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Prevention of bronchiolitis obliterans—the realization of a hope?

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Bronchiolitis obliterans is a small airway disease triggered by injury of small airway epithelial cells and sub-epithelial structures, followed by an abnormal healing response with excessive fibrosis that constricts the airways.¹ Bronchiolitis obliterans is a frequent and disabling complication after lung transplantation, occurring in >50% of lung transplant recipients within 5 years of the transplant.² Current treatments are only partially effective and include increasing immunosuppression and administering low-dose macrolide antibiotics, leukotriene-receptor antagonists and combinations of inhaled bronchodilators and glucocorticoids.¹ Because of the multiplicity of mechanisms causing the initial lesion to the epithelial surfaces of the bronchi, involving both innate and adaptive immunity responding either to allo-antigens or infectious/toxic insults,¹ prevention of the initial lesions may not be possible or feasible in time to prevent the fibrotic response. Thus, bronchiolitis obliterans remains a major cause of graft failure.²

In this issue, Watanabe et al² report that imatinib, a specific tyrosine kinase inhibitor, prevents obstruction of the airways in the heterotopic tracheal transplantation animal model of bronchiolitis obliterans. The anti-fibrotic properties of imatinib, were first described by Daniels et al³ and Aono et al⁴ more than 10 years ago. These investigators showed that imatinib decreased fibrosis and fibroblast proliferation through inhibition of platelet-derived growth factor tyrosine kinase and transforming growth factor-beta. A year later, Majhail et al⁵ showed that administration of imatinib ameliorated bronchiolitis obliterans in a patient with chronic myeloid leukemia relapse after hematopoietic stem cell transplantation.

More recently, realizing the potential of imatinib to improve the clinical manifestations of bronchiolitis obliterans, Watanabe et al⁶ reported imatinib's efficacy in 2 subjects in preventing progression, and to some extent reversing, bronchiolitis obliterans after hematopoietic stem cell transplantation. With their report in this issue of *JHLT*,² the authors begin to address how imatinib may prevent fibrosis in the context of transplantation. They show how imatinib prevents fibrosis by 2 mechanisms. In one, imatinib blocks migration of blood-derived fibrocytes owing to blockade of the platelet-derived growth factor (PDGF)/PDGF receptor pathway and, in another, imatinib inhibits differentiation of monocytes into fibrocytes. Because differentiation of fibrocytes is thought to occur in the grafted tissue, the

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authors suspect that migration of fibrocytes may not be as important to pathology as inhibition of fibrocyte differentiation. Bronchiolitis obliterans after human lung transplantation develops in chronic rather than in acute fashion. The model studied by the authors only allows examination of acute pathology. We hope that the promise of tyrosine kinase inhibition for the treatment/prevention of bronchiolitis obliterans will inspire further research to address the efficacy to treat the chronic form of the disease this condition. The findings by Watanabe and colleagues⁶ support a role for tyrosine kinase inhibition in the prevention of bronchiolitis obliterans in those at risk.

References

1. Barker AF, Bergeron A, Rom WN, et al. Obliterative bronchiolitis. *N Engl J Med*. 2014; 370:1820–8. [PubMed: 24806161]
2. WatanabeS, , KasaharaK, , WasedaY. , et al. [Accessed September 7, 2016] Imatinib ameliorates bronchiolitis obliterans via inhibition of fibrocyte migration and differentiation. [e-pub ahead of print]. *J Heart Lung Transplant*2016
3. Daniels CE, Wilkes MC, Edens M, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest*. 2004; 114:1308–16. [PubMed: 15520863]
4. Aono Y, Nishioka Y, Inayama M, et al. Imatinib as a novel antifibrotic agent in bleomycin-induced pulmonary fibrosis in mice. *Am J Respir Crit Care Med*. 2005; 171:1279–85. [PubMed: 15735062]
5. Majhail NS, Schiffer CA, Weisdorf DJ. Improvement of pulmonary function with imatinib mesylate in bronchiolitis obliterans following allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2006; 12:789–91. [PubMed: 16785069]
6. Watanabe S, Waseda Y, Kimura H, et al. Imatinib for bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2015; 50:1250–2. [PubMed: 26052911]