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Advances in PH Journal

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The number of approved therapies for pulmonary hypertension continues to increase. This article reviews the literature related to pediatric use of these thereapies from the past 5 years. The evidence-based algorithm for pulmonary hypertension treatment in adults is discussed with respect to children.

It has been 5 years since Dr Erika Berman Rosenzweig last reviewed the topic of therapies for pediatric pulmonary hypertension (PH) in this publication.[1] In that short time, the number of specific pulmonary arterial vasodilators approved for use in the United States has doubled, from 6 to 12 (including different formulations). Alas, except for sildenafil in Europe, none of these medications to date carries a specific pediatric indication due to lack of data, leaving those of us who treat young patients with PH to continue to extrapolate from knowledge learned in adults. Fortunately, the little data that have been published on the effect of these therapies in children seem to support their use. In addition, based on the number of studies being undertaken specifically in pediatrics, it seems as if the importance of this information is being increasingly recognized. Therefore, it is quite fitting to review the published literature

from this recent time frame and also to present ongoing and planned studies. The purpose of this article is to provide updated information and review current strategies for the therapeutic management of pediatric PH patients.

The grim prognosis for children with untreated idiopathic pulmonary arterial hypertension (IPAH), which was even worse than for adults, was clearly demonstrated in the 1980s National Institutes of Health (NIH) natural history study.[2] Survival has drastically improved with calcium channel blockers when appropriate and epoprostenol treatment,[3,4] and the improvement due to the latest era of expanded oral and inhaled therapies is starting to be understood.[5] Dr Mary Mullen will cover survival and other aspects of IPAH and pulmonary arterial hypertension (PAH) associated with congenital heart disease in a separate article. Dr Steven Abman will write about neonatal PH, including a discussion about chronic lung disease of development and persistent PH of the newborn. In addition, the mechanisms of action of the 3 basic classes of medications (prostanoids, endothelin receptor antagonists, phosphodiesterase inhibitors) have been well described elsewhere and will not be reviewed here.[6]

At the 2008 World Symposium on Pulmonary Hypertension in Dana Point, an evidence-based treatment algorithm for adults was developed with varying levels of strength of recommendations and quality of evidence (Figure 1).[7] While pediatric PH is somewhat different than in adults with respect to etiology, natural history, and level of heart failure on presentation, the overall similarities have led to recommendations by expert consensus to follow the same treatment algorithm in children.[8] Furthermore, expert opinion is to follow the same therapeutic goals, despite general lack of data. Treatment options within each category of the treatment algorithm will be discussed, highlighting information published since 2006.

Figure 1:

*Evidence-based treatment algorithm for PAH patients (for Group 1 patients only). *To maintain arterial blood O_2 pressure ?8 kPa (60 mm Hg). †Under regulatory review in the European Union. §IIa-C for WHO-FC II. APAH = associated pulmonary arterial hypertension; BAS = balloon atrial septostomy; CCB = calcium channel blocker; ERA = endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; PDE5 I = phosphodiesterase type-5 inhibitor; WHO-FC = World Health Organization functional class. Reprinted with permission from: Gallè N, Hoeper MM, Humbert M, et al; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30(20):2493-2537.*

GENERAL MEASURES

The expert consensus recommendations for general measures in adults and children[7,9] include avoidance of pregnancy and use of birth control in girls of reproductive age. Supplemental oxygen during travel in airplanes and to high altitude may be advisable in those

with hypoxia at sea level or signs of heart failure. Immunization against known influenza and pneumococcus is recommended, as well as prophylaxis against respiratory syncytial virus in infants.[10] School-aged children need specific recommendations for participation in physical education based on symptom limitations, but all children should be encouraged to be active with the ability to self-limit. They will likely require an IEP (individualized education program), which includes plans for safe activity level as well as medication administration during school hours and an emergency action plan. To this end, support groups can be very helpful to parents navigating these issues. In addition, teenaged patients may need extra support from the medical team to create therapeutic regimens that can be adhered to.[11] No new data have emerged about the use of diuretics, oxygen, anticoagulation, and digoxin in children.

CALCIUM CHANNEL BLOCKERS

High dose calcium channel blocker therapy continues to be recommended in patients who respond to acute vasodilator testing, as does the recommendation for serial testing for acute vasodilator responsiveness. The Sitbon criteria for acute responders in adults (a fall in mean pulmonary artery pressure to <40 mm Hg by ?10 mm HG without a fall in cardiac output)[12] now seems to be used as often as the previous criteria, but is not known to be better than the old rule in pediatrics (?20% decrease in mean arterial pressure without a fall in cardiac output[2]).[8] Although inhaled nitric oxide is now considered the preferred vasodilator in adults, a recent study in pediatrics shows that a combination of inhaled nitric oxide and oxygen combination identifies more responders, both for treatment with calcium channel blockers or for repair of congenital heart disease.[13] The incidence of acute responders was thought to be about 40% in children[3] compared with 7% in adults.[12] The UK experience shows a rate of 7% using the newer criteria, which is similar to adults.[14] Very recent data from an international registry of pediatric PH reports 36% of children to be acute responders to vasodilator testing, but criteria were not specified.[15]

PROSTACYCLINS

Intravenous Epoprostenol.

Intravenous prostacyclin epoprostenol, in the form of Flolan®, continues to be a mainstay of therapy in children due to improvements in symptoms, hemodynamics, and survival. Recent data from the UK confirm this.[16] Indications for use include PAH and PAH associated with congenital heart disease. The ability to tolerate higher doses with less severe side effects has been well described in children as compared to adults. The risks include line infection, local infection, catheter dislodgment, and thromboembolism.[1]

The current adult treatment algorithm reserves epoprostenol for those patients who are in severe heart failure or those who have failed to respond to oral or inhaled medication. However, a strong argument can be made for children that early and aggressive initiation of intravenous epoprostenol may be most beneficial in the long term.[17] This is based on the

observation in certain situations that children have been able to transition off chronic epoprostenol, when its long-term antiproliferative and vascular remodeling effects may have coupled with active growth of the lungs and pulmonary vasculature in childhood.[18,19]

The room temperature stable formulation of epoprostenol (Veletri) was just approved in 2010. Clearly, carrying epoprostenol pumps without ice bags is an improvement for children of all ages. However, infants and children on low doses will not be able to benefit, as concentrations less than 15,000 ng/mL are not considered to be stable at room temperature. Currently, there are no specific pediatric data; however, a registry for patients on Veletri will soon be underway.

Treprostinil.

The intravenous form of this prostacyclin with longer half-life was approved in 2005. There is one report of pediatric patients successfully switching from intravenous epoprostenol, with fewer side effects, but needing a higher dose.[18] At one point, the risk of catheter-associated infections seemed to be increased with treprostinil,[20] but with improved guidelines[21] and specific catheter systems in pediatric patients,[22] the risk can be decreased. Practical benefits of intravenous treprostinil over epoprostenol for children include the potential use of a miniature pump when stable dose are reached and the freedom from ice packs. For school-aged children, the longer half-life may provide the needed cushion of comfort for parents and school officials to allow children to attend school without direct medical supervision.

Subcutaneous Treprostinil

Historically, the use of subcutaneous treprostinil has been limited in children due to concern about site pain. A recent small series from France has shown that subcutaneous treprostinil in combination therapy can be tolerated in quite young children.[23] This may lead to increased willingness to try subcutaneous prostacyclin in situations where there is substantial elevated risk for intravenous therapy: for example, in developing nations or in adolescent patients who are highly motivated to transition off intravenous prostacyclin.

Inhaled Iloprost.

The first inhaled prostanoid therapy, was approved in 2004. There is only one article to date with pediatric data describing safety and efficacy after transitioning from intravenous prostacyclin.[24] However, bronchospasm that improves with cessation of medication and is reversible with bronchodilators was described, which had not previously been a concern in

adults.[24] In addition, because the delivery system requires a fair amount of cooperation and coordination of breaths, outpatient iloprost use is best limited to those who can comply, usually ages 8 and over. Adhering to the 6-9 times a day frequency of inhalation can also be difficult. In the inpatient critical care setting of congenital heart disease, inhaled iloprost has been shown to be equally as good as inhaled nitric oxide for lowering mean pulmonary artery pressure and pulmonary vascular resistance[25] and has been used as rescue therapy for persistent PH of the newborn.[26]

Treprostinil.

Inhaled treprostinil (Tyvaso) was approved in 2009. Similar to iloprost, inhalation requires cooperation but less coordination of breaths, which may be easier for younger children, as recently reported in an abstract.[27] In addition, inhalations are only needed 4 times a day, which can greatly simplify treatment for school-aged children. The association with bronchospasm is not known.

Oral

Beraprost, an oral prostanoid, continues to be approved and available in Japan, but not in the United States. Currently, clinical trials studying oral treprostinil that include children down to age 12 are ongoing.

ENDOTHELIN RECEPTOR ANTAGONISTS

Bosentan

Bosentan, approved as the first oral targeted PH therapy in 2001, already had 3 pediatric studies reporting on its safety, efficacy, and utility in weaning off epoprostenol in idiopathic PAH by 2006.[28–30] A recent review summarizes data on bosentan safety, efficacy, and use in pediatric PAH.[31]

The recent European postmarketing surveillance program report[32] demonstrates that bosentan is more safely tolerated in children than adults. Elevated transaminase levels were reported in 2.7% of children, compared with 7.8% of patients 12 years and older, and the overall discontinuation rate from bosentan was 14% in children, compared with 28% in patients 12 years and older, mainly related to death, hospitalization, or adverse events.

Two retrospective patient studies describe the largest cohorts of pediatric bosentan users. In the UK, 40 patients with mean follow-up of 13 months tolerated bosentan well, but over half needed the addition of epoprostenol therapy.[33] In the US, 86 patients with median follow-up of 39 months showed that functional class stayed the same or improved, but half of the children stopped bosentan due to lack of improvement or deterioration or adverse events, and almost half received additional pulmonary vasodilator therapy.[34]

The BREATHE-5 study and extension study of bosentan vs placebo in Eisenmenger patients showed that bosentan was well tolerated and improved exercise capacity, hemodynamics, and WHO functional class without compromising peripheral oxygen saturation.[35,36] In a study including both children and adults with PAH and systemic-to-pulmonary shunt, bosentan therapy produced short-term improvement in WHO functional class and 6-minute walk distance. However, there was a progressive decline in the beneficial effect of bosentan after 1 year, with a more pronounced decline in the children, who tended to have more severe disease at baseline.[37]

The prospective FUTURE-1 trial[38] utilized a pediatric-specific formulation, which allowed for greater ease of dosing for young children, at doses of 2 mg/kg. The pharmacokinetic study showed that doses higher than 2 mg/kg did not increase plasma concentration, and that children were not able to match concentrations historically reached in adults with twice-daily dosing. The study confirmed that bosentan is well tolerated, and that children generally experience no clinical worsening or clinical improvement. The pediatric formulation is approved in Europe. The adult tablets, which can be cut and dissolved in hot water, continue to be used for young children in the US, but accurate dosing becomes difficult in infants. The FUTURE-3 trial, which examines twice-daily vs 3-times-daily dosing with the pediatric formulation, is underway.

Ambrisentan

This once-daily selective endothelin receptor-A antagonist was approved for use in adults in 2007. Starting in March 2011, monthly liver transaminase monitoring is no longer required, because of overall lower risk of hepatotoxicity.[39] The ease of once-daily dosing is an attractive option for teenaged or older school-aged children for obvious reasons. In addition, for younger children who may have more difficulty with blood draws for technical and emotional developmental reasons, minimizing monthly needle pokes is also an obvious benefit. However, compared to bosentan, there are very limited published data regarding ambrisentan. An open label study of pharmacokinetics, tolerability, safety, and efficacy in pediatric patients ages 8 and older is underway.

Sitaxsentan

This selective endothelin receptor-A antagonist had been approved for use in the EU, Canada, and Australia, but was withdrawn from the worldwide market in 2010 due to

concerns of fatal liver disease.

PHOSPHODIESTERASE-5 INHIBITORS

Sildenafil

The EMEA approved sildenafil for patients age 1 to 17 with PAH in May 2009. Data that support the use of oral sildenafil in children include 2 case series in patients with idiopathic PAH[40] and PAH associated with congenital heart disease.[41] Initial results of the randomized placebo-controlled trial in pediatrics were presented in abstract form in 2009,[42] and showed that oral sildenafil is well tolerated and associated with improvements in exercise, hemodynamics, and disease severity. The full results of the initial trial will provide valuable data once published, as will the outcome of the subsequent long-term study when completed. Despite the paucity of data, sildenafil appears to be more widely and variably used in pediatrics than other oral treatments.[43] Factors that may explain this include the recognition of the therapeutic potential of sildenafil prior to its approval for PAH, the broad availability partly due to the initial indication of erectile dysfunction, its favorable side-effect profile, and lastly, the ease of dosing for infants and young children in compounded form. Reported uses in pediatrics reflects the spectrum of etiology of PAH in children, such as chronic lung disease,[44] congenital heart disease,[45] and cardiomyopathy.[46]

The intravenous form of sildenafil, which was approved in 2009 for use when patients are temporarily unable to take the oral form, has been studied in postoperative congenital heart disease[47] and persistent PH of the newborn.[48] However, the intravenous form may have more risk of systemic hypotension and worsened V/Q mismatching, and should be used cautiously in any hemodynamically compromised patients.

Tadalafil

This long-acting phosphodiesterase-5 inhibitor was approved in 2009 for adult PAH. The only pediatric data available were presented in abstract form,[49] and suggested that tadalafil is similar to sildenafil with regard to safety and hemodynamic effects. A trial to assess efficacy and safety of tadalafil is planned soon.

COMBINATION THERAPY

The current treatment algorithm in adults recommends combination therapy if there is lack of

adequate clinical response to initial single therapy, although the recommendation is at the IIa-B or C level (weight of evidence/opinion is in favor of usefulness/efficacy; data derived from a single randomized clinical trial or large nonrandomized studies/consensus of opinion of the experts and/or small studies, retrospective studies, registries).[7] While it is reasonable to simultaneously treat the multiple pathophysiological pathways present in PAH, there is simply a lack of pediatric data with regard to indication and order of additional therapy. In this regard, registries such as REVEAL[50] in the United States and the international pediatric TOPP[51] may be best suited to provide information.

PLATELET-DERIVED GROWTH FACTOR RECEPTOR/TYROSINE KINASE INHIBITORS

The adult phase II trial demonstrated that imatinib is well tolerated in patients with PAH, and patients with greater hemodynamic impairment may respond better than patients with less impairment.[52] A pediatric trial of imatinib will be underway soon.

INTERVENTIONAL AND SURGICAL TREATMENT

There are no new data concerning atrial septostomy. However, the surgical creation of a Potts' shunt has been suggested[53,54] to improve heart failure in refractory cases. As survival with PAH increases with new treatments, the outcomes for lung transplantation are also improving. A relatively large recent case series from a single center for pediatric lung transplantation in children with idiopathic PAH showed median survival rates of 5.8 years,[55] and a 3.8-year median survival was recently reported by European investigators.[56] Thus lung transplantation is still reserved for patients who are worsening despite maximal medical therapy.

CONCLUSION

Over the past decade, the development of new therapies for the treatment of PH has led to an improvement in the care of pediatric patients. While there has been a lack of adequate pediatric studies compared to adult studies, the current number of trials centered on children is encouraging for the future. It is clear that collaboration among pediatric researchers in the form of registries will be important to further define the best therapeutic approaches for children with PAH.

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