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Should we use the oral selective IP receptor agonist selexipag off-label in children with pulmonary arterial hypertension?

Martin Koestenberger[1] and Georg Hansmann[2]; on behalf of the European Pediatric Pulmonary Vascular Disease Network

[1]Division of Pediatric Cardiology, Department of Pediatrics, Medical University of Graz, Austria; [2]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Germany

Abstract

We discuss the currently available data on the use of the prostacyclin mimetic selexipag in children and adolescents with pulmonary arterial hypertension (PAH). Future indications may include transitioning from intravenous prostacyclin/prostacyclin analog to oral selexipag, and vice versa, or adding selexipag as a third oral PAH-targeted agent in children not responding well to dual PAH therapy.

Keywords

Pediatric, prostacyclin receptor agonist, pulmonary arterial hypertension, selexipag

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Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive disease with a poor prognosis.[1,2] The currently approved therapeutic agents target three pathways known to be involved in the pathobiology of PAH: endothelin-1, nitric oxide, and prostacyclin (PGI_2) (IP).[3] Dual-combination therapy is established as the standard of care for patients with more than mild PAH, and is increasingly chosen in clinical practice, often as an upfront approach.[3] A recent pilot study demonstrated that triple-combination therapy may be of benefit for treatment-naive adult patients with severe PAH.[4] During the past few years, PAH-targeted therapy has undergone a significant evolution, resulting in the regulatory approval of more than 10 PAH drugs for adults, including up to five pharmacological classes and four different routes of administration. However, emerging therapeutic strategies for adult PAH, such as oral triple-combination therapy, have not been studied at all in children. Selexipag is the first orally administered IP receptor agonist with a nonprostanoid structure.[5] Selexipag is a prostacyclin mimetic that induces vasodilation and inhibits vascular smooth muscle cell proliferation.[6] The major, active metabolite of selexipag, ACT-333679, has high selectivity to the IP receptor, and its long half-life enables a twice-a-day oral dosing regimen.[6] We are convinced that the use of selexipag in children with idiopathic PAH (IPAH), or PAH associated with congenital heart disease (PAH-CHD), after repair of the underlying defect, is likely of clinical benefit. Selexipag may be especially useful when the pediatric PAH is severe and/or poorly responsive to the initial pharmacotherapy.

Herein, we summarize the—admittedly—sparse available data on the therapeutic use of selexipag in pediatric populations (at present limited to IPAH and PAH-CHD). Off-label use of selexipag in children with severe PAH remains low relative to other PAH-targeted therapies to date. Those expert centers that pursue pediatric "compassionate use" of selexipag mostly administer selexipag to PAH patients as an

Corresponding authors:
Georg Hansmann, Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany.
Email: georg.hansmann@gmail.com

Martin Koestenberger, Department of Pediatrics, Medical University of Graz, Auenbruggerplatz 34/2, Graz 8036, Austria.
Email: martin.koestenberger@medunigraz.at

add-on drug, i.e. together with a phosphodiesterase 5 inhibitor (PDE-5i) and an endothelin receptor antagonist (ERA), resulting in triple-oral combination PAH-targeted therapy.

In the Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study, the risk of the primary composite endpoint of death or a complication related to PAH (hospital admission for PAH exacerbation/right ventricle failure) was reported to be significantly lower on selexipag, with 1156 adult PAH patients comparing selexipag with placebo.[7] More than 70% of the patients were receiving one or more PAH therapeutic drugs at baseline, and about 30% were treated with dual combination therapy (an ERA and a PDE-5i). In the GRIPHON trial, the risk of morbidity and mortality events decreased by 40% in the selexipag group vs the comparative group.[7] A GRIPHON substudy in 376 PAH patients highlighted the importance of preventing disease progression in adult patients with PAH.[8] This substudy showed that the addition of selexipag to dual combination therapy with an ERA and PDE-5i led to an incremental benefit similar to that seen in the overall population, including patients with World Health Organization (WHO) functional class (FC) II or III symptoms at baseline.[8]

Safety concerns regarding common and rare adverse effects of selexipag have been raised and widely discussed.[9–11] The pharmacovigilance risk assessment committee of the European Medicines Agency provided an in-depth evaluation of five deaths in France and found that these fatal PAH cases were not selexipag associated; the observed mortality rates in patients treated with selexipag were similar to those treated with other PAH medications.[9] A GRIPHON substudy investigated a temporary interruption of oral selexipag in the enrolled PAH patients, 85% of whom received background medication.[10] Interruption of selexipag occurred quite frequently (111 of 574 patients), mostly due to side effects, but was well tolerated and manageable.[10] There were no episodes of acute deterioration detected during treatment interruption in these patients.[10] A more detailed discussion about selexipag use in adult PAH can be found in recent reviews.[8,10–12]

Data on the use of selexipag for pediatric PAH to date are rare. The European Pediatric Pulmonary Vascular Disease (PVD) Network currently is collecting the initial pediatric experience on the use of selexipag for PAH. The first clinical case of selexipag administration in pediatric PAH was published in 2017, demonstrating clinical and hemodynamic improvements by means of cardiac catheterization in a 12-year-old female with hereditable PAH.[13] So far, we have used selexipag in nine patients ranging from 1.5 to 17 years of age (7–76 kg, three male) and administered oral final doses of 400 to 1600 mcg twice daily. The initial incremental dosing regimen was performed with continuous monitoring in an inpatient setting, toward the best-tolerated dose. Careful dose increases from the "hospital discharge dose" to the final (maximum, best-tolerated) dose were conducted more recently during a close outpatient follow-up. In three of the nine patients, we noted desaturations of more than five percentage points, so that the dose at the time of such worsened pulse oximetry was reduced by 200 mcg per single dose. Such a mild dose reduction of selexipag in mild hypoxemia resulted in significant improvement of systemic saturations probably due to less intrapulmonary arteriovenous (right-to-left) shunting and subsequently lower circulating drug metabolite levels. In our experience, the most common adverse effects in children included nausea/vomiting, flushing and headache, which all decreased in severity and could be prevented or treated with antiemetics in severe cases.

Gallotti et al.[14] recently published their experience with selexipag in four children (IPAH, PAH-CHD). We and Gallotti et al.[13,14] emphasized the need for a detailed evaluation of children with PAH by applying the gold-standard cardiac catheterization and a noninvasive diagnostic method, i.e. ventricular function and pulmonary artery flow variables determined with echocardiography. Pediatric inpatients with PAH, ill-appearing PAH patients, and those with hemodynamics and biomarkers suggesting "high risk" are usually started on a PDE-5i plus ERA simultaneously (as an upfront combination)—in accordance with the most recent consensus statements.[15–17] Prior to the start of an additional third agent (i.e. intravenous treprostinil, epoprostenol, or oral selexipag), all of the patients reported by Gallotti et al. or us were on PDE5i plus ERA dual therapy. Gallotti et al. transitioned their PAH children from a continuous intravenous treprostinil infusion to overlapping, outpatient selexipag, following a protocol by which selexipag is uptitrated while treprostinil is weaned.[14] Selexipag has also been used in one child with single-ventricle physiology before and after a surgical total cavopulmonary connection (TCPC);[14] however, it should be realized that Fontan (TCPC) patients are per se a high-risk population; selexipag may worsen oxygenation by opening intrapulmonary arteriovenous shunts, according to our personal experience in children with biventricular circulation. Moreover, selexipag impairs platelet function—a safety concern that must be taken into account in PAH patients, especially in those with von Willebrand disease and those with a true indication for oral anticoagulation.

Biomarkers have rarely been studied in children with PAH as discussed in the expert consensus statement of the European Pediatric PVD Network.[17,18] There is currently no knowledge on biomarker dynamics before and during the initiation and follow-up of oral selexipag in pediatric PAH. Nevertheless, in our opinion it is most desirable to monitor biomarkers—besides pharmacokinetics/pharmacodynamics, hemodynamics and functional capacity—before and during treatment with selexipag.

One rationale for transitioning from intravenous treprostinil to oral selexipag is the concern for central venous line infections; however, innovative subcutaneously implanted, central intravenous catheter pumps most likely do have

lower complication rates including central line infection[19] than percutaneously tunneled central venous catheters. Adding selexipag as a third oral PAH-targeted agent can be of benefit in patients not responding to dual therapy, patients who would otherwise be strongly recommended to receive intravenous treprostinil, and possibly be listed for lung transplantation. The concept of add-on oral selexipag to dual-oral combination therapy (PDE5i + ERA) is powered by the idea of avoiding central venous lines, especially in very small children but also in adolescents with severe PAH who often deny central venous lines. Selexipag may be used for clinical stabilization (if feasible, since guidelines recommend intravenous prostanoid therapy in WHO class IV), and, if necessary, as a bridge to bilateral lung transplantation or reverse Potts shunt creation in pediatric PAH.[2,16]

It should be noted that the current, sparse clinical data on the oral use of selexipag in children with PAH [13–15] do not allow any conclusions regarding short-, mid-, or long-term efficacy. We found that oral selexipag has been safe in the small number of PAH children we treated off-label. Moreover, Gallotti et al.[14] reported that transitioning from parenteral to oral prostanoid in children can be pursued safely under a strict protocol. The authors also described the initiation of oral triple therapy with selexipag in a child with severe PAH.[14] Since the first clinical data on selexipag in children with PAH are now available,[13,14] we foresee that oral selexipag use will increase over the next months and years in the pediatric age group.[20] Our assumption is supported by a biocomparison study investigating a pediatric tablet (containing 50 μg selexipag) in adults:[21] Pharmacokinetic characteristics of selexipag and its metabolite ACT-333679 were comparable in both groups,[21] making it interesting for pediatric usage, potentially in small children.

The add-on use of oral selexipag must still be considered "experimental therapy" and we suggest strict patient selection and enrollment in any appropriate clinical study that should include frequent echocardiographic evaluations[22] and also cardiac catheterization before and six months after the start of selexipag, as previously described.[13] The efficacy of selexipag was demonstrated in adult PAH patients, but this medication, although mentioned as a possible add-on therapy in current pediatric guidelines,[15,17] is to date recommended only in adult PAH patients in combination with an ERA and/or a PDE-5i. Nevertheless, the available clinical experience on the use of oral selexipag for pediatric PAH, with more such studies ahead, is promising. Thus, the decision to add selexipag as a third oral PAH agent, or to replace intravenously administered PAH drugs with oral selexipag in rather "stable" pediatric PAH patients, might become a future strategy.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. McLaughlin VV and Suissa S. Prognosis of pulmonary arterial hypertension: The power of clinical registries of rare diseases. *Circulation* 2010; 122: 106–108.
2. Hansmann G. Pulmonary hypertension in infants, children, and young adults. *J Am Coll Cardiol* 2017; 69: 2551–2569.
3. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
4. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: A pilot study. *Eur Respir J* 2014; 43: 1691–1697.
5. Hardin EA and Chin KM. Selexipag in the treatment of pulmonary arterial hypertension: Design, development, and therapy. *Drug Des Devel Ther* 2016; 10: 3747–3754.
6. Duggan ST, Keam SJ and Burness CB. Selexipag: A review in pulmonary arterial hypertension. *Am J Cardiovasc Drugs* 2017; 17: 73–80.
7. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 2522–2533.
8. Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: Insights from the randomized controlled GRIPHON study. *Am J Cardiovasc Drugs* 2018; 18: 37–47.
9. European Medicines Agency. EMA reviewing safety of Uptravi for pulmonary arterial hypertension (14 February 2017), http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/02/WC500221423.pdf (accessed 31 May 2018).
10. Preston IR, Channick RN, Chin K, et al. Temporary treatment interruptions with oral selexipag in pulmonary arterial hypertension: Insights from the Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study. *J Heart Lung Transplant* 2018; 37: 401–408.
11. Greene RA. Safety concerns regarding selexipag in pulmonary arterial hypertension. Am J *Health Syst Pharm* 2018; 75: 419–420.
12. McLaughlin VV, Hoeper MM, Channick RN, et al. Pulmonary arterial hypertension-related morbidity is prognostic for mortality. *J Am Coll Cardiol* 2018; 71: 752–763.
13. Geerdink LM, Bertram H and Hansmann G. First-in-child use of the oral selective prostacyclin IP receptor agonist selexipag in pulmonary arterial hypertension. *Pulm Circ* 2017; 7: 551–554.
14. Gallotti R, Drogalis-Kim DE, Satou G, et al. Single-center experience using selexipag in a pediatric population. *Pediatr Cardiol* 2017; 38: 1405–1409.

15. Hansmann G and Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016; 102(Suppl 2): ii67–ii85.
16. Hansmann G and Apitz C. The need for comprehensive cardiac catheterization in children with pulmonary hypertension. *J Am Coll Cardiol* 2016; 67: 1009–1010.
17. Hansmann G, Apitz C, Abdul-Khaliq H, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016; 102(Suppl 2): ii86–ii100.
18. Pattathu J, Gorenflo M, Hilgendorff A, et al. Genetic testing and blood biomarkers in paediatric pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016; 102(Suppl 2): ii36–ii41.
19. Ewert R, Richter MJ, Steringer-Mascherbauer R, et al. Intravenous treprostinil infusion via a fully implantable pump for pulmonary arterial hypertension. *Clin Res Cardiol* 2017; 106: 776–783.
20. Koestenberger M and Hansmann G. Future applications of the selective prostacyclin (IP) receptor agonist selexipag in pediatric pulmonary hypertension. *Pediatr Cardiol* 2017; 38: 1523–1524.
21. Boehler M, Bruderer S, Ulč I, et al. Biocomparison study of adult and paediatric dose strengths of the prostacyclin receptor agonist selexipag. *Eur J Drug Metab Pharmacokinet* 2018; 43: 115–120.
22. Koestenberger M, Apitz C, Abdul-Khaliq H, et al. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016; 102(Suppl 2): ii14–ii22.