

Update on Therapies for Pulmonary Arterial Hypertension in Children

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Advances in the treatment of pulmonary arterial hypertension (PAH) over the past 20 years have made a significant impact on the course of this disease in infants and children. The approval of epoprostenol by the Food and Drug Administration (FDA) on September 21, 1995 and inhaled nitric oxide on December 23, 1999 introduced therapies for stabilization and improved early survival.¹ Development of alternative agents has provided more options for long-term management. These therapies include other prostanoids (iloprost and treprostinil), as well as the endothelin antagonist bosentan and sildenafil, a phosphodiesterase type 5 (PDE 5) inhibitor. This issue of the newsletter will review several recent PAH studies, as well as preliminary safety and efficacy data for two new once-daily treatments, ambrisentan and tadalafil.

Reviews of PAH Treatment

Two recent review articles provide an excellent overview of the current management of PAH in the pediatric population. A review by Ivy in *Current Opinion in Cardiology* describes the diagnosis and classification of PAH, as well as epidemiological and survival data in children generated from several international registries.² In addition to reviewing current therapies, the author reproduces two treatment algorithms from earlier papers, allowing for comparison of these approaches. A brief section on investigational therapies is also included. In another review, Steinhorn provides a more detailed description of the mechanisms of action for drugs currently used in the treatment of PAH.³ The article covers pediatric studies with nitric oxide, sildenafil, the prostanoids, milrinone, bosentan, and ambrisentan. The author includes information about current FDA approval status, drug dosing, adverse effect profile, and storage or handling issues that may affect drug selection. Both reviews are extensively referenced.

Additional information on the adverse effects of current PAH therapies comes from a recent review of reports submitted to the FDA Adverse Event Reporting System.⁴ Maxey and colleagues evaluated 588 reports submitted between

November 1997 and December 2009. While the adverse effects reported with bosentan were similar to those identified in clinical trials (elevations in serum transaminases and bilirubin, thrombocytopenia, and cardiac failure), the reports involving epoprostenol and sildenafil included reactions not previously documented. There were 23 cases of pulmonary hemorrhage and 14 cases of hemoptysis with epoprostenol, as well as 13 cases of cardiac arrest. Hemoptysis, pneumonia, plural effusion, pulmonary hemorrhage, and cardiac arrest were also reported with sildenafil (all in fewer than 10 children). While the authors acknowledge that causality was not established in the majority of these reports, they underscore the fact that not all adverse effects are evident in clinical trials and highlight the need for continued surveillance.

Prostanoid Analogs

Inhaled iloprost has been used in children with PAH for nearly ten years, primarily as a means of testing pulmonary vascular reactivity and providing initial treatment after diagnosis. Two recent articles evaluate its potential as long-term therapy. Alehan and colleagues conducted a retrospective study of 20 children treated over a period of 7 years.⁵ The patients ranged from 4 months to 19 years of age (median 3.8 years). Eight children had hereditary or idiopathic PAH, and 12 had PAH associated with congenital heart disease (CHD). Fifteen were receiving combination therapy. The median time of follow-up was 18 months, with a range of 6 to 74 months. Inhaled iloprost was initiated at a delivered dose of 7.5 mcg/day for patients < 10 kg, 12.5 mcg/day for patients 10-20 kg, 17.5 mcg/day for patients 20-30 kg, 22.5 mcg/day for patients 30-40 kg, and 30 mcg/day for those > 40 kg. The frequency of administration was initially 6 times per day, but was increased up to 9 times per day as needed.

The median 6-min walk test for the group increased from 420 to 490 meters after starting iloprost ($p = 0.028$). Other measurements of response, however, showed little change. World Health Organization (WHO) functional class,

evaluated in 18 patients at baseline and 6 months, improved in seven patients, remained unchanged in ten and worsened in one. Six patients died during follow-up, including five with underlying cardiac defects. None of the indices measured in the six children who underwent a second cardiac catheterization (mean pulmonary arterial pressure, aortic pressure, pulmonary vascular resistance, and pulmonary/vascular resistance) demonstrated significant change from baseline after the addition of iloprost. Brain natriuretic peptide levels declined from a median of 125 pg/mL to 80 pg/mL, but the difference failed to reach statistical significance ($p = 0.349$). Therapy was generally well tolerated. One patient developed a perioral rash associated with the mask used to deliver his iloprost doses and one had headaches requiring dose reduction. None of the children discontinued therapy.

A systematic review of pediatric iloprost studies was published last year by Mulligan and Beghetti in *Pediatric Critical Care Medicine*.⁶ The authors reviewed 28 papers, including seven prospective studies, four retrospective studies, four case series and 13 case studies. A total of 195 infants and children were treated. The dose of iloprost ranged from 1 to 20 mcg/kg/day, given six to nine times daily. The average dose delivered was difficult to estimate because of differences in the duration of nebulization, the equipment used, or the need to administer the drug during mechanical ventilation. Most papers included a mix of patient types: children undergoing acute pulmonary vasoreactivity testing, patients with CHD and PAH after cardiac surgery, and neonates with persistent pulmonary hypertension. While the majority reported positive results, variation in methodology makes summarizing their findings difficult. Moreover, response during pulmonary vasoreactivity testing during catheterization has not been found to provide a reliable prediction of improved cardiac index or long-term survival. While inhaled iloprost offers an alternative to continuous infusion of prostanoids, variation in the amount of drug delivered and the requirement for administration 6 or more times per day make this therapy less than ideal.

Treprostinil, a prostanoid developed for parenteral administration, was approved by the FDA for administration by inhalation in adults in 2010. The primary advantage of inhaled treprostinil is the longer duration of effect, allowing dosing four times per day versus the six to nine times per day schedule for inhaled iloprost. Two recent papers describe its use in children with PAH. Earlier this year, Takatsuki and colleagues published a prospective study of 13 children (ages 4-17 years) given inhaled treprostinil during cardiac catheterization for acute pulmonary vasodilator testing.⁷ All of the children initially received inhaled nitric oxide

and were then allowed to return to baseline status. Once at baseline, they received treprostinil at a median dose of 1.53 mcg/kg (range 0.71-2.89 mcg/kg) over 6-9 breaths. Eight (62%) of the children were acute responders. Treprostinil produced results similar to nitric oxide, with a significant drop in mean pulmonary artery pressure (31 mmHg compared to 33 mmHg at baseline, $p < 0.05$) and pulmonary vascular resistance index (4.8 units/m² versus 6.7 units/m² at baseline, $p < 0.05$). There were no significant changes in cardiac index, pulmonary/systemic vascular resistance index, right arterial pressure, pulmonary capillary wedge pressure, systemic blood pressure, or arterial pressure of carbon dioxide. All patients tolerated treprostinil without clinical worsening, although one child with asthma developed a cough and two experienced hypotension.

Krishnan, Takatsuki, and colleagues reported their experience with inhaled treprostinil as add-on therapy in 29 children (ages 3.2 to 19 years) with PAH at two children's hospitals, Columbia University and Children's Hospital Colorado.⁸ Therapy was initiated at a dose of 3 breaths (6 mcg/breath) four times per day. The dose was titrated weekly as needed to a maximum of 9 breaths per treatment. Follow-up ranged from 1.9 to 26.5 months. Three children were weaned off intravenous prostanoids after starting inhaled treprostinil and six were transitioned from inhaled iloprost. Nineteen patients demonstrated improvement in WHO functional class and ten remained in the same class. Results of the 6-min walk test, assessed in 13 children, improved from 456 ± 72 to 498 ± 70 meters ($p = 0.017$). Brain natriuretic peptide levels fell from 93 ± 77 to 58 ± 62 pg/mL ($p = 0.003$). Exercise capacity and peak oxygen consumption were also significantly improved. Treprostinil was discontinued in one patient because of worsening disease and in three patients because of desaturations, dyspnea, or bronchospasm. Other adverse effects included cough in nine patients, sore throat in six, and headache and nausea in four. Two children died during follow-up.

Endothelin Antagonists

While bosentan has been used in the management of pediatric PAH for many years, a new study suggests that a second endothelin-1 antagonist, ambrisentan, may have a role in these patients as well. Ambrisentan was approved by the FDA in 2007 for the treatment of PAH in adults. Unlike bosentan, which is a dual antagonist for endothelin types A and B, ambrisentan is highly selective for endothelin type A. It has been found in several clinical trials to produce improvement in WHO functional class, exercise tolerance, and dyspnea scores in adults. Earlier this year, Takatsui and colleagues conducted a preliminary study of the pharmacokinetics, safety, and efficacy of ambrisentan in children.⁹ Safety and efficacy

were assessed in a retrospective study of 38 children receiving ambrisentan over a 4-year period at Columbia University Medical Center and Children's Hospital Colorado. The children ranged from 2 to 18 years of age (mean 10.1 ± 4.1 years). Concomitant therapies included epoprostenol, treprostinil, iloprost, sildenafil, and tadalafil. The majority (87%) received a combination of sildenafil and ambrisentan. Forty percent of the patients were being transitioned from bosentan. Eight children were switched for the ease of once daily dosing with ambrisentan, six for adverse effects with bosentan, and one for lack of efficacy with bosentan.

Patients weighing less than 20 kg received an initial dose of 2.5 mg once daily, while children between 20 and 40 kg were treated with either 2.5 or 5 mg and those over 40 kg were treated with an initial dose of 5 mg. All of the patients started on 2.5 mg were eventually titrated to 5 mg. Of the patients given 5 mg initially, 37% were titrated to 10 mg. The mean maintenance dose was 0.19 ± 0.1 mg/kg/day. Length of follow-up ranged from 4 to 44 months (median 20 months). The number of children reporting PAH symptoms remained consistent during follow-up, other than a decrease in the incidence of dyspnea (reported in 45% of children before and only 37% after treatment). Three children (8%) required hospitalization for worsening symptoms and three were started on inhaled treprostinil. There were no deaths.

Both the children transitioning from bosentan and those with ambrisentan added to their PAH regimen had a significant decrease in mean pulmonary artery pressure at follow-up (median 21 months). In the transition group, the mean was 55 ± 18 mmHg on bosentan and 45 ± 20 mmHg on ambrisentan ($p = 0.04$). In the add-on group, the mean before ambrisentan was 52 ± 17 mmHg, compared to 45 ± 19 mmHg after ($p = 0.03$). Overall, 31% of children experienced an improvement in functional class. In the transition group, all six of the patients in class III improved to class II and one of the 21 patients in class II improved to class I. Neither of the two patients in class IV at initiation of treatment changed class. In the add-on group, none of the four patients in class III or IV changed classes, but six of the 16 in class II improved to class I.

Neither group had significant changes in brain natriuretic peptide levels, mean right arterial pressure, pulmonary vascular resistance index, pulmonary/systemic vascular index ratio, or cardiac index. Mild adverse effects were reported in 26%, including nasal congestion in nine children, headache in eight, and flushing in one. Five children discontinued therapy: two for headaches, one for an episode of syncope, and two for lack of efficacy. None of the patients had elevation of serum transaminases or bilirubin levels. Based on their results, the authors suggest

that ambrisentan may be a useful tool in the management of children with PAH and merits further study.

Six of the children in this study were also enrolled in an open-label pharmacokinetic study. The mean ambrisentan dose for the group was 0.20 ± 0.09 mg/kg/day. Serum sampling was done over a 12-hour period following a dose, after the patient had been on treatment for at least 30 days. The mean maximum concentration was 738 ± 452 ng/mL, with a time to peak of 3.2 ± 2.1 hrs. Mean area under the concentration curve (AUC), adjusted for dose, was 1249 ± 656 ng•hr/mL/mg, with a mean elimination half-life of 7.6 ± 2.6 hrs. These values are similar to those reported previously in adults.

Phosphodiesterase Inhibitors

Sildenafil has become one of the most widely used therapies for PAH in both children and adults. In 2011, the results of STARTS-1, a 16 week randomized, double-blind, placebo-controlled sildenafil dose-ranging study in 235 children with PAH and the preliminary findings from START-2 study, an open-label extension study, were published.¹⁰ The authors found that that sildenafil monotherapy was well tolerated and produced improvements in peak oxygen consumption, functional class, and hemodynamic parameters. They suggested that the medium dosing regimen used in the STARTS-1 study produced the most favorable response (a dose of 10 mg for patients weighing 8-20 kg, 20 mg for patients 21-45 kg, and 40 mg for patients > 45 kg, given three times daily). Subsequent concern over the mortality rate in the high-dose group in the STARTS-2 preliminary data (assessed at 3 years), however, led the FDA to issue a warning against the use of sildenafil in all pediatric patients with PAH.¹¹

In the March 15, 2013 issue of the *American Journal of Respiratory and Critical Care Medicine*, Abman and colleagues (writing on behalf of the Pediatric Pulmonary Hypertension Network), examined the data from the STARTS trials and the implications of the FDA warning.¹² Their conclusions regarding the relative risks and benefits of sildenafil, as well as the recommendations they provide for patient care and future research, make this article essential reading for all healthcare providers involved in the care of infants and children with PAH.

While sildenafil has been the most widely studied PDE 5 inhibitor in children with PAH, reports of the efficacy of once-daily tadalafil in adult PAH patients has led to interest in the use of this agent in the pediatric population. In 2012, Takatsuki, Calderbank, and Ivey reported the results of a single-center retrospective study of the safety and efficacy of tadalafil in 33 children with PAH over a 3-year period.¹³ The patients ranged in age from 4 to 18 years (mean 10 years)

and included 16 children with underlying congenital heart disease, 14 idiopathic cases, one child with a connective tissue disease, and two others. Eleven children were WHO functional class I, thirteen were class II, eight were class III, and one was class IV at the start of therapy. Twenty-nine of the patients were being transitioned from sildenafil. Children weighing 40 kg or more received a tadalafil dose of 40 mg (the standard adult dose), while those between 20 and 40 kg received 20 mg, and those weighing less than 20 kg received 10 mg.

After the transition, there were significant improvements in mean pulmonary arterial pressure (53.2 ± 18.3 mmHg with sildenafil compared to 47.4 ± 13.7 mmHg with tadalafil, $p < 0.05$), pulmonary vascular resistance index (12.2 ± 7.0 versus 10.6 ± 7.2 units/m², $p < 0.05$), and pulmonary/systemic vascular resistance ratio (0.89 ± 0.47 versus 0.75 ± 0.35 , $p < 0.05$). Despite the improvement in these areas, no differences were found in mean right arterial pressure, cardiac index, brain natriuretic peptide levels, or the 6-min walk test. Functional class improved in four of the 29 children, 21 remained unchanged and status worsened in four (one patient went from class I to class II and three went from class III to class II). A similar degree of improvement was noted in the children who had not previously been treated with sildenafil.

Only one child required the addition of another agent due to worsening symptoms during the study and none required hospitalization. Adverse effects were generally mild, with nasal congestion and myalgia occurring most frequently, followed by reports of headache, nausea, and flushing. Overall, the adverse effect profile was similar to that observed in adults with PAH. Two patients discontinued treatment, one because of migraines and the other for an allergic reaction. None of the male patients experienced priapism.

Summary

While these studies offer useful information on the medications currently used in infants and children with PAH, there is still considerable work to be done. Multicenter prospective clinical trials are needed, with consistent outcome measurements and sample sizes large enough to identify significant effects on function and disease progression. In addition, future studies should separate patients with idiopathic PAH from those with PAH associated with CHD to identify potential differences in short and long-term response between these etiologies.

References

1. U.S. Food and Drug Administration. Drugs@FDA: FDA approved drug products. April 2013. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (accessed 4/22/13).
2. Ivy D. Advances in pediatric pulmonary arterial hypertension. *Curr Opin Cardiol* 2012;27:70-81.

3. Steinhorn RH. Pharmacotherapy for pulmonary hypertension. *Pediatr Clin North Am* 2012;59:1129-46.
4. Maxey DM, Ivy DD, Ogawa MT, et al. Food and Drug Administration (FDA) postmarket reported side effects and adverse events associated with pulmonary hypertension therapy in pediatric patients. *Pediatr Cardiol* 2013; E-pub ahead of print. DOI 10.1007/s00246-013-0688-2.
5. Alehan D, Yildirim I, Sahin M, et al. Long-term inhaled iloprost use in children with pulmonary arterial hypertension. *Cardiol Young* 2012;22:396-403.
6. Mulligan C, Beghetti M. Inhaled iloprost for the control of acute pulmonary hypertension in children: a systemic review. *Pediatr Crit Care Med* 2012;13:472-80.
7. Takatsuki S, Parker DK, Doran AK, et al. Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterial hypertension. *Pediatr Cardiol* 2013;34:1006-12.
8. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. *Am J Cardiol* 2012;110:1704-9.
9. Takatsuki S, Rosenzweig EB, Zuckerman W, et al. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. *Pediatr Pulmonol* 2013;48:27-34.
10. 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;125:324-34.
11. U.S. Food and Drug Administration. FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension. August 30, 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm> (accessed 4/29/13).
12. Abman SH, Kinsella JP, Rosenzweig EB, et al. Implications of the US Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. *Am J Respir Crit Care Med* 2013;87:572-5.
13. Takatsuki S, Calderback M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. *Pediatr Cardiol* 2012;33:683-8.

The editors would like to thank Dr. W. Gerald Teague for reviewing this article prior to publication.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their May meeting:

1. An inhaled formulation of epoprostenol (Veletri®) was approved for the treatment of patients with pulmonary arterial hypertension.
2. Apixaban (Eliquis®) was approved for anticoagulation in patients with nonvalvular atrial fibrillation.
3. Acetaminophen combination products were deleted from the Formulary to reduce the risk for exceeding the recommended total daily acetaminophen dose.

Contributing Editor: Marcia Buck, Pharm.D.

Editorial Board: Kristi N. Hofer, Pharm.D.

Clara Jane Snipes, R.Ph.

Susan B. Cogut, Pharm.D.

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at <http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/home.html>. For comments or suggestions for future issues, please contact us at mlb3u@virginia.edu.