The Pediatric Sildenafil Trial

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While we have long understood pulmonary arterial hypertension (PAH) to be a chronic disorder of the pulmonary vasculature that can lead to right heart failure and death if untreated, there are currently no therapies approved for children. Recommendations for treatment for children have been derived from evidence-based adult guidelines. However, limited data suggest benefits for children utilizing drugs approved for adults. This landmark study is the first randomized, double-blind, placebo-controlled trial of a PAH therapy in children.

The Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study was a 16-week, randomized, double-blind study of treatment-naïve children to evaluate the effects of oral sildenafil in pediatric PAH.[1] Children (n=234) with PAH (aged 1-17 years, >8 kg) received low-dose, medium-dose, or high-dose sildenafil (based on 3 body weight cohorts: >8 to ≤20 kg, 20 to 45 kg, and ≥45 kg) or placebo orally 3 times daily.

The primary comparison was percentage change in peak oxygen consumption (pVO_2), measured during cycle exercise testing for the 3 sildenafil doses combined from baseline to Week 16; exercise testing was performed only in children able to exercise reliably. Secondary endpoints, including mean pulmonary artery pressure (mPAP), pulmonary vascular resistance index (PVRI), and functional class (FC), were assessed in all enrolled patients, including those unable to exercise reliably. The estimated mean percentage change in pVO_2 for the low dose, medium dose, and high dose combined vs placebo was 7.7+/−4.0% (95% confidence interval, −0.2% to 15.6%; P=0.056). Peak VO_2, FC, mPAP, and PVRI improved with the medium-dose and high-dose groups compared with placebo, whereas the low dose was ineffective compared with placebo at Week 16 compared with baseline.

Upper respiratory tract infections, pyrexia, and vomiting occurred more often with sildenafil than placebo. A long-term extension study included children continued on sildenafil monotherapy. In STARTS-2 (the ongoing long-term extension study), increased mortality was observed with children started on high doses compared with lower doses. When participating subjects had completed 3 years and some as long as 7 years, more deaths were observed in those initiating high-dose sildenafil. The incidence of deaths in the subjects started on high-, medium-, and low-dose sildenafil as of 2011 was 20% (20 of 100), 14% (10 of 74), and 9% (5 of 55), respectively. Deaths in the STARTS-2 extension study were related to PAH etiology and baseline disease severity. The majority of deaths occurred in patients with idiopathic PAH/familial PAH as compared with PAH associated with congenital heart disease patients. Of patients who died, most had baseline values above median values for PVRI, mPAP, and right atrial pressure.

This landmark study is the first randomized, double-blind, placebo-controlled trial of a PAH therapy in children. The primary endpoint of an improvement in pVO_2 comparing the 3 dose groups, that is, the low-, medium-, and high-dose groups vs placebo was not statistically significant (P=0.056). On evaluation of secondary endpoints, the low dose was ineffective, with improvements in hemodynamics and exercise capacity in children treated with medium- and high-dose sildenafil compared with sildenafil at Week 16 vs baseline. Due to the higher mortality observed in children initiating PAH therapy with sildenafil high-dose monotherapy during long-term follow-up, it is reasonable to avoid the higher dose range used in the STARTS-1 study. The dosing for sildenafil as add-on therapy has not been studied and thus remains unknown.

Sildenafil is approved for use in chil-

Sildenafil Thrice-Daily Dose in the STARTS-1 Trial

Body Weight (kg)	Sildenafil Dose (mg)		
	Low	Medium	High
≥8 to 20	NA†	10†	20
>20 to 45	10	20	40
>45	10	40	80

†Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8- to 20-kg patients (ie, patients would receive the same dose because of the available tablet strengths); consequently, there was no low dose for this group.[1]

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dren with PAH in Europe: 10 mg orally 3 times daily in patients up to 20 kg, and 20 mg orally 3 times daily in children who weigh more than 20 kg; however, this dosing strategy was not based on the STARTS-1 trial. To date, sildenafil is not approved for children with PAH in the United States. At this time, definite US dosing guidelines cannot be made for sildenafil in children with PAH.

Reference

1. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. *Circulation*. 2012;125(2)324-334.