September 2013 Pulmonary Journal Club: Riociguat; Pay the Doctor

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Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, Oudiz RJ, Boateng F, Scalise AV, Roessig L, Semigran MJ; Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation. 2013;128(5):502-11. [CrossRef] [PubMed]

Three articles appeared within the past month describing clinical trials with riociguat, a new therapy for pulmonary arterial hypertension (PAH). Riociguat is a soluble guanylate cyclase stimulator. Guanylate cyclase is the enzyme that is stimulated by nitric oxide which results in arterial smooth muscle relaxation. All three trials were phase 3, multicenter, randomized, placebo-controlled studies sponsored by Bayer, the manufacturer.

In the first trial, 261 patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were randomized to receive placebo or riociguat. The primary end point was the change from baseline to the end of week 16 in the distance walked in 6 minutes. Secondary end points included changes from baseline in pulmonary vascular resistance, N-terminal pro-brain natriuretic peptide (NT-proBNP) level, World Health Organization (WHO) functional class, time to clinical worsening, Borg dyspnea score, quality-of-life variables, and safety. By week 16, the 6-minute walk distance had increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group ($P<0.001$). Pulmonary vascular resistance, NT-proBNP level and WHO functional class significantly improved with riociguat.

In the second trial, 443 patients with symptomatic pulmonary arterial hypertension were randomized to received placebo or riociguat in individually adjusted doses of up to 2.5 mg three times daily. Patients who were receiving no other treatment for pulmonary arterial hypertension and patients who were

receiving endothelin-receptor antagonists or (nonintravenous) prostanoids were eligible. The primary endpoint and the secondary endpoints were the same as in the first trial and the results were also similar. Six minute walk, pulmonary vascular resistance, NT-proBNP level and WHO functional class all significantly improved with riociguat.

The third trial studied 201 patients with pulmonary hypertension caused by systolic left ventricular dysfunction. Currently, no treatment is approved for this indication. The primary outcome in this trial was not the 6 minute walk but the mean pulmonary artery pressure. Although there was a decrease in mean pulmonary artery pressure with riociguat, the difference was not significantly different compared to placebo (P=0.10). However, the secondary end points cardiac and stroke volume index, pulmonary vascular resistance and the Minnesota Living with Heart Failure score all significantly improved with riociguat.

In all three trials the drug was well tolerated and the side-effects were those expected which can result from systemic peripheral vasodilatation-syncope, lightheadedness, and peripheral edema.

An FDA panel of outside experts voted unanimously to approve riociguat for PAH as well as chronic pulmonary thromboembolic hypertension. The FDA seems likely accept the panel's recommendation. The drug will be sold as Adempas.

Although we have frequently warned about over-enthusiasm with the first publications on new therapies, the results with riociguat appear promising and realistic. However, it is unclear how this drug will fit into the ever expanding armamentarium of anti-PAH drugs. Will the drug be most effective when combined with other phosphodiesterase agonists such as sidenafil or tadalafil or combined with other drugs such as endothelin receptor antagonists such as bosentan?

Petersen LA, Simpson K, Pietz K, Urech TH, Hysong SJ, Profit J, Conrad DA, Dudley RA, Woodard LD. Effects of individual physician-level and practice-level financial incentives on hypertension care: a randomized trial. JAMA. 2013;310(10):1042-50. [CrossRef] [PubMed]

Pay for performance is intended to align incentives to promote high-quality care, but results have been contradictory. The authors randomized 83 Veterans Administration (VA) physicians and 42 nonphysician personnel (nurses, pharmacists, etc) to receive individual financial incentives, practice-level incentives, both, or none for adhering to guideline-recommended care. They found that the proportion of patients who had controlled hypertension or who (appropriately) had their treatment tweaked as a result of persistent hypertension increased in all of the groups where incentives were received, but not in the group without any financial incentives. The best-performing group, and the only group where the changes reached statistical significance, was the group

receiving individual pay-for-performance payments. In none of the groups did financial incentives improve use of guideline-recommended medications compared with controls. There was no increase in hypotension among patients treated in the course of the study, suggesting that overtreatment (in the hopes of more financial rewards) was not a problem. The performance gains among physicians during the pay-for-performance period of the study did not tend to last during a "washout" period when the payments were stopped.

This is a small study where the measures for the most part did not reach statistical significance. Despite these limitations, this is a welcome investigation. Pay-for-performance initiatives are part of the US Affordable Care Act. It is also heartening that the VA, which was one of the first organizations to do pay for performance back in the 1990's, is investigating the issue. The VA initiated a pay for performance model where incentives were paid to VA administrators, not physicians, for compliance with a number of chronic disease indicators (1). Although some of the indicators were evidence-based, the evidence supporting the three that improved the most (pneumococcal vaccination, advice to quit smoking and hospital discharge instructions) could generously be described as weak (2). This points to a danger to all pay-for-performance programs, i.e., who decides on the performance standards. If the performance standards are weak or non-evidence based, it is likely that pay-for-performance will not improve patient outcomes and are a waste of money. On the other hand, if the performance standards are supported by level 1 evidence (data from >1 properly randomized controlled trial) or better, pay-for-performance shows promise to improve patient care. This article suggests that paying physicians is the best way to improve performance.

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