Improving the Outcome of Childhood Pulmonary Arterial Hypertension

The Effect of Bosentan in the Setting of a Dedicated Pulmonary Hypertension Clinic*

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Pulmonary arterial hypertension during childhood is a heterogeneous disease that appears to have a genetic basis, and mutations involving bone morphogenetic protein receptor 2, activin receptor-like kinase 1, endoglin, and transforming growth factor beta receptors have been documented (1–4). However, the rationale that underlies the use of drugs to treat pulmonary vascular disease has resulted from observations that mediators of vasodilation and constriction, as well as platelet, endothelial, and smooth muscle cell activity, influence vascular remodeling. The L-arginine nitric oxide cyclic guanosine monophosphate and the prostacyclin cyclic adenosine monophosphate pathways are regarded as beneficial. They promote vasodilation, decrease platelet activation, and attenuate smooth muscle proliferation. The generally opposite and undesirable effects of endothelin and thromboxane counter these effects. Until recently, treatment with continuous intravenous prostacyclin was the only medical treatment for severe unreactive pulmonary hypertension. It is an extraordinarily challenging therapy for the family and child to embark upon, with painful side effects and serious complications. Newer drugs that can be administered orally or by inhalation have particular relevance to the treatment of small children. These therapies include aerosolized iloprost, inhaled nitric oxide, and sildenafil, as well as combination therapy.

Pulmonary arterial hypertension is a relentlessly progressive disease, and because inevitable patient attrition may obscure benefits of new therapies, most trials have focused on demonstrating functional benefit at 6 to 12 weeks. The long-term impact of therapy on disease is less secure, and attrition at one, three, and five years remains substantial (5). As a prelude to the current study, a 12-week open-label study of the pharmacokinetics of bosentan in children demonstrated that bosentan was safe, could be dosed appropriately, and resulted in generally beneficial effects in children over the short term (6). In this issue of the Journal, Rosenzweig et al. (7) have reported a retrospective review of the longer term effects of bosentan, an orally administered endothelin A and B receptor antagonist, in 86 children with heterogeneous pulmonary arterial hypertension. The primary end point of therapy was the change in World Health Organization (WHO) functional class. In patients treated with bosentan, WHO functional class improved in 46% and remained unchanged in 44%. In an inevitably progressive disease, like pulmonary arterial hypertension, unchanged WHO functional status suggests important prevention of deterioration. In 49 children, modest but significant hemodynamic improvement was demonstrated at serial cardiac catheterization. Figure 3 of Rosenzweig et al. (7) is the most telling and, at one year, of 32 patients treated with bosentan alone, 3% had died, 9% had discontinued bosentan, and 12% received additional therapy. Similarly, of 32 patients treated with prostanoids and bosentan, 3% died and 13% discontinued bosentan. At two years, there was an impressive survival of 91% for all causes of pulmonary arterial hypertension (with 88% survival for primary pulmonary arterial hypertension and 96% for secondary pulmonary arterial hypertension).

There is a dearth of information to guide the therapy of childhood disease, and the report by Rosenzweig et al. (7) is important, not only because it provides guidance on the use of a drug specifically in childhood disease, but also because it highlights the many difficulties faced by investigators of treatments for rare and chronic childhood illness. Although by definition the diagnosis of pulmonary arterial hypertension requires documentation of an elevated pulmonary artery pressure, it is clear that patients' symptoms and survival depend much more on right ventricular performance and the ability of the right ventricle to compensate for the increased afterload (8,9). However, cardiopulmonary testing with measurement of maximal oxygen consumption or tests of distance walked in 6 min are almost impossible to perform in children younger than five to seven years of age.

In addition, the results of such tests are more easily confounded in children and adolescents by the vagaries imposed by a change in routine. These include an early start to the day with a long journey to the clinic and inevitable interruption of eating and sleep schedules. Thus, Rosenzweig et al. (7) have chosen to follow a functional surrogate, described by the change in WHO class with therapy. This approach has merit because the final arbiter of therapy, from a patient's point of view, is not hemodynamic but improvement in lifestyle. However, the need is obvious for validated quality-of-life questionnaires and easily accomplished reproducible tests of functional ability or surrogates thereof that span the age from infancy to adolescence. Children

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compensate for disability remarkably, and often it is only with hindsight that even parents recognize the degree of limitation present before an intervention, such as, for example, correction of congenital heart disease.

There was no control group in this study. Therefore, other factors could have contributed to the improved outcomes. The care of children with pulmonary arterial hypertension is challenging. The study originates from two centers of excellence in childhood pulmonary hypertensive disease. At both centers, there is an organized approach to childhood pulmonary hypertensive diseases with a dedicated clinic composed of experienced and skillful physicians, nurses, technicians, and support staff with established lines of communication to patient and family support groups. Although the report by Rosenzweig et al. (7) focuses on the use of bosentan, the importance of the environment in which it was administered should not be diminished. Centers with few patients and insufficient resources to provide all the benefits of a dedicated pulmonary hypertension clinic for children will not reproduce the results reported by Rosenzweig et al. (7).

In summary, the report by Rosenzweig et al. (7) demonstrates the effect of bosentan when administered in the setting of a dedicated childhood pulmonary hypertension service. The place of bosentan in the treatment of childhood pulmonary hypertension, whether as single or combination therapy, awaits further investigation. However, it highlights also the need for better and more specific tools with which to assess the quality of life and functional outcome of interventions for childhood disease.

**REFERENCES**