Therapeutic Options for Childhood Pulmonary Hypertension

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Idiopathic pulmonary arterial hypertension (IPAH) is a rare progressive disorder with a lethal outcome if not diagnosed and treated in a timely manner.[1] The prevalence of pulmonary arterial hypertension (PAH) is estimated to be <1 per 100,000 children with an incidence of 1 to 2 new cases/million/year.[2] Prior to the current era, the median survival after diagnosis of IPAH was reported in the National Institutes of Health Primary Pulmonary Hypertension Registry as 2.8 years in adults and only 10 months in children.[3] In the modern era, with early diagnosis and initiation of therapy, survival at 1, 2, and 3 years has been reported to be 99%, 96%, and 84% in children and 88%, 76%, and 63% in adults.[3-5] Interest in finding newer therapies for PAH was prompted by the discovery of prostacyclin in 1976, and its subsequent use in patients since the early 1980s.[4,6] This spawned a whole new field of translational research, with the quest for finding triggers for PAH at the molecular level and the development of targeted therapies. Advances in treatment have not only increased the life expectancy for these patients, but also improved quality of life.[1-9] Although there is yet no cure for PAH, nor a single therapeutic approach that is uniformly successful, therapy has dramatically improved over the past several decades, resulting in sustained clinical and hemodynamic improvement as well as increased survival in children with various types of PAH.[10-11] The recently published American Heart Association/American Thoracic Society guidelines outline the current approach and summarize recommendations for treatment.[12] At the current time, no targeted therapy for PAH is US Food and Drug Administration approved for use in the pediatric age group, and all the medications are used off-label and based on the experience obtained from adults and smaller studies in children. Hemodynamic and noninvasive studies obtained prior to initiating therapy (as well as periodically thereafter) are useful in guiding changes in therapeutic regimens, particularly in light of recent advances with various novel therapeutic agents.[13,14]

GENERAL MEASURES

The pediatrician plays an invaluable role in the care of children with PAH. Since children often have a more reactive pulmonary vascular bed than adult patients, respiratory infections resulting in alveolar hypoxia can result in pulmonary hypertensive crisis if not treated aggressively. Annual influenza and pneumococcal vaccinations are recommended. Antipyretics should be administered for temperature elevations greater than 101° F (38° C) to minimize the consequences of increased metabolic demands on an already compromised cardiorespiratory system. Children may also require additional targeted therapy during an acute respiratory illness: eg, inhaled nitric oxide (iNO) for acute pulmonary hypertensive crises occurring with episodes of respiratory or other infections. Children may also require mild antitussive medications during upper respiratory infections to prevent pulmonary hemorrhage. Decongestants with pseudoephedrine should be avoided as they may exacerbate the pulmonary hypertension (PH). Diet and/or medical therapy should be used to prevent constipation, since Valsalva maneuvers transiently decrease venous return to the right side of the heart and may precipitate syncopal episodes. These general measures are an important complement to the use of targeted PAH therapy. Primary goals of therapy for PAH include: improvement in symptoms, quality of life, and hemodynamics; increase in life expectancy; and reduction of morbidity. If possible, this could be achieved by halting progression of the disease process and possible remodeling and reversal of changes at the vascular endothelial level.

Prior to choosing a pharmacotherapy, it is important to risk stratify based on multiple clinical, echocardiographic, and hemodynamic parameters (see Figures 2 and 3 in the original guidelines document).[12] Depending on the results of acute vasodilator testing (AVT) during

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right heart catheterization and risk stratification, a decision on targeted therapy is made. If a child is robustly responsive to AVT and is over 1 year of age and deemed low risk, a calcium channel blocker (CCB) is indicated. Patients in the low-risk category may be started on a single medication, either a phosphodiesterase type 5 (PDE-5) inhibitor or an endothelin receptor antagonist (ERA) depending on user preference. A higher-risk patient should be started on initial combination therapy with both PDE-5 inhibitor and ERA; or parenteral prostanoids, especially if the initial presentation is syncope or heart failure (see Table 3 in the original guidelines document).[12] Regardless of the initial treatment choice, it is critical that there are frequent reassessments to ensure response to the chosen therapy. In the absence of a good clinical response or in the presence of clinical worsening, treatment selection should be adjusted and/or escalated in a timely fashion.

ANTICOAGULATION

Consideration of chronic anticoagulation in children with PAH is based on studies in adults with IPAH.[3,8] The lung histopathology often demonstrates thrombotic lesions in small pulmonary arteries of adult patients with IPAH. Warfarin has been shown to be associated with improved survival in adult patients. Whether chronic anticoagulation is efficacious as well as safe for children with PAH remains to be determined. It is recommended to anticoagulate children who are hypercoagulable or have signs of right heart failure with a poorly functioning dilated right ventricle and dilated right atrium as well as those with atrial or ventricular arrhythmias. Children who are on a micro pump for intravenous (IV) treprostinil also need to be on anticoagulation to prevent pump tubing blockage. Age and activity considerations are important with regard to weighing the risks and benefits of anticoagulation in young children.

CALCIUM CHANNEL BLOCKADE

Calcium channel blockers are a chemically heterogeneous group of compounds that inhibit calcium influx through the slow channel into cardiac and smooth muscle cells. Chronic calcium channel blockade is efficacious for patients who demonstrate a robust response to AVT. In contrast, patients who do not respond acutely fail to respond to long-term calcium channel blockade.[4,8,10,13,14] In general, these acute "nonresponders" will respond to long-term treatment with IV prostacyclin, ie, epoprostenol, and may respond to other newer oral and inhaled treatments. A greater percentage of children than adults are acute "responders," and can be effectively treated with chronic oral calcium channel blockade.[15] For acute adult responders, most studies have used CCBs at relatively high doses: eg, long-acting nifedipine 120-240 mg daily, and a pediatric dose of 2-5 mg/kg/day has been suggested.[10,12]

Serial reevaluation, including repeat AVT to maintain an "optimal" chronic therapeutic regimen, is essential to the care of children with PAH. Acute "responders" continue to do well as long as they remain AVT-responsive on repeat cardiac catheterization. In contrast, children who no longer demonstrate acute vasoreactivity deteriorate clinically and hemodynamically despite continuation of CCB therapy, but will likely improve with chronic epoprostenol therapy, similar to the experience with children who are initial "nonresponders."[15]

INHALED NITRIC OXIDE

Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells (SMC), which increases cyclic guanosine monophosphate (cGMP) leading to SMC relaxation. iNO may also have antiproliferative effects on smooth muscle and inhibit platelet adhesion. Per the pediatric American Heart Association (AHA)/American Thoracic Society (ATS) guidelines, iNO is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with persistent pulmonary hypertension of the newborn (PPHN) or hypoxemic respiratory failure with an oxygenation index that exceeds 25 (class I, Level A). This is the only indication that the US Food and Drug Administration (FDA) has approved a medication for PH for pediatric use. iNO can also be beneficial for preterm infants with severe hypoxemia primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (class IIa, Level B).[12] iNO is also used for AVT during right heart catheterization, and for treating acute PAH crises in IPAH patients as well as for acute PAH following cardiac surgery. If acute pulmonary edema develops after starting iNO, conditions with elevated postcapillary pressures including pulmonary venous obstruction, elevated left atrial or left ventricular end diastolic pressures, or rarely alveolar capillary dysplasia should be ruled out and iNO discontinued.

PROSTACYCLINS

The discovery of the role of prostacyclin in pulmonary vasodilation has revolutionized therapy for PAH. Indeed, the natural history of IPAH can be divided into 2 eras: the pre- and post-prostanoid eras, with improvement in life expectancy and quality of life after the introduction of IV epoprostenol. Epoprostenol has been shown to improve hemodynamics, quality of life, and exercise capacity in patients with PAH. Chronic IV epoprostenol lowers pulmonary artery pressure; increases cardiac output; increases oxygen transport; and improves exercise capacity, hemodynamics, and survival in patients with IPAH.[15-17] These effects occur with long-term use even in patients unresponsive to AVT, suggesting that epoprostenol may cause pulmonary vascular remodeling in addition to its vasodilator properties. The epoprostenol dose (ng/kg/min) is titrated incrementally, with the most rapid increases occurring in the first few months after initiating therapy, and slower thereafter. The dose needs to be increased possibly because of development of tachyphylaxis. The mean dose at 1 year in children is closer to 50-80 ng/kg/min, but there is a significant patient variability of the "optimal" dose.

Because epoprostenol is chemically unstable at neutral pH/room temper-

ature, and has a short half-life (1 to 2 minutes), a continuous IV delivery system with cold packs is needed to maintain stability. Veletri is a newer form of IV epoprostenol that is pH stable and does not require ice packs, but shares the other properties of epoprostenol. An indwelling central venous line is necessary, with associated complications including thrombosis and line occlusion, local and systemic infection, and catheter breakage. In addition, pump malfunction may rarely lead to administration of a sudden bolus of epoprostenol (leading to systemic hypotension) or interruption of the medication, which can cause severe rebound PAH. Therefore, a search for alternate routes of drug delivery has led to the clinical investigation of oral, inhaled, subcutaneous, and more stable and longer-acting IV prostacyclin analogues.

Prostacyclin Analogues: Oral Prostacyclin Analogue

Beraprost sodium is an oral prostacyclin analogue with potency approximately 50% that of epoprostenol. It is approved for PAH treatment in Japan, but is not approved for use in the United States. Oral treprostinil is now FDA approved and is being used in adults. In addition, selexipag, a prostacyclin receptor agonist, was recently approved by the FDA for the treatment of PAH in adults. There is no pediatric data available to date on use.

INHALED PROSTACYCLIN ANALOGUES

Inhaled iloprost and inhaled treprostinil are increasingly being used in patients requiring prostanoid therapy. They are attractive options because inhaled delivery may avoid the systemic side effects of IV epoprostenol use. Iloprost is a stable synthetic analogue of prostacyclin that acts through prostacyclin receptors on vascular endothelial cells. Iloprost has a short biological half-life, ie, 20 to 25 minutes, and needs to be administered every 1 to 4 hours depending on patient acuity. It has been used in neonates and infants with bronchopulmonary dysplasia and is thought to cause less ventilation/perfusion (V/Q) mismatch than IV prostanoids.[18,19] Inhaled treprostinil is longer acting and can be given on a 6-hourly basis with sustained effects. A recent study documented its use in children as young as 3 years with improvement in exercise capacity, b-type natriuretic peptide (BNP) levels, and hemodynamics.[19] However, the inhaled device for use and requirement for coordination of breaths can pose a challenge for younger children. Longer-term studies are required in children to validate these preliminary findings.

Treprostinil sodium is a prostacyclin analogue with a neutral pH, longer half-life, and is stable at room temperature and shares the same pharmacologic actions as epoprostenol. It can be administered both intravenously and subcutaneously. Double-blind, randomized, placebo-controlled trials demonstrated improved exercise capacity, clinical signs, and symptoms as well as hemodynamic measurements in patients with PAH including children.[20] With subcutaneous administration, the risks associated with an IV line are minimized. Although no serious adverse events related to subcutaneous treprostinil have been reported, discomfort at the infusion site has been noted. Recent studies from Spain and in the United States have described the use of subcutaneous trepostinil in infants and young children.[20,21]

ENDOTHELIN RECEPTOR ANTAGONISTS

Endothelin (ET)-1 is one of the most potent vasoconstrictors implicated in the pathobiology of PAH, and plasma ET-1 levels are increased in patients with IPAH and correlate inversely with prognosis. The oral nonselective ERA bosentan has been shown to improve exercise capacity, quality of life, and cardiopulmonary hemodynamics in patients with PAH.[22,23] An open-label study of 19 children with Group 1 PAH and World Health Organization (WHO) functional class II and III was performed with measurements of pharmacokinetic and hemodynamic parameters at baseline and 12-week follow-up.[23] Hemodynamic improvement was demonstrated at 12 weeks and the drug was well tolerated. Risks associated with ERAs include acute hepatotoxicity (dose-related), teratogenicity, and possibly male infertility. Ambrisentan, a selective ET_A receptor blocker (which can be administered once a day and has been reported with no hepatotoxicity) was found to be efficacious in children with an acceptable safety profile.[24] Macitentan is a tissue-specific ERA that is now FDA approved for use in adult PAH, and studies in pediatric patients are ongoing.

PDE-5 INHIBITORS

PDE-5 inhibitors prevent the breakdown of cGMP, thereby raising cGMP levels.[25-28] PDE-5 inhibitors are particularly beneficial in postoperative patients in preventing rebound PH at the time of iNO withdrawal. An early, randomized, double-blind, crossover design study of patients with IPAH compared the efficacy of sildenafil with placebo. Exercise capacity increased by 44%, and there was an increase in cardiac index and improvement in the dyspnea and fatigue components of a quality-of-life questionnaire. A multicenter, randomized, placebo-controlled, double-blind study analyzing low-, medium-, and high-dose sildenafil monotherapy in children (STARTS1 study) suggested that long-term use of higher doses of sildenafil monotherapy in children with IPAH (not congenital heart disease) may be associated with increased mortality. Subsequently, the European Medicines Agency only approved use of low-dose therapy for children.[27] The doses of sildenafil approved in Europe are 10 mg TID for children weighing <20 kg and 20 mg TID for children weighing >20 kg. Another PDE-5 inhibitor, tadalafil, which has similar pharmacologic effects as sildenafil but is longer acting, requiring only once-a-day administration, is approved for use in adults, but larger studies in children are awaited.[28] When used in infants with chronic lung disease, care must be taken to watch for signs of increasing acid reflux, airway compromise from edema in already narrow airways (especially in chronically ventilated ex-preterm infants and those with Down syndrome), and worsening V/Q mismatch after starting pulmonary vasodilator therapy.

Additional Pharmacotherapy

Treatment of heart failure with inotropes and digoxin, diuretic therapy, and

supplemental oxygen is important in the management of these patients. Prompt management of arrhythmias is vital as atrial flutter or fibrillation often precipitate an abrupt decrease in cardiac output and clinical deterioration due to the loss of the atrial component. Ventricular arrhythmias may complicate right ventricular (RV) failure and need to be treated appropriately.

Atrial Septostomy and Potts Shunt

Children with recurrent syncope in severe right heart failure have a very poor prognosis.[1,4] In Eisenmenger syndrome, cardiac output can be maintained because of right-to-left shunting, and syncope is rare. Increased survival has been reported in patients with IPAH with a patent foramen. Successful palliation of symptoms with atrial septostomy has been reported in several series. In our experience, patients with PAH with recurrent syncope or right heart failure significantly improve clinically, as well as hemodynamically following atrial septostomy.[29,30] In our experience, atrial septostomy results in a survival benefit, ie, survival rates at 1 and 2 years are 87% and 76%, respectively, compared with conventional therapy (64% and 42% at 1 and 2 years, respectively). Thus, although atrial septostomy does not alter the underlying disease process, it may improve quality of life and represent an alternative for selected patients with severe IPAH. However, this invasive procedure is not without risk; our indications for the procedure include: recurrent syncope or RV failure despite maximal medical therapy, as well as a bridge to transplantation.

The use of palliative Potts shunt for children with suprasystemic PAH was reported from France, where 24 children underwent surgical or interventional Potts shunt over a 10-year period, with significant improvement in WHO functional class, growth, and symptomatology in 21 of the 24 children.[31] Thus, this procedure could be another modality allowing prolonged survival and possibly a bridge to transplant in selected children with severe refractory PAH.

Lung Transplantation

A limited number of centers perform lung transplantation in children and the availability of suitable donors is inadequate. Currently, the overall 1-year, 5-year, and 10-year survival for lung transplantation for PAH patients is 64%, 44%, and 20%, respectively.[32] For untreated Eisenmenger patients, the 5-year and 25-year survival is greater than 80% and 40%, respectively, as opposed to following lung transplantation (52% and 39%).[33] Thus, transplantation should be reserved for WHO functional class IV patients with PAH who have progressed despite optimal medical therapy. Ideally, children should be listed when their probability of 2-year survival without transplantation is 50% or less. Although lung and heart/lung transplantation are imperfect therapies for PAH, when offered to an appropriately selected population, transplantation may improve survival with an improved quality of life. The use of ECMO and RV assist devices as a bridge to recovery (in acutely decompensated patients) as well as a bridge to transplant may also be a viable option in selected patients.[33]

CONCLUSION

In summary, the use of targeted PAH agents has grown from a single drug to over a dozen, now available for the use in adult PAH. The pediatric AHA/ATS guidelines are a good resource to guide practitioners on the use of these agents; however, we should always remember that the natural history of childhood Group 1 PAH is worse than in adults, and that data on the use of these agents in children are very limited. Therefore, decisions should be individualized for each patient with close monitoring to ensure a suitable response. The ultimate treatment goal for children is to select agents that enable them to participate in the usual activities of a child, including attending school, playing with friends, and being as active as they physically can.

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