dynamics of transforming growth factor beta signaling in wound healing and scarring. *Adv Wound Care*. 2013;2:195-214.
6. Mortensen A, Cherrier L, Walia R. Effect of pirfenidone on wound healing in lung transplant patients. *Multidiscip Respir Med*. 2018;13:16.
7. Delanote I, Wuyts WA, Yserbyt J, Verbeken EK, Verleden GM, Vos R. Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series. *BMC Pulm Med*. 2016;16:156.
8. Leuschner G, Stocker F, Veit T, Kneidinger N, Winter H, Schramm R, et al. Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy. *J Heart Lung Transplant*. 2017 [Epub ahead of print].