Review Article

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Riociguat, a guanylate cyclase stimulator for the treatment of pulmonary hypertension

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ABSTRACT

Pulmonary hypertension (PH) is a rare disease and it is classified into five major categories as per WHO classification. Pulmonary arterial hypertension (PAH) (Category 1) is the increased resistance of pulmonary vasculature due to familial; idiopathic or associated with other connective tissue disorders. The medical therapy forms the major treatment of PAH and inoperable chronic thromboembolic PH (Category 4). Despite the medical therapy available the prognosis remains poor and there is a need for new drugs with a novel mechanism of action. Riociguat is an oral guanylate cyclase stimulator with dual mechanism of action recently approved for PH. The clinical trials have shown that the drug is efficacious in improving 6 min walking distance and other hemodynamic parameters. The drug was efficacious at doses of 1-2.5 mg and it was well tolerated in most of the patients. Observed adverse effects were hypotension, head ache, dizziness, and vomiting.

Key words: Chronic thromboembolic pulmonary hypertension, guanyl cyclase stimulator, pulmonary hypertension, riociguat

INTRODUCTION

Pulmonary hypertension (PH) is a rare progressive disease characterized by increased pressure in the pulmonary vasculature and the diagnosis is made by the observation of pulmonary arterial pressure (PAP) more than 25 mm Hg or 30 mm Hg with exercise.[1,2] The cause may be idiopathic or secondary due to heart and lung diseases. The 1 year mortality rate of PH is around 10-15%.[3] The WHO classification of PH includes five major categories, including pulmonary arterial hypertension (PAH)(idiopathic origin), PH due to left heart disease, chronic obstructive pulmonary disease (COPD), chronic thromboembolic pulmonary hypertension (CTEPH) and PH due to unclear mechanisms.[4,5]

PAH belongs to Category 1 in the classification of PH and it is mainly of idiopathic origin. The pathogenesis is that the resistance of the pulmonary vasculature is increased and it is mainly diagnosed by right heart catheterization.[6] The three major pathways involved in pathogenesis include nitric oxide (NO) pathway, prostacyclin pathway, and endothelin system.[7] The balance between vasoconstrictors and vasodilators is disturbed and the current therapies mainly target to re-establish this balance.[8] The drugs for PH include endothelin receptor antagonists, prostacyclin analogs, phosphodiesterase type 5 inhibitors and calcium channel blockers. There is a 43% reduction in the mortality rate in patients on medical treatment.[9] Despite the current

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treatment available PH remains incurable. The unmet need of the disease, adverse effects of the currently used drugs, and poor response increases the need for the development of new drugs.[10] The tolerance developed due to long-term use of nitrates and the lack of specificity toward pulmonary circulation is the major limitations.[11]

RIOCIGUAT

Riociguat is the first NO independent heme soluble guanylate cyclase (sGC) stimulator approved for the treatment of PH and it has a dual role in NO pathway mediated vasodilatation. It has two major actions like sensitizing the sGC to NO and stimulating guanyl cyclase directly independent of NO.[12-14]

MECHANISM OF ACTION

sGC is an enzyme which transduces the intracellular signals and it is composed of α and β subunits. When NO binds with the reduced heme moiety in β subunit ferrous form is cleaved from the histidine residue thereby activating the soluble guanyl cyclase.[15] The activated enzyme mediates the conversion of guanosine triphosphate to cyclic guanosine monophosphate and thus resulting in relaxation of the blood vessels.[11]

Preclinical studies

The efficacy of riociguat was tested both in *in vitro* and *in vivo* models of PAH (BAY 63-2521). The drug showed efficacy in two well established models i.e. hypoxia induced PH in mice and monocrotaline infusion induced PH in rats. Thus, the pre-clinical studies showed that the drugs were effective in rodent models.[16,17]

CLINICAL TRIALS

Phase I trial

In Phase I trial the safety and pharmacokinetic parameters of riociguat were evaluated in 58 healthy volunteers. The dosage forms used were immediate release tablets or single oral dose solution. A dose of 2.5 mg was tolerated whereas 5 mg resulted in hypotension in a patient and so 2.5 mg was selected in the next part of trial to evaluate the efficacy. The doses used were 0.25-2.5 mg in solution form and the immediate release tablets at a dose of 2.5 mg. The plasma concentration attained maximum peak levels at 0.5-1.5 h and the individuals showed a high inter individual variation in the levels.[18,19]

Phase II trial

Riociguat at doses of 1-2.5 mg thrice daily was efficacious in 75 patients with PH after 12 weeks. The parameters mainly assessed were 6 min walking distance, PAP, pulmonary vascular resistance (PVR), cardiac index and a significant improvement was observed in patients treated with riociguat.[8,20]

A Phase IIb double blinded placebo controlled dose ranging study investigated the efficacy of riociguat in patients with heart failure due to PH associated with left ventricular systolic dysfunction. The results of the study showed that there was no significant improvement in the primary end point (6 min walking distance), but there were a significant improvement in secondary end points.[21,22]

Phase III trial-PATENT-1 and 2 (PAH sGC stimulator trial)

PATENT-1 was a Phase III double blinded placebo-controlled trial and PATENT-2 was an open-label long-term extension trial phase (PATENT-2).

In PATENT-1 study, 443 patients with PAH participated and they were randomized to receive either placebo or two doses of riociguat orally for 12 weeks. The initial 8 weeks was the titration period in which the doses were titrated from 1 to 2.5 mg thrice daily. In the next 4 weeks, the patients were followed up as maintenance phase with their last dose. The primary end point was the improvement in 6 minute walk distance compared with the baseline. The change in PVR, N-terminal pro brain natriuretic peptide, Borg dyspnea score, WHO functional class, and time taken for clinical worsening were the major secondary end points. There was a significant improvement in the 6 min walking distance and the secondary end points in patients who were on riociguat group.[23]

PATENT-2 was the open-label long-term extension study of PATENT-1, which included blinded (sham) for the initial 8 weeks and the maintenance phase for next 40 weeks. Only 396/443 patients from PATENT-1 study entered PATENT-2.[24]

CHEST-1 and II in CTEPH

Chronic thromboembolic hypertension belongs to Category 4 and the main mode of the treatment is the pulmonary artery endarterectomy.[4] Riociguat was used as a medical option in patients in whom the intervention is not possible or there is recurrence after surgery.[25] A phase-III

double-blinded multi-centric placebo controlled trial CHEST-1 study in which 261 patients with recurrent PH after the intervention and CTEPH showed that riociguat significantly showed improvement in the primary end point and secondary end point.[25,26]

PH due to lung disease (interstitial lung disease)

The safety tolerability and efficacy of riociguat was assessed in patients with PH due to interstitial lung disease. The primary end points were the safety and tolerability and the secondary end points were the hemodynamic parameters and 6 min walking distance. The drug was tolerated in most of the patients with improvement in the secondary end points.[27]

EFFICACY PROFILE OF RIOCIGUAT

The doses 1 mg and 2.5 mg were efficacious and resulted in significant reductions in mean PAP in the first hemodynamic study. The dose up to 2.5 mg was well-tolerated and the efficacy was superior compared with NO.[28]

PHARMACOKINETICS OF RIOCIGUAT

The first hemodynamic study showed that the plasma half-life of the drug was 10-12 h and the peak levels were attained at 0.25-1.5 h.[28] The pharmacokinetics parameters of patients with hepatic impairment and controls were compared, which showed that there is no difference in Cmax at <1.5 h. The half-life and AUC parameters were mainly affected in patients with hepatic impairment. The dose has to be titrated in patients with renal impairment.[29,30]

INDICATIONS FOR THE USE

It is indicated in patients with PAH of idiopathic origin and adults with chronic thromboembolism induced PAH (persistent or recurrent i.e. rise in PAP after surgery) or if the patient is inoperable.[31,32]

ADVERSE EFFECT PROFILE OF RIOCIGUAT

The drug is well-tolerated in clinical trials (CHEST-1) except that hypotension occurred in 9% of the patients. Headache, peripheral edema, nausea, vomiting, abdominal disturbances, and dizziness are the other side-effects.[31]

The major adverse effects are hypotension, bleeding tendencies, and teratogenicity. The drug has a boxed warning that it should not be used in pregnant women and pregnancy test should be performed in females of reproductive age group before initiating the therapy. The other contraindication is pulmonary veno occlusive disease.[33]

CONCLUSION

Riociguat was approved by FDA for PAH and recurrent CTEPH. The drug with its novel mechanism of action was proved to be efficacious in Phase II and Phase III trials with improvement in primary and secondary end points. However, the drug also has its own adverse effects with hypotension, head ache being the major ones. The ongoing clinical trials evaluate the drug for its use in PH due to COPD, bone metabolism, its pharmacodynamic effect on blood pressure.[34]

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