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Review article

Individual dose adjustment of riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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ABSTRACT

Riociguat is a soluble guanylate cyclase stimulator that has been approved for the treatment of pulmonary arterial hypertension and inoperable chronic thromboembolic pulmonary hypertension or persistent/recurrent pulmonary hypertension following pulmonary endarterectomy. Riociguat is administered using an 8-week individual dose-adjustment scheme whereby a patient initially receives riociguat 1.0 mg three times daily (tid), and the dose is then increased every 2 weeks in the absence of hypotension, indicated by systolic blood pressure measurements and symptoms, up to a maximum dose of 2.5 mg tid. The established riociguat dose-adjustment scheme allows the dose of riociguat to be individually optimized in terms of tolerability and efficacy. The majority of patients in the phase III clinical trials and their long-term extension phases achieved the maximum riociguat dose, whereas some patients remained on lower doses. There is evidence that these patients may experience benefits at riociguat doses lower than 2.5 mg tid, with improvement in exercise capacity being observed after only 2–4 weeks of treatment in the phase III studies and in the exploratory 1.5 mg–maximum patient group of PATENT-1. This review aims to provide an overview of the rationale behind the riociguat dose-adjustment scheme and examine its application to both clinical trials and real-life clinical practice.

Contents

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1. Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare diseases that are characterized by increased pulmonary vascular resistance (PVR), and can ultimately lead to right heart failure and death. In PAH, increased PVR is caused by remodeling of the small pulmonary arteries [1–4], whereas CTEPH is due to obstruction of the pulmonary vasculature by organised thromboembolic material, as a consequence of major vessel thromboembolism [2,5,6].

PAH is primarily treated with pharmacologic therapies including phosphodiesterase type 5 inhibitors, prostanoids, and endothelin receptor antagonists [2]. Despite the number of available therapies, PAH remains incurable and mortality remains high [7]. In contrast to PAH, the gold standard treatment for CTEPH is a surgical procedure—pulmonary endarterectomy (PEA). PEA is potentially curative [2,5,8], but 24–37% of patients with CTEPH are ineligible for PEA, and 17–35% of patients undergoing PEA develop persistent/recurrent pulmonary hypertension (PH) postoperatively [9–15]. These patients are therefore also candidates for pharmacologic therapy [5].

Riociguat is the first member of the soluble guanylate cyclase (sGC) stimulator class of therapeutic agents for PH [16–19] and has a dual mode of action. It directly stimulates sGC, independent of nitric oxide (NO), and sensitizes sGC to endogenous NO by stabilizing NO–sGC binding. As a result, riociguat restores the NO–sGC–cyclic guanosine monophosphate (cGMP) pathway and leads to increased levels of intracellular cGMP [18–20].

Riociguat has shown efficacy for two separate PH indications: PAH and inoperable or persistent/recurrent CTEPH [21,22], and it is approved at doses up to 2.5 mg three times daily (tid) in these patients [23,24]. Riociguat is administered according to an 8-week dose-adjustment schedule (Fig. 1). The recommended starting dose is 1 mg tid and if systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, the dose should be increased by 0.5 mg tid every 2 weeks up to a maximum of 2.5 mg tid [23–25] (Fig. 1). Dose adjustment leads to an individually optimized dose for each patient in terms of clinical effect and tolerability. Here we review the rationale for the riociguat individual dose-adjustment schedule, and examine its application in clinical trials and daily clinical practice.

2. Development and rationale of riociguat dose adjustment

2.1. Phase I and phase II studies

The development of the riociguat dose-adjustment scheme was based on results from phase I and phase II studies. In the first phase I study of riociguat, the safety and tolerability of single riociguat doses were investigated [26]. Healthy volunteers (n = 58) received single doses of riociguat from 0.25 mg to 5.0 mg. Doses of 0.5–2.5 mg were safe and well tolerated, but 5.0 mg was associated with an increased incidence of adverse events (AEs). The pharmacokinetics of riociguat were dose proportional with single doses of 0.5–5.0 mg. Heart rate, a non-invasive parameter for indirect estimation of the effect of a vasodilating agent on the cardiovascular system, increased with increasing riociguat dose. Likewise, diastolic and mean arterial blood pressure decreased with increasing riociguat dose, with the first significant effects observed with the 1 mg dose.

In the first phase II study of riociguat [27], the optimal tolerated riociguat dose for patients with PH was investigated. Four patients received hourly incremental doses of riociguat (0.5 + 1.0 + 1.0 mg or 1.0 + 2.0 + 2.0 mg), five received single doses of 1.0 mg of riociguat, and ten patients received single doses of 2.5 mg. Both the 1.0 mg and 2.5 mg doses demonstrated greater efficacy than inhaled NO, and significantly improved pulmonary hemodynamics, with reductions in mean pulmonary artery pressure and PVR, and an increase in cardiac index. Riociguat also had systemic hemodynamic effects, with a balanced decrease in both systemic vascular resistance and systolic blood pressure with increasing riociguat dose.

Although the observed effects of riociguat on systemic vascular resistance and systolic blood pressure were asymptomatic in phase II trials, the individual dose-adjustment scheme was developed to reduce the risk of hypotension. In this scheme, riociguat dose is guided by systolic blood pressure and signs and symptoms of hypotension (Fig. 1). Three times daily dosing was chosen to ensure a low peak:trough ratio and to ensure a constant riociguat plasma concentration, taking into account variability of exposure to riociguat (see below). The 2-week interval between dose increases was based on the time taken to establish a hemodynamic steady state, and convenience for the patient. This dosing scheme has been used

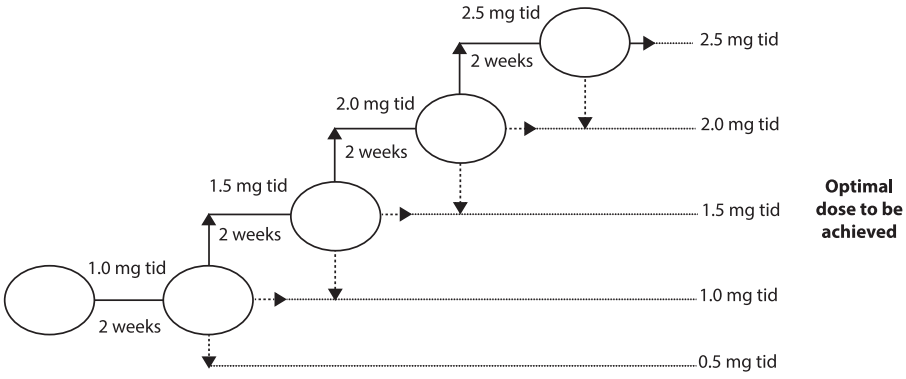

Fig. 1. Riociguat individual dose-adjustment strategy. The starting dose of riociguat is 1.0 mg tid. If SBP remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, the dose should be increased by 0.5 mg tid every 2 weeks, to a maximum dose of 2.5 mg tid. If SBP decreases below 95 mmHg and the patient shows signs or symptoms of hypotension, the current dose should be decreased by 0.5 mg tid.
SBP, systolic blood pressure; tid, three times daily.
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