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Molecular Rescue in Pulmonary Arterial Hypertension

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In this issue of the *Journal*, Humbert et al.[1] report on a new approach to the treatment of pulmonary arterial hypertension, particularly the idiopathic and heritable forms of the disease. The treatment, which is given subcutaneously every 3 weeks, is a fusion protein that impairs activation of one limb of the proproliferative transforming growth factor β (TGF-β) pathways. Why would inactivation of a TGF-β pathway be an effective approach? The answer is in the genes. Approximately 70 to 80% of cases of heritable pulmonary arterial hypertension and roughly 20 to 30% of cases of idiopathic pulmonary arterial hypertension are consequences of impaired TGF-β function in the pathway that involves bone morphogenetic protein (BMP) receptor type 2 (*BMPR2*).[2] Mutation and impairment of *BMPR2* may lead to a permissive function in other proproliferative and proinflammatory TGF-β pathways that may result in pulmonary vascular occlusion and fibrosis.[3] Therefore, it has been inferred that unmutated *BMPR2* acts as a "brake" on these disease pathways and that mutated *BMPR2* is ineffective in blocking them. Why *BMPR2* is involved in fibrosis and occlusion of small pulmonary arterioles in addition to bone function remains a mystery.[2,4]

The discovery of dysfunction of BMPR-II signaling in patients with pulmonary arterial hypertension led to the hypothesis that the receptor signaling could be "rescued" pharmacologically or could be rebalanced by suppressing other sites in the large family of TGF-β ligands and receptors.[5] This hypothesis is consistent with the early observation that the wild-type allele of *BMPR2* is an important determinant of net BMPR-II function when a variant is present on the second allele.[6] Although attempts at rescue or rebalancing of BMPR-II signaling have had mixed success, such measures have therapeutic potential and deserve to be pursued.[2,7] Many biologic approaches are under study; these include microRNAs, ligand enhancement with BMP9, blocking antibodies, and others.[4,8]

What is the nature of the fusion protein sotatercept? Sotatercept was designed to bind and trap the TGF-β family ligand activin[9]; it consists of the extracellular domain of the human activin receptor type II A fused to the Fc domain of human IgG1. The activin receptor is involved in hereditary hemorrhagic telangiectasia, which has an infrequent but well-known association with pulmonary arterial hypertension. The activin receptor in the fusion protein binds extracellular activin and prevents it from activating the native cellular activin receptor, thus trapping it. The Fc region appears to be a stabilizing portion of the protein.[10]

Other biologic therapies such as adalimumab and etanercept are also Fc-linked fusion proteins.[10]

How effective was sotatercept in the treatment of pulmonary arterial hypertension in the trial by Humbert et al.? The trial involved patients with stable disease that was classified as World Health Organization functional class II or III. In total, 70% of the patients who received sotatercept had idiopathic or heritable disease, and 20% had pulmonary arterial hypertension associated with connective-tissue disease. Mutations in *BMPR2* rarely occur in patients with connective-tissue disease, but BMPR-II function may be impaired in these patients. Results from the trial are presented in the article as least-squares means, probably because of uneven recruitment at various sites, a point that was not raised in the article. The benefits of sotatercept treatment over placebo were a greater reduction in pulmonary vascular resistance (least-squares mean difference between the higher-dose [0.7 mg per kg of body weight] group and the placebo group, –239.5 $dyn \cdot sec \cdot cm^{-5}$, or approximately 3 Wood units); greater improvement in 6-minute walk distance (least-squares mean difference, 21.4 m), which can be considered weak improvement, although the patients' conditions were not clinically advanced; and a reduction in the N-terminal pro–B-type natriuretic peptide level (least-squares mean difference, –651 pg per milliliter). We are not told whether the use of diuretic agents was altered in any patients, but such treatment is a known modifier of N-terminal pro–B-type natriuretic peptide levels. Across the sotatercept 0.3-mg-per-kilogram and 0.7-mg-per-kilogram groups, 23% of the patients had improved clinical functioning. The least-squares mean (±SE) change from baseline in pulmonary artery pressure in the sotatercept groups was a decrease of 10.5±1.1 mm Hg with minimal change in wedge pressure; surprisingly, there was also minimal change in cardiac output. In most previous reports of effective drugs in the treatment of pulmonary arterial hypertension, small increases in cardiac output have been observed as a component of reduction in pulmonary vascular resistance. This finding implies that sotatercept has a direct effect on the pulmonary circulation. Somewhat surprisingly, systolic excursion of the tricuspid annular plane — a measure of right ventricular contractility — remained largely unchanged, which suggests that the patients had well-compensated pulmonary arterial hypertension at the time of enrollment. Future studies involving sicker patients are warranted to evaluate the broad efficacy of the drug.

Sotatercept is a first-in-class drug with excellent theoretical potential to rebalance the TGF-β system, and in a 24-week trial, it showed beneficial effects.[1] The results of the trial justify the need for longer trials and inclusion of sicker patients. Testing of other ligands and receptors in the large TGF-β family that might be involved in the development of pulmonary arterial hypertension may also be warranted. The adverse effects that were observed during the trial were manageable and largely predictable. An increase in hemoglobin levels in some patients was predictable on the basis of results from previous studies, given that TGF-β is involved in hematopoiesis.[8] Other potential long-term effects on inflammatory responses, wound healing, bone function, and right ventricular function must await longer trials. This is a propitious advance for this difficult and fatal disease.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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