Respiratory Medicine Case Reports 22 (2017) 39–43

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Switching from sildenafil to riociguat for the treatment of PAH and inoperable CTEPH: Real-life experiences

Asger Andersen*, Kasper Korsholm, Søren Mellemkjær, Jens Erik Nielsen-Kudsk

Department of Cardiology, Aarhus University Hospital, Denmark

ARTICLE INFO

Article history:
Received 11 April 2017
Received in revised form
6 June 2017
Accepted 6 June 2017

Keywords:
Case report
Pulmonary arterial hypertension
Chronic thromboembolic pulmonary hypertension
Sildenafil
Riociguat

ABSTRACT

Riociguat is a novel soluble guanylate cyclase stimulator that is approved for the treatment of patients with pulmonary arterial hypertension (PAH) and patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or persistent/recurrent CTEPH after pulmonary endarterectomy (PEA). As riociguat is a relatively new drug, experience of its use in clinical practice is limited, especially in patients who would not have met the inclusion criteria for the pivotal Phase III clinical trials, PATENT-1 and CHEST-1.

This article shares our initial practical and clinical experience in switching patients with PAH and CTEPH from the phosphodiesterase type-5 inhibitor sildenafil to riociguat, based on three selected case reports of patients who discontinued sildenafil therapy owing to side effects or disease progression (one patient with idiopathic PAH and two patients with persistent/recurrent CTEPH after PEA). Two cases illustrate our experience with direct switch from sildenafil to riociguat (6–8 h between the last sildenafil dose and the first riociguat dose), and one case illustrates switch to riociguat in a patient who underwent treatment with other PAH-specific therapies between stopping sildenafil and starting riociguat. Symptoms improved with riociguat therapy in two cases; in the third case the patient experienced worsening symptoms 1 month after initiating riociguat and was switched back to sildenafil. These case experiences contribute practical information to assist clinicians in the switch from sildenafil to riociguat therapy in patients with PAH or CTEPH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease characterised by vasoconstriction and remodelling of the small pulmonary arteries, which increases pulmonary vascular resistance (PVR) and leads to right heart failure and ultimately death [1]. PAH-specific therapy aims to dilate the pulmonary vessels and inhibit vascular cell proliferation by targeting three main pathways: the nitric oxide (NO) pathway (targeted by phosphodiesterase type-5 [PDE5] inhibitors and a soluble guanylate cyclase [sGC] stimulator), the endothelin pathway (targeted by endothelin receptor antagonists) and the prostacyclin pathway (targeted by prostanoids) [2,3]. However, despite improvements with modern management, PAH remains incurable with a reported 3-year survival rate 58–73% [4–8], emphasising the need for continued development of PAH-specific therapies.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) characterised by segmental distribution of chronic organised thromboembolic lesions in the pulmonary arteries [9]. Most, but not all, patients with CTEPH have a previous history of acute pulmonary embolism (PE) and the estimated risk of developing CTEPH after acute PE has been reported as 0.4–9% [10–15]. The treatment of choice for CTEPH is removal of the organised thrombus by surgical pulmonary endarterectomy (PEA), which can be curative [9]. However, up to 37% of patients with CTEPH may be deemed technically inoperable due to prominent distal disease or comorbidities [16,17], while 17–31% of patients have residual or recurrent symptomatic PH after PEA [16,18,19]. Until recently, there were no pharmacological therapies approved for the treatment of CTEPH [9].

PDE5 inhibitors (such as sildenafil and tadalafil) are the most commonly used treatments for PAH [8,20] and are effective in many cases; however, a substantial proportion of patients do not achieve satisfactory management of their disease with these agents

* Corresponding author. Department of Cardiology, Palle Juul-Jensens Boulevard 99, DK-8200, Aarhus N, Denmark.
E-mail address: asger.andersen@ki.au.dk (A. Andersen).

http://dx.doi.org/10.1016/j.rmcr.2017.06.005

[21–23]. Riociguat is a sGC stimulator that acts on the NO pathway at a different molecular target compared with PDE5 inhibitors and has a dual mechanism of action, directly stimulating sGC and sensitising sGC to endogenous NO, which leads to pulmonary vasodilation and inhibition of vascular cell proliferation [24,25]. As such, there is a biological rationale for switching from PDE5 inhibitors to riociguat, because the former are dependent on endogenous NO production, which is often impaired in PAH [26]. Riociguat has recently been approved for the treatment of patients with PAH and is currently the only approved medical therapy for patients with inoperable CTEPH or persistent/recurrent CTEPH after PEA. These approvals were based on results from the pivotal Phase III studies, PATENT-1 and CHEST-1, in which riociguat (up to 2.5 mg three times daily [TID]) showed beneficial effects on 6 min walking distance (6MWD; the primary endpoint) and secondary endpoints including World Health Organization functional class (WHO FC) and PVR, compared with placebo, in patients with PAH and in patients with inoperable CTEPH or persistent/recurrent CTEPH after PEA, respectively [27,28]. Furthermore, the beneficial effects of riociguat on 6MWD and WHO FC in patients with PAH and CTEPH were shown to be sustained at 2 years of treatment in the long-term extension studies PATENT-2 and CHEST-2, respectively [29,30].

Coadministration of PDE5 inhibitors and riociguat is contraindicated due to the increased risk of hypotension as an adverse event [31]. This contraindication is mainly based on the long-term, open-label extension of the PATENT PLUS study, which showed potentially unfavourable safety signals with sildenafil plus riociguat, most importantly systemic hypotension, and no evidence of a positive benefit:risk ratio [32]. A recent interim analysis of data from the open-label, uncontrolled, Phase IIIb RESPITE (Riociguat Clinical Effects Studied in Patients With Insufficient Treatment Response to PDE5 Inhibitor) study suggested that switching from PDE5 inhibitors to riociguat improved a range of clinical and haemodynamic endpoints in patients with PAH who have had an inadequate response to PDE5 inhibition [33]. In addition, a recent case study described substantial improvements in exercise capacity and haemodynamics in a patient with progressive CTEPH after switching from sildenafil to riociguat while continuing inhaled treprostinil [34]. However, real-world data regarding the switching of patients with CTEPH or PAH from PDE5 inhibitors to riociguat are scarce.

The aim of this article is to share real-life practical clinical experience of switching from sildenafil to riociguat based on three selected case studies from the Department of Cardiology at Aarhus University Hospital. This is the only centre in Denmark with a PEA programme for patients with CTEPH. The programme was initiated in 1994 in collaboration with the University of California San Diego Medical Centre, and operations have since been performed on >239 patients with CTEPH in Aarhus University Hospital. In-hospital mortality for all cases from 2005 to 2016 was 4.3% and the 5-year survival rate was 77%. Outcomes for patients with PAH treated at our centre have been published previously, and are comparable to the findings of larger registries, with a 5-year survival rate of 64% [8]. The centre is experienced in using riociguat therapy in patients with PAH and CTEPH. To date, 39 patients have been treated with riociguat in our centre; of these, three were included in the PATENT-1 and -2 trials, seven in the CHEST-1 and -2 trials, and 13 in the CTEPH Early Access Study (EAS). A further 16 patients were initiated on riociguat after inclusion in the PATENT, CHEST and EAS studies had ended (i.e. initiation was not part of a clinical trial protocol), based on clinical decision. Of the patients treated with riociguat off-study, four were treatment-naïve, 10 were switched from sildenafil to riociguat due to sildenafil side effects or disease progression, one was switched from ambrisentan to riociguat and one received riociguat as add-on therapy to macitentan treatment. The patients that where switched from sildenafil to riociguat had a mean pulmonary pressure of 58 mmHg (±14 mmHg); 6 min. walking distance of 509m (±85m); 5 patients where in WHC functional class (WHO FC) 3 and 5 patients in WHO FC 2; 6 of the patients where women, and before switching from sildenafil, 5 patients where treated with endothelin receptor antagonists and of these, 3 where treated with prostacyclin analogues as well. One of the treatment-naïve patients stopped riociguat due to hypotension. In patients who switched from sildenafil to riociguat, the main reasons for non-adherence to riociguat (n = 5) were headache (n = 1), gastrointestinal symptoms (n = 3), bleeding (unexplained anaemia and haemoptysis) (n = 1) or lack of improvement in symptoms (n = 4). Twelve patients were still receiving riociguat at the end of the observation period (February 2010 until December 2016), and seven patients were deceased (five were still receiving riociguat at the time of death).

2. Methods

We performed a retrospective review of all patients treated with riociguat up to 31 December 2016 in the Department of Cardiology, Aarhus University Hospital, Denmark. Based on review of the files of patients from our PAH outpatient clinic, we selected three typical patients for detailed characterisation who illustrated the issues involved in switching from a PDE5 inhibitor to riociguat in PAH and CTEPH. Informed consent for inclusion in this article was obtained from the patients, in line with guidelines from the Danish Health Authority.

For initiation of riociguat treatment, we predominantly used the dose-adjustment protocol described in the label [31,35], with a starting dose of 1 mg TID (or 0.5 mg TID in patients considered to be at greater risk of hypotension) and dose adjustment by 0.5 mg TID every 2 weeks based on home blood pressure (BP) measurements and telephone consultations. Briefly, the dose was increased by 0.5 mg TID if the systolic BP was >95 mmHg and if the patient had no symptoms of systemic hypotension. The maximum dose was 2.5 mg TID. If the patient developed hypotension (systolic BP < 95 mmHg) or symptoms suspected to be related to low BP (e.g. dizziness), the dose was decreased by 0.5 mg TID. In some patients who showed no change in BP with the first doses, we were able to shorten the dose-adjustment period without causing hypotension or other adverse effects.

3. Case reports

The three selected cases comprised two patients (one male and one female) with CTEPH who had residual PH after undergoing PEA, and one male patient with idiopathic PAH. The patients underwent switching from sildenafil to riociguat because of side effects or disease progression.

3.1. Case 1

A 58-year-old man presented with a massive PE in 2004. He was referred in December 2005 with severe CTEPH in WHO FC III and with a 6MWD of 230 m, mean pulmonary arterial pressure (mPAP) 72 mmHg, cardiac index 1.7 L/min/m^2, PVR 18.2 Wood Units (WU), severe proximal and distal disease in both lungs, and stenosis of the left anterior descending coronary artery (LAD) on coronary angiography. PEA and coronary artery bypass surgery (left internal mammary artery to LAD) were performed with technical difficulties due to a large proportion of distal pulmonary vascular disease that was not technically operable. The patient was discharged with sildenafil treatment 50 mg TID, and on follow-up 12 months after