Review Article

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Selexipag: A New Therapeutic Option in Pulmonary Arterial Hypertension

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Abstract

Pulmonary Arterial Hypertension (PAH) is a disease with high mortality and morbidity. Current pharmacotherapy includes prostacyclin analogues, endothelin antagonists and phospho-diesterase inhibitors. The limitation of these molecules coupled with the modest efficacy has fueled research for better drug candidates in the treatment of PAH. Selexipag is a novel non–prostanoid IP receptor agonist. The drug inhibits the proliferation of vascular smooth muscle cells and induces vasodilation in the pulmonary circulation. The drug is hydrolyzed to its active metabolite ACT – 333679 which has high affinity for prostanoid receptor. In the GRIPHON study, a multi-centric phase III clinical trial, selexipag was found to reduce mortality as compared to placebo, when given for over a year. Common adverse events with selexipag use includes headache, jaw pain, nasopharyngitis, nausea and pain in the extremity. The drug is given at a dose of 200 to 1600 mcg twice daily via oral route. Although selexipag is yet to be evaluated for its long term effects in PAH, its entry into the market is likely to usher hope and reduce the bleak prognosis associated with this devastating illness.

Keywords: Selexipag; Pulmonary Arterial Hypertension (PAH); Non–Prostanoid IP Receptor Agonist; New Drug; Mortality.

Introduction

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary arterioles characterised by progressive increases in pulmonary artery pressure and pulmonary vascular resistance [1]. It is a rare disease with an estimated prevalence ranging from 10 to 52 cases per million [2]. Every year between 10-15 cases per million population are detected with PAH in the US [3]. Most of the people may die within five years [4], who may be diagnosed with PAH at the age of 45 years. Currently available pharmacotherapy for PAH targets the prostacyclin(PGI -2), endothelin, and nitric oxide pathways [5,6].

The first drugs to be approved in each class were epoprostenol, bosentan, and sildenafil, respectively [7]. Although these drugs have been in the market for PAH for a considerable duration they are associated with several drawbacks. The use of epoprostenol is plagued with difficulties such as need for familiarity with the techniques of sterile drug preparation, operation of the pump and skill in using intravenous catheter which is surgically implanted, catheter-related infections and pump malfunction. High rates of gram negative infection were found in Teprostinil. Beraprost, which is marketed only in Japan has a limitation of ineffectiveness when used for more than a year. Although endothelin receptor antagonists such as bonestan, ambrisentan and sitaxsentan have similar efficacy, they are known to cause peripheral edema and hepatotoxicity as adverse effects [8]. The limitations of the present drug molecules and the modest efficacy seen with these drugs has fueled the search for a better drug molecule in the treatment of PAH. The most recent drug approved for PAH is selexipag, an oral selective IP prostacyclin receptor agonist that is structurally distinct from prostacyclin [9,10].

Mechanism of Action

The pulmonary vascular homeostasis is to a large extent maintained by prostacyclin PGI_2. Patients with PAH have a reduced differentiation, proliferation and migration of the prostacyclin pathway. Selexipag is non-prostanoid IP receptor agonist. It is hydrolyzed to its active metabolite, ACT-333679, which has a high affinity for prostanoid receptor. This metabolite causes vasodilation and is not affected by EP3 receptor antagonism. The metabolite is also able to induce cAMP accumulation and thereby inhibiting proliferation of vascular smooth muscle cells, which is a key factor in PAH pathogenesis [11] The metabolite unlike the prostaglandin analogues such as iloprost, beraprost and teprostinil does not result in IP receptor internalization and desensitization. Thus the tachyphylaxis that can occur with repeated doses is prevented [12,13].

Efficacy in Clinical Trials

There are limited studies that have assessed the efficacy of selexipag in PAH. The GRIPHON study was a double blind, multi-centre, phase III clinical trial in PAH in which 1156 patients were randomized to receive selexipag (200 μg orally twice daily) or placebo in addition to endothelin antagonists and or phosphodiesterase 5 inhibitors for a little over a year. It was observed that the risk of death was reduced by 40 % in the selexipag group as compared to placebo. There was a lesser proportion of the primary outcome event in the selexipag than control group (27 vs 41.6%). There was also a significant improvement in the 6 minute walk distance among selexipag users when compared to placebo [14].

Safety

Headache, jaw pain, pain in an extremity, nausea, and nasopharyngitis were reported in the patients who received selexipag. The majority of adverse events in the selexipag group were classified as mild (n = 55; 15.2%) or moderate (n = 520; 60.6%). Six patients in the selexipag group experienced at least one serious adverse event(18.2%) Serious adverse events include the hospitalization for worsening of PAH, death due to PAH, death from any cause [14].

Pharmacokinetics

Selexipag is given via oral route (PO) at a starting dose of 200 mcg twice daily. The dose can be increased to a maximum of 1600 mcg twice daily gradually in increments of 200 mcg. Selexipag has a mean terminal half-life of 0.8-2.5 hours. The apparent oral clearance of selexipag is on average 35 L/hour. Selexipag and its active metabolite, reaches maximum plasma concentrations at 2.5 and 4 h, respectively, with mean half-lives of 0.7-2.3 and 9.4-14.22 h. There is no accumulation in plasma, either of parent compound or active metabolite [15].

Current Status

Selexipag was approved by US FDA and EMA in 2015 for the treatment of PAH [16]. It is being evaluated by regulatory bodies of several other countries. The optimal usage of the drug and its place among other anti-PAH therapies requires further clarity. A study is currently looking at the efficacy of selexipag in patients who switched over from prior inhalational teprostinil [17]. The efficacy of this drug among drug naïve patients is also under investigation [18,19]. The drug has not been studied for its long term safety when taken for more than a year and future studies intend to explore this aspect [20].

Conclusion

Pulmonary arterial hypertension is a condition that is associated with poor outcomes. Although several drugs such as endothelin antagonists, prostacyclin analogues and phosphodiesterase inhibitors are currently available as pharmaco-therapeutic options, the prognosis of this disease is rather bleak and it is in this context that the development of a new drug molecule for this disease is a promising trend. However the evidence for the drug's safety and efficacy is relatively sparse and the drug needs intensive scrutiny even in the post marketing phase as far as its safety is concerned particularly in the population at large.

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