Research Letter

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Riociguat treatment for portopulmonary hypertension: a subgroup analysis from the PATENT-1/-2 studies

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Abstract

In patients with portopulmonary hypertension (n = 13) included in the 12-week randomized placebo-controlled PATENT-1 trial, riociguat was well tolerated and improved 6-min walking distance (6MWD), World Health Organization functional class (WHO FC), and other efficacy parameters; 6MWD and WHO FC improvements were sustained over two years in the open-label extension, PATENT-2.

Keywords

soluble guanylate cyclase stimulator, portal hypertension, pulmonary arterial hypertension

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Portopulmonary hypertension (POPH) is a serious complication of portal hypertension from cirrhotic and non-cirrhotic causes. POPH is defined as the presence of pulmonary arterial hypertension (PAH) resulting from portal hypertension, and is classified in pulmonary hypertension (PH) group 1.[1] In an analysis of the REVEAL registry, patients with POPH, including those with relatively better hemodynamics and functional classification at diagnosis, had significantly worse survival than patients with idiopathic or familial PAH.[2] Other REVEAL data for risk levels in PAH subtypes based on predicted one-year survival classified POPH as high risk (70–85% survival), with worse outcomes (<70% survival) only in scleroderma-related PH.[3] Despite this poor prognosis, there is a lack of data from randomized controlled trials (RCTs) on the safety and efficacy of PAH-targeted therapies in POPH owing to the exclusion of such patients from most RCTs of PAH therapies to date.

Riociguat is the first-in-class soluble guanylate cyclase (sGC) stimulator[4] and is approved in two separate PH indications: PAH and inoperable or persistent/recurrent chronic thromboembolic PH.[4,5] Riociguat acts indirectly and synergistically with endogenous nitric oxide and also directly stimulates sGC independently of nitric oxide.[6] In PATENT-1, riociguat significantly improved exercise capacity and functional class (FC), and delayed clinical worsening, in patients with PAH.[4] The improvements in exercise capacity and FC were sustained at two years in the long-term extension, PATENT-2.[7]

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PATENT-1 was unique among PAH RCTs as it did not exclude patients with POPH. We performed an exploratory post-hoc analysis to evaluate riociguat treatment in patients with POPH who were included in the PATENT studies.

Methods

The full design and methodology for PATENT-1 and PATENT-2 have been published previously.[4,7] PATENT-1 was a 12-week, multicenter, double-blind, phase 3 study that investigated riociguat therapy in patients with symptomatic PAH.[4] Patients were randomized to either placebo or riociguat individually dose-adjusted up to 2.5 mg three times daily (t.i.d.), according to systolic blood pressure and signs and symptoms of hypotension. The primary endpoint was change from baseline to week 12 in 6-min walking distance (6MWD). Secondary endpoints included changes in World Health Organization (WHO) FC, *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, pulmonary vascular resistance (PVR), Borg dyspnea score, quality of life, and time to clinical worsening (first occurrence of: all-cause death; heart/lung transplantation; atrial septostomy; hospitalization due to persistent worsening of PAH; start of new PAH treatment or modification of pre-existing prostanoid treatment; persistent decrease of 6MWD >15% from baseline or > 30% versus the last study-related measurement due to worsening PAH; or persistent worsening of WHO FC due to PAH deterioration). Exploratory hemodynamic endpoints included cardiac index, mean pulmonary artery pressure (mPAP), and right atrial pressure. Patients completing PATENT-1 without ongoing riociguat-related serious adverse events (SAEs) were eligible for the open-label, long-term extension, PATENT-2, in which all patients received riociguat up to 2.5 mg t.i.d.

The studies were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. Institutional review board approval of the protocol was obtained at each participating center before enrollment. All patients provided written informed consent.

An exploratory, post-hoc analysis was conducted for the subgroup of patients with POPH. Endpoints were analyzed descriptively using observed data and were presented as individual patient data or analyzed as change from baseline to the last observed value (not including follow-up) among patients who completed the study or withdrew. Continuous data are presented as medians; categorical data are presented as counts and percentages.

Results

Study population

Of 443 patients enrolled in PATENT-1, 13 had POPH; of these, 11 were randomized to receive riociguat 2.5 mg–maximum t.i.d. and two received placebo. The mean ± standard deviation age of the POPH subgroup was 57 ± 9 years (median 60 years), and the majority were women (n = 10, 77%) and in WHO FC III (n = 8, 62%) (Table S1).

Efficacy

In the POPH subgroup, at PATENT-1 week 12, median 6MWD increased from baseline by + 48 m in riociguat-treated patients and + 3 m in placebo patients (Table S2). Changes from baseline in 6MWD in the POPH subgroup were maintained over two years in PATENT-2 (Fig. S1) and appeared comparable to those previously reported in the overall PATENT-2 population.[7] At PATENT-1 week 12, WHO FC improved, stabilized, or worsened in four, six, and zero riociguat-treated patients and one, one, and zero placebo patients, respectively (Table S2). Improvements in WHO FC were maintained at two years in PATENT-2 (Fig. S2). Median NT-proBNP levels and median PVR decreased from baseline at week 12 with riociguat and increased with placebo (Table S2). Fig. 1 shows individual patient data for change in 6MWD, NT-proBNP, PVR, cardiac index, and mPAP over 12 weeks in PATENT-1.

In PATENT-1, one (riociguat-treated) patient with POPH experienced a clinical worsening event (death due to sepsis; not considered study drug-related). In PATENT-2, when most patients had received riociguat for ≥ 2 years, there were four clinical worsening events in two patients (17%) with POPH: one hospitalization due to worsening PH; one start of new PH treatment; and two deaths.

Safety

In the POPH subgroup of PATENT-1, the most frequent adverse events (AEs) with riociguat were peripheral edema and headache, which occurred with comparable incidence to the overall PATENT-1 population (Table S3).[4] One riociguat-treated patient experienced an SAE of acute renal failure (considered study drug-related), and later experienced SAEs of bronchopneumonia and sepsis, resulting in death (not considered study drug-related).

In the POPH subgroup of PATENT-2 (n = 12), the most common AEs were nasopharyngitis (n = 5), peripheral edema (n = 4), anemia (n = 4), and cough (n = 4). Nine patients experienced an SAE in PATENT-2; in one patient the SAE (acute renal failure) was considered study drug-related. One patient had a particularly high NT-proBNP level (Fig. 1), was hospitalized due to PAH during PATENT-2, and subsequently died.

Discussion

In this post-hoc, exploratory analysis of the PATENT-1/-2 studies,[4,7] riociguat-treated patients with POPH showed improvements in 6MWD, WHO FC, PVR, and several other secondary efficacy parameters over 12 weeks. The improvements in 6MWD and WHO FC were maintained

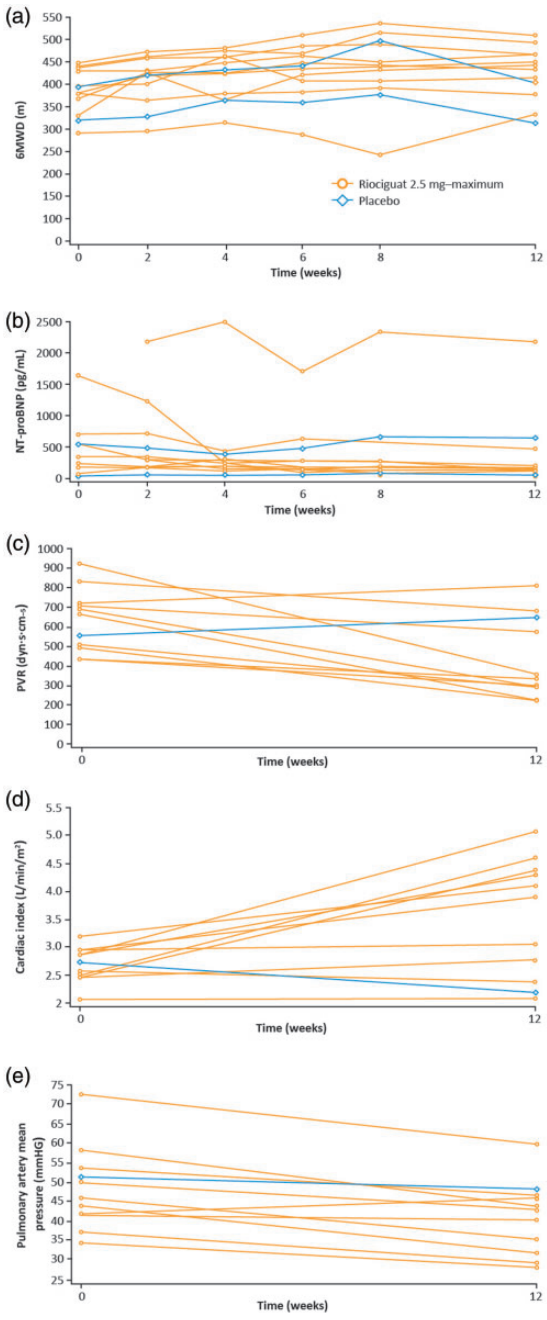

Fig. 1. Individual patient data for (a) 6MWD, (b) NT-proBNP level, (c) PVR, (d) cardiac index, and (e) mPAP over time in patients with POPH in PATENT-1. 6MWD, 6-min walking distance; mPAP, mean pulmonary arterial pressure; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance.

over two years in PATENT-2.[7] Riociguat was well tolerated by patients with POPH, with a comparable safety profile to other PAH subgroups in PATENT-1[8–10] and PATENT-2.[7]

Although POPH treatment typically follows the same algorithm as for other PAH subtypes, patients with POPH have been excluded from most RCTs of PAH therapies to date. Uncontrolled, small series and case reports have suggested that PAH-targeted therapies could benefit patients with POPH,[11–14] e.g. as a preoperative "bridge" to liver transplantation. By improving hemodynamic and clinical parameters, PAH therapy can induce a response that meets liver transplantation eligibility criteria;[15] however, careful patient selection is required and this approach is not currently generally established. Specific guidelines for managing POPH have been recently published;[16] however, there have been no peer-reviewed, published data until now on the role of new medications, such as riociguat, in POPH treatment, nor any published case reports describing the outcomes of sGC stimulators in POPH.[11,15] Our post-hoc analysis is thus of importance as PATENT-1 is the first RCT in PAH that included patients with POPH (3% of the PATENT-1 overall population).[4,17]

Riociguat is approved in patients with group 1 PAH to improve exercise capacity and FC, and to delay clinical worsening.[17] POPH is one cause of group 1 PAH. Riociguat may have potential advantages in patients with POPH because of its generally favorable liver safety profile and the possibility to combine it with a prostanoid. Routine liver function monitoring is not required during treatment. However, as higher riociguat exposure has been observed in patients with moderate hepatic impairment (Child–Pugh Class B),[18] particular care is required during individual dose adjustment in these patients. Riociguat is not recommended in patients with severe hepatic impairment (Child–Pugh Class C) due to a lack of data in these patients. The risk of hypotension is another concern in the POPH population, and riociguat should be used cautiously in these patients. Preclinical data also suggest a potential additional benefit of riociguat on liver characteristics; riociguat significantly decreased portal pressure and liver fibrosis in cirrhotic rat models, although this effect has yet to be demonstrated in humans.[19]

Our study has several limitations. First, this is a post-hoc analysis of a large RCT. Second, the low number of patients (and predominance of women) in this analysis precludes firm conclusions. Third, PATENT-1 excluded patients receiving intravenous prostanoids and the effect of riociguat in such patients is unknown. Patients receiving phosphodiesterase type 5 inhibitors were also excluded; riociguat is contraindicated in combination with these agents owing to high rates of hypotension and treatment discontinuation in such patients.[20] Finally, details of liver-related clinical characteristics and outcomes associated with the small POPH population are lacking.

In conclusion, in this post-hoc analysis of the first RCT in PAH to include patients with POPH, riociguat treatment appeared to be associated with improvements in important primary and secondary efficacy parameters over 12 weeks in patients with POPH. Riociguat was generally well tolerated, with a similar safety profile to that seen in the overall PATENT-1 population and the long-term PATENT-2 study. Given the small sample size, larger prospective studies are warranted to investigate riociguat for the treatment of POPH.

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Conflict of interest

RC-C has nothing to disclose. MHa reports personal fees (lectures) from Actelion, Bayer AG, GlaxoSmithKline, Merck Sharp & Dohme, and Optimal Medical Therapies (OMT); non-financial support (travel) from Actelion and OMT; and other (advisory board) from Actelion, Bayer AG, and GlaxoSmithKline (GSK), outside the submitted work. H-AG reports grants from DFG (German Research Foundation); honoraria from Actelion, Bayer, Ergonex, Gilead, GSK, Novartis, and Pfizer; consultancy fees from AbbVie, Actelion, Bayer, Bellerophon Pulse Technologies, Ergonex, Gilead, GSK, Medscape, Merck Sharp & Dohme, Novartis, OMT, Pfizer, and Web MD Global; and speaker's bureau fees from Actelion, Bayer, Ergonex, Gilead, GSK, Novartis, and Pfizer. MHu reports personal fees from Actelion, Arena, Bayer, GSK, Merck, Novartis, Pfizer, and United Therapeutics. JM and AF are full-time employees of Bayer AG. MK reports involvement in the steering committee for the PORTICO trial, supported by Actelion, during the conduct of the study.

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