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Case report

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

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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

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[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

PEA (April 2007) the patient was still in WHO FC III with a 6MWD of 380 m, mPAP 47 mmHg, cardiac index 1.5 L/min/m^2 and PVR 12 WU. Bosentan 125 mg twice daily (BID) was added to the sildenafil treatment, along with furosemide 40 mg BID. Subsequent haemodynamic improvements were observed (mPAP 48 mmHg, cardiac index 2.8 L/min/m^2, PVR 6.9 WU), though the patient was still in WHO FC III with a 6MWD of 375 m. Additional inhaled iloprost 10 mcg five times daily slightly improved the patient's symptoms over the following years. In September 2014, the patient was in WHO FC II with a 6MWD of 421 m. In an attempt to further improve the clinical condition, he was switched from sildenafil to riociguat 2.5 mg TID while maintaining his other PAH treatment (bosentan 125 mg BID and inhaled iloprost 10 mg five times daily). Six hours after the last dose of sildenafil he received a single dose of riociguat 2.5 mg while being observed in our outpatient clinic. The test dose was well tolerated and there was no evidence of hypotension (systolic/diastolic BP was 115/74 mmHg before and 107/63 mmHg 1 h after administration). The patient was continued on riociguat 2.5 mg TID, with follow-up conducted via home BP measurements, telephone consultations and clinical visits after 3, 9 and 15 months. During the 9 months following initiation of riociguat, the patient experienced a marked improvement in symptoms (WHO FC II, 6MWD 437 m). This was despite a reduction and ultimately discontinuation of inhaled iloprost. He experienced no side effects. At the follow-up 9 months after initiation of riociguat, bosentan treatment was reduced to 125 mg daily and diuretics were halved. At the latest follow-up visit (15 months after starting riociguat), the patient described improved symptoms overall. He was in WHO FC II with a 6MWD of 420 m despite the reductions in iloprost and bosentan therapy.

3.2. Case 2

A 54-year-old woman with inflammatory bowel disease and arterial hypertension had a diagnosis of CTEPH in 2008. She had a 6MWD of 575 m, with mPAP 41 mmHg, cardiac index 2.7 L/min/m^2 and PVR 8.5 WU. PEA was performed in late 2009, with difficulties due to the presence of peripheral pulmonary vascular disease. She continued to have residual PH after PEA, and therapy was therefore initiated in hospital with sildenafil 50 mg TID. However, the treatment was discontinued after a few weeks due to visual side effects. Bosentan 62.5 mg BID was started in 2011, but without improvement in symptoms and was discontinued after 4 months due to development of side effects (dizziness, nausea, palpitations and general discomfort). Ambrisentan 5 mg once daily was initiated next, but was discontinued after a few weeks of treatment due to nausea. The patient's 6MWD and functional capacity were progressively worsening, and in February 2012 she was admitted for invasive evaluation. At that time, she was in WHO FC III with 6MWD 480 m, mPAP 50 mmHg, cardiac index 2.4 L/min/m^2 and PVR 10.3 WU. Pulmonary angiography revealed only peripheral changes. Treatment was supplemented with continuous oxygen therapy, with only mild improvement of symptoms. Riociguat treatment was started in April 2013 when the patient was in WHO FC III with 6MWD 436 m. An initial dose of 1 mg was given in our outpatient clinic without any decrease in BP. The riociguat dose was adjusted from 1 mg TID to a final dose of 2.5 mg TID according to the established dose-adjustment scheme [31,35]. The treatment was well tolerated, apart from minimal orthostatic dizziness, and the patient experienced a pronounced and sustained improvement in functional capacity (September 2015: WHO FC II; 6MWD 580 m) that was still present at the last visit at our outpatient clinic (March 2016: WHO FC II; 6MWD 567 m).

3.3. Case 3

A 38-year-old obese man was diagnosed with idiopathic PAH in 2011. His 6MWD was 412 m, with mPAP 70 mmHg, cardiac index 1.7 L/min/m^2 and PVR 14.9 WU. Ambrisentan 10 mg daily and diuretic treatment were initiated with subsequent improvement in symptoms and an increase in 6MWD to 474 m. Invasive follow-up 3 months later showed improved haemodynamics (mPAP 57 mmHg, cardiac index 2.2 L/min/m^2, PVR 8.6 WU). Sildenafil 50 mg TID was added to ambrisentan with a further improvement in 6MWD to 580 m 3 months later. However, in early 2014 the patient worsened and developed right heart decompensation. The diuretic treatment was adjusted. Right heart catheterisation revealed deterioration in haemodynamic parameters (mPAP 72 mmHg, cardiac index 1.9 L/min/m^2, PVR 11.8 WU). The patient's 6MWD was 445 m, and his N-terminal prohormone of brain natriuretic peptide level was 2000 pg/mL. Sildenafil 50 mg TID was switched to riociguat 2 mg TID during an in-hospital stay, with the first dose of riociguat administered 8 h after the last dose of sildenafil, and the intention being to dose adjust riociguat to 2.5 mg TID within 1 month. However, the patient reported general discomfort, worsening dyspnoea and reduction in functional capacity 1 month after starting riociguat. He was therefore switched back to sildenafil 50 mg TID via telephone consultation. The first dose of sildenafil was administered 12 h after the last dose of riociguat; after 1 week, the patient reported improvement of symptoms, and after 3 months, the patient's clinical condition was stable, with WHO FC III and 6MWD of 435 m. Parenteral treprostinil was thereafter initiated as an add-on therapy, and dose adjusted to 0.035 μg/kg/min, to further improve the patient's clinical condition. However, in December 2015 (1 year after the addition of treprostinil), right heart catheterisation showed no improvement in haemodynamic parameters (mPAP 65 mmHg, cardiac index 1.7 L/min/m^2, PVR 13.8 WU) and 6MWD of 405 m. The patient was switched from ambrisentan to macitentan 10 mg daily; however, despite receiving triple therapy, his clinical condition declined over the following year. The patient's obesity meant that he was not considered to be suitable for lung transplantation, and he subsequently developed right heart decompensation and died in early 2017.

4. Discussion

We have presented three different cases of patients who underwent switch to riociguat after stopping sildenafil treatment owing to side effects or disease progression. Two of the patients underwent direct switch from sildenafil to riociguat, whereas the remaining patient underwent treatment with other PAH therapies between stopping sildenafil and starting riociguat. In all three cases, the switch to riociguat was not associated with hypotension. Furthermore, two of the patients experienced improvement of their symptoms after starting riociguat, whereas one patient had worsening symptoms after 1 month and was successfully switched back to sildenafil.

Although sildenafil and riociguat have different mechanisms of action, they both target the NO pathway to promote vasodilation [3]. They therefore may have additive systemic BP-lowering effects when coadministered, leading to an increased risk of hypotension [31]. The effects of concomitant riociguat and sildenafil treatment were examined in the PATENT PLUS study and its open-label long-term extension. High rates of discontinuation due to hypotension were observed in the PATENT PLUS long-term extension phase, with no evidence for a positive benefit:risk ratio [36]. Therefore, coadministration of riociguat with PDE5 inhibitors is contra-indicated [31]. To avoid an exposure overlap and thus reduce the risk of hypotension, a sufficient wash-out period must be included

when switching from a PDE5 inhibitor to riociguat. The RESPITE clinical trial protocol specified a wash-out period of at least 24 h for patients on sildenafil and at least 72 h for those on tadalafil [37]. The recently updated US label for riociguat also states that riociguat should not be administered within 24 h of sildenafil [38]. However, our experience with the two cases of direct switch reported here suggests that, with careful observation and BP monitoring (in hospital or in an outpatient clinic), switch from sildenafil to riociguat may be achieved over a shorter time period (6–8 h) than the recommended timeframe, at least in some patients. In agreement with our findings, another recent case report described a successful overnight switch from sildenafil (last dose taken in the evening) to riociguat (first dose taken in the morning) [39].

In two of our three cases, switch to riociguat led to a marked improvement in symptoms and functional capacity, and the patients were still receiving riociguat at their last follow-up visit. The third patient experienced rapid development of his disease, which may have reduced the effect of riociguat. Similarly, data from the RESPITE study showed that four of 30 patients experienced clinical worsening after switching from a PDE5 inhibitor to riociguat [33]. Thus, while RESPITE showed that replacing PDE5 inhibitor therapy with riociguat may be an effective treatment strategy for patients with PAH who have an insufficient clinical response to PDE5 inhibitor therapy, it is not yet determined whether this is an effective approach to the general management of patients with PAH, or for a subset of patients.

In two of the three patient cases presented in this article, the switch to riociguat was well tolerated. The third patient experienced some general discomfort along with worsening dyspnoea and reduction in functional capacity after receiving riociguat. The safety findings in the three cases presented are consistent with a previous case study of a patient with CTEPH who transitioned from sildenafil/treprostinil to riociguat/treprostinil with no adverse effects [34], and with clinical trial data. In the PATENT-1 and CHEST-1 clinical trials, adverse events occurring more frequently (by $\geq$3%) in patients receiving riociguat than in those receiving placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhoea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anaemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%) and constipation (5% vs 1%) [27,28,35]. In the CTEPH EAS, a Phase IIIb surveillance study which aimed to evaluate the safety and tolerability of riociguat in a setting more closely related to real-life clinical practice, 26% of patients transitioned to riociguat from other PAH therapies, including 20% who had previously received PDE5 inhibitors [40]. Interim exploratory analysis data showed that riociguat was well tolerated with a similar safety profile in the overall population and in the subset of patients who had transitioned from other PAH therapies; no new safety signals were observed compared with the CHEST-1 study.

Of the 10 patients who switched from sildenafil to riociguat in our centre, four patients tolerated the switch to riociguat, one died while receiving riociguat and five stopped treatment as a result of possible side effects or lack of effect. Hypotension did not affect any of the 10 patients who switched from sildenafil to riociguat (although one previously treatment-naïve patient in our centre developed hypotension during riociguat therapy). Results from the PATENT and CHEST studies suggest that hypotension occurs less frequently with longer-term use of riociguat, with most hypotensive events occurring during the initial dose-adjustment phase [41]. In patients receiving riociguat up to 2.5 mg TID, the incidences of hypotension per 100 patient-years were 47.7 and 31.2 in PATENT-1 and CHEST-1, respectively, compared with 6.2 and 4.0 in the long-term extension studies PATENT-2 and CHEST-2, respectively [29,30]. Nevertheless, caution and careful monitoring should be used when administering riociguat to patients at increased risk of hypotension, such as those aged >65 years, and riociguat should not be administered to patients with systolic BP < 95 mmHg [31].

5. Conclusion

Our case reports provide practical real-life experience to assist clinicians in the switch from sildenafil to riociguat therapy in patients with PAH or CTEPH, at a time when no formal switching protocol is available. Our experience was that switching to riociguat may be performed with an interval of 6–8 h between the last dose of sildenafil and the first dose of riociguat in some patients, with careful observation including monitoring of BP. In particular, we recommend a cautious approach in patients with low baseline systemic BP, as has previously been noted by other authors [39]. However, our findings are based on only a small number of individual cases and therefore require confirmation in larger studies. Preliminary data from the Phase IIIb RESPITE study suggest that switching from PDE5 inhibitors to riociguat improves a range of clinical and haemodynamic endpoints in patients with PAH who have had an inadequate response to PDE5 inhibition [33], and the final data are awaited. The efficacy of switching to riociguat compared with continuing PDE5 inhibitor therapy is currently being investigated further in the ongoing REPLACE study (ClinicalTrials.gov: NCT02891850).

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Conflict of interest

AA and JENK have received teaching honoraria from MSD. SN and JENK were investigators in the PATENT-1 and CHEST-1 trials. KK declares no conflicts of interest.

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