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REVIEW

Treatment of patients with chronic thromboembolic pulmonary hypertension: focus on riociguat

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Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of the pulmonary vascular bed that is characterized by elevations in the mean pulmonary artery pressure in the setting of perfusion defects on ventilation–perfusion scan, and subsequently confirmed by pulmonary angiography. CTEPH, or World Health Organization (WHO) group 4 pulmonary hypertension, is a result of unresolved thromboembolic obstruction in the pulmonary arteries. Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH as it is a potentially curative therapy. However, up to one-third of patients are not candidates for the surgery, either due to distal and inaccessible nature of the lesions or comorbid conditions. Due to remodeling that occurs in nonobstructed pulmonary vessels, a portion of patients who have undergone PEA have residual CTEPH after the procedure, attributable to high shear stress prior to PEA. This phenomenon has led to the understanding of a so-called "two-compartment model" of CTEPH, opening the door to pharmacologic treatment strategies. In 2013, riociguat, a soluble guanylate cyclase stimulator, was approved in the US and Europe for the treatment of inoperable or persistent/recurrent CTEPH. This article reviews the current management of CTEPH with a focus on riociguat.

Keywords: riociguat, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, pulmonary hypertension

Introduction

Pulmonary hypertension (PH) defines a group of clinical conditions presenting with abnormal elevation in the pulmonary circulation pressure ultimately leading to right ventricular failure if left untreated.[1] A resting mean pulmonary artery pressure (mPAP) ≥25 mmHg on right heart catheterization (RHC) is diagnostic for PH.[2] PH is further categorized into five groups based on the underlying etiology of the abnormally elevated mPAP: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to lung disease or hypoxic conditions, chronic thromboembolic pulmonary hypertension (CTEPH), and PH of unclear multifactorial etiology.[3] These are designated as Groups I–V, respectively.

CTEPH is caused by persistent obstruction of pulmonary arteries following pulmonary embolism (PE). The estimated prevalence of CTEPH after an acute PE is 0.1%–4.0% after 2 years.[4] However, up to 25% of patients have no previous diagnosis of PE.[5] If suspected, CTEPH is screened for with a transthoracic echocardiogram and radionuclide ventilation/perfusion (VQ) scan, followed by an RHC with pulmonary angiography for disease confirmation and assessment of operability.[6] The current treatment of choice for CTEPH includes lifelong anticoagulation and referral to

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specialized high-volume centers for pulmonary endarterectomy (PEA) in the event that the clot is not prohibitively distal.[4,7] It has been observed that the degree of pulmonary vascular resistance (PVR) does not directly correlate with the clot burden which contributed to an eventual understanding of a two-compartment model of disease, with vascular remodeling that occurs in vessels unobstructed by clot. This understanding, in addition to a cohort of patients with recurrent CTEPH following PEA, opened the door to pharmacologic therapy.[8] Drug therapy utilized in CTEPH prior to the approval of riociguat in 2013 was off-label and provided an unclear benefit given the mixed results of previous clinical trials.[9]

Riociguat is the first approved medication from the soluble guanylate cyclase (sGC) stimulator class and the sole agent approved for CTEPH.[10] Riociguat was approved based on the demonstration of significantly improved exercise capacity in those with inoperable or symptomatic disease despite PEA.[11]

CTEPH review

CTEPH is defined as an elevated mPAP ≥25 mmHg caused by persistent obstruction of the pulmonary arteries after PE that has not resolved despite 3 months of therapeutic anticoagulation.[12] Nonresolving acute PE is the most common cause of CTEPH and can occur after recurrent episodes.[4] Up to 50% of patients have residual perfusion defects 6 months after diagnosis of PE.[12] The estimated prevalence of symptomatic CTEPH after a PE is as high as 4% at 2 years.[13] Classification of the severity of patient symptoms is done according to the World Health Organization (WHO) functional class (FC) scheme.[14] The FC scheme ranges from I to IV, with FC I being asymptomatic to FC IV being severely symptomatic (Table 1). Risk factors for developing CTEPH after an acute PE include history of lower-limb varicose veins, intermediate-risk PE, size of the initial thrombus, elevated systolic pulmonary artery pressure >50 mmHg in the acute phase and residual emboli at 3-month follow-up.[15,16] Other risk factors associated with the diagnosis of CTEPH include increased factor VIII levels, increased von Willebrand factor levels, abnormalities in fibrinogen, splenectomy, ventriculoatrial shunt, osteomyelitis, inflammatory bowel disease, antiphospholipid syndrome, hypothyroidism, and cancer.[16] Clinical prediction scores are currently under development to identify patient-specific prognostic factors associated with the progression of an acute PE to CTEPH.[14] The mortality rate of untreated CTEPH is as high as 90% at 3 years.[17]

The current recommendation for optimal management of CTEPH upon diagnosis is referral to a center with expertise in PEA to assess surgical candidacy.[6,18] PEA is the only curative treatment for CTEPH, with periprocedural mortality ranging from <2% to 5% in experienced centers.[19] A center is considered to have adequate expertise if it performs at least 20 PEAs per year with a mortality rate <10%.[20] Despite this curative procedure, recent registries indicate that a significant portion of patients are inoperable candidates (36.4%), do not undergo PEA despite being candidates (12.6%), or have persistent disease symptoms despite PEA.[5,6] Prior to riociguat, inhaled iloprost, sildenafil, and bosentan were the only agents studied in patients with CTEPH.[21–23] These agents were unable to show a statistically significant difference in 6-minute walk distance (6MWD) in the CTEPH population.[6] Riociguat is the first agent to demonstrate a significant change in 6MWD and hemodynamic parameters in patients with inoperable disease or persistent or recurrent symptoms after PEA.[11]

Riociguat mechanism of action and pharmacology

Riociguat is a sGC stimulator that increases the maximal catalytic rate and activation of sGC, thereby increasing the synthesis of cyclic guanosine monophosphate (cGMP) in smooth muscle cells and producing antiproliferative effects, vasodilatory effects, and reducing platelet aggregation.[24] In vitro, sGC stimulator activity is synergistic in the presence of nitric oxide (NO) but may also occur in an NO-independent fashion.[24] Riociguat increases sGC activity 73-fold independent of NO and 122-fold in the presence of NO, as evidenced by its 12 times more potent vasorelaxant properties in

Table 1 Pulmonary hypertension functional classification

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

nitrate-refractory vessels compared with glycerol trinitrate (an NO donor).[25,26] Riociguat demonstrated ten times more potent vasorelaxant properties than its principle and active M1 metabolite, with neither entity resulting in sensitization or tachyphylaxis after sustained exposure.[26]

Phase II efficacy, safety, and dose ranging studies in CTEPH

Riociguat was first studied in patients with CTEPH in a Phase II, dose-finding study.[27] For the dose-finding phase, four patients with PAH and CTEPH were administered three doses of riociguat, each 1 hour apart, for a total dose of either 2.5 or 5 mg. One patient in the high-dose group experienced asymptomatic hypotension while supine.[27]

Pharmacokinetic variables were assessed after administering a single dose of riociguat.[27] The minimum dose was 1 mg, and the maximum dose was 2.5 mg. Time to maximum serum (C_{max}) concentration of riociguat (T_{max}) ranged from 15 to 90 minutes. Volume of distribution (V_d) was 0.35±0.03 and 0.38±0.08 L/kg in the riociguat 1 mg and 2.5 mg groups, respectively, which was similar to the results obtained for healthy volunteers.[27–29] The elimination half-life ($t_{1/2}$) for riociguat was 10.0±1 and 11.7±4 hours after doses of 1 and 2.5 mg, respectively. The dose-adjusted C_{max} was 1.5–2 times higher and the dose-adjusted area under the time–concentration curve (AUC) was three times higher than observed in healthy subjects.[27–29]

Hemodynamic variables were assessed after NO inhalational testing and, after a brief washout period, a single dose of riociguat.[27] Mean decrease in hemodynamic parameters after receiving a single dose of riociguat 1 and 2.5 mg, respectively, was as follows: systolic blood pressure (SBP) by 24.0 and 28.6 mmHg; systemic vascular resistance (SVR) by 690.0 and 545.9 dyn·s/cm^5; mPAP by 6.8 and 5.1 mmHg; and PVR by 296.5 and 168.1 dyn·s/cm^5. Mean increase in cardiac index was 0.65 and 0.95 L/min/m^2, respectively.[27]

Clinical trial data

In a 12-week multicenter, open-label, noncontrolled Phase II study, patients with CTEPH (n=42) or PAH (n=33) in WHO FC II or III received riociguat titrated according to SBP. Patients on background phosphodiesterase 5 inhibitor (PDE5) inhibitors or prostacyclin derivatives were excluded. Riociguat was titrated by 0.5 mg increments at 2-week intervals based on patient SBP from a starting dose of 1 mg to a maximum of 2.5 mg by mouth (PO) three times daily (TID) by week 8. The primary outcomes were safety and tolerability. Secondary outcomes were changes in 6MWD, WHO FC, and cardiopulmonary hemodynamics. Demographic information for the CTEPH population is presented in Table 2. Forty-one of the 42 (96%) enrolled patients with CTEPH completed the study. The tolerability results were not separated by PAH or CTEPH status. At the end of the study, 52 of the 72 (72%) patients were receiving the maximum dose and four (5%) were receiving the starting dose. One patient was receiving the 0.5 mg PO TID dose. The dose was reduced by 0.5 mg because of asymptomatic hypotension in two patients. Median SBP for the group was

Table 2 Baseline demographic data

Demographics	Ghofrani et al[30]	Ghofrani et al[11]		Simonneau et al[31]
	Riociguat (n=41)	Placebo (n=88)	Riociguat (n=173)	Riociguat (n=237)
Age, mean ± SD, years	63 (56–70)[a]	59±13	59±14	59±13
Female, n (%)	18 (44)	54 (61)	118 (68)	153 (65)
Operable status, n (%)				
Inoperable	41 (100)	68 (77)	121 (70)	172 (73)
Postoperative	0 (0)	20 (23)	52 (30)	65 (27)
WHO functional class, n (%)				
I	0 (0)	0	3 (2)	1
II	10 (24)	25 (28)	55 (32)	31
III	31 (76)	60 (68)	107 (62)	65
IV	0 (0)	2 (2)	8 (5)	3
6-minute walk distance, mean ± SD, m	390 (330–441)[a]	356±75	342±82	351±78
Right heart catheterization, mean ± SD				
mPAP, mmHg	44 (38–51)[a]	44±10	45±13	–
PVR, dyn·s/cm^5	686 (516–859)[a]	779±401	791±432	–
Cardiac index, L/min/m^2	2.31 (1.94–2.68)[a]	–	–	–
Cardiac output, L/min	–	4±1	4±1	–

Notes: [a]Median (interquartile range). – Not reported. From *N Engl J Med*, Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, 369(4):319–329, Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[11] Reproduced with permission of the European Respiratory Society ©: *European Respiratory Journal* Oct 2010, 36(4):792–799. DOI: 10.1183/09031936.[30] Reproduced with permission of the European Respiratory Society ©: *European Respiratory Journal* May 2015, 45(5):1293–1302. DOI: 10.1183/09031936.00087114.[31]
Abbreviations: SD, standard deviation; WHO, World Health Organization; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

significantly reduced from baseline at week 12 (120 mmHg vs 111 mmHg; P=0.0067). Table 3 provides the description of adverse effects (AEs) observed in clinical trials. The WHO FC improved in 22 of the 72 (31%) patients. In the CTEPH subgroup, 6MWD improved by 55 m (95% CI: 17–105) from baseline ($P<0.0001$). In 29 patients who underwent a repeat RHC at week 12, a significant change was seen in mPAP (–4.5 mmHg; 95% CI: –1–7), PVR (–200 dyn·s/cm^5; 95% CI: 155–288), and cardiac index (0.44 L/min/m^2; 95% CI: 0.23–0.76). The authors concluded that riociguat had a favorable safety profile and may improve exercise capacity, symptoms, and hemodynamics in CTEPH.[30]

In a 16-week multicenter, double-blind, placebo-controlled Phase III study, patients aged 18–80 years with inoperable CTEPH or persistent or recurrent CTEPH after PEA were randomized in a 2:1 ratio to receive riociguat or placebo. Additional inclusion criteria were 6MWD of 150–450 m, PVR >300 dyn·s/cm^5, and mPAP >25 mmHg. Patients on background PDE5 inhibitors, endothelin receptor antagonists, or prostacyclin derivatives were excluded. Riociguat or placebo was titrated by 0.5 mg increments at 2-week intervals based on a patient's SBP or signs or symptoms of hypotension, from a starting dose of 1 mg to a maximum of 2.5 mg PO TID. The dose was increased if the SBP was >95 mmHg, maintained if the SBP was 90–94 mmHg, decreased (by 0.5 mg PO TID) if the SBP was <90 mmHg without symptomatic hypotension, and temporarily discontinued if SBP was <90 mmHg with symptoms of hypotension. If discontinued due to an SBP <90 mmHg, the medication was restarted in 24 hours with a 0.5 mg dose reduction. The primary outcome was change in 6MWD from baseline to 16 weeks. Secondary end points included changes in PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, and AEs from baseline to 16 weeks. A total of 261 patients were randomized to either riociguat (n=173) or placebo (n=88). Demographic characteristics are included in Table 2. At week 16, 77% of the patients still in the study were taking the maximal riociguat dose of 2.5 mg PO TID, with 12%, 6%, 4%, and 1% taking riociguat at doses of 2.0, 1.5, 1.0, and 0.5 mg PO TID, respectively. The dose was decreased in 18 patients (10%)

Table 3 Frequency of adverse effects described in clinical trials

Adverse effect	Ghofrani et al[30] (n=75)[a]	Ghofrani et al[11] (n=173)	Simonneau et al[31] (n=237)
Any AE, n (%)	65 (87)	159 (92)	228 (96)
Serious AE, n (%)	11 (15)	12 (7)	100 (42)
Drug-related AE, n (%)	42 (56)	–	109 (46)
Discontinuation of therapy due to AE, n (%)	3 (4)	5 (3)	8 (3)
Death related to AE, n (%)	0 (0)	2 (1)	0 (0)
AE reported in trial population, n (%)			
Abdominal pain	7 (9)	–	–
Constipation	5 (7)	10 (6)	–
Cough	–	9 (5)	32 (14)
Diarrhea	4 (5)	17 (10)	33 (14)
Dizziness	6 (8)	39 (23)	45 (19)
Dyspepsia	18 (24)	31 (18)	–
Dyspnea	–	8 (5)	27 (11)
Fatigue	7 (9)	–	–
Headache	12 (16)	43 (25)	–
Hemoptysis	–	3 (2)	7 (3)
Hypotension	11 (15)	16 (9)	14 (6)
Increased INR	–	10 (6)	–
Nasopharyngitis	4 (5)	26 (15)	55 (23)
Nausea	–	19 (11)	–
Peripheral edema	9 (12)	27 (16)	43 (18)
Right ventricular failure	–	5 (3)	–
Syncope	4 (5)	3 (2)	17 (7)
Tachycardia	9 (12)	–	–
Upper respiratory tract infection	4 (5)	10 (6)	26 (11)
Vomiting	6 (8)	17 (10)	–
Vertigo	6 (8)	–	–

Notes: [a]Data included for both pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension groups. – Not reported. From *N Engl J Med*, Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, 369(4):319–329, Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[11] Reproduced with permission of the European Respiratory Society ©: *European Respiratory Journal* Oct 2010, 36(4):792–799. DOI: 10.1183/09031936.[30] Reproduced with permission of the European Respiratory Society ©: *European Respiratory Journal* May 2015, 45(5):1293–1302. DOI: 10.1183/09031936.00087114.[31]

Abbreviations: AE, adverse effect; INR, international normalized ratio.

in the riociguat group, as compared to three (3%) in the placebo group. At week 16, the 6MWD had increased from baseline by a mean of 39 m in the riociguat group, compared to a 6 m decrease in the placebo group (least square mean difference [LSMD], 46 m; 95% CI: 25–67; $P<0.001$). PVR decreased by 226 dyn·s/cm^5 in the riociguat group compared to an increase of 23 dyn·s/cm^5 in the placebo group (LSMD, −246 dyn·s/cm^5; 95% CI: −303 to −190; $P<0.001$). Riociguat was also associated with significant improvement in mPAP (LSMD, −5 mmHg; 95% CI: −7 to −3; $P<0.001$) and cardiac output (LSMD, 0.9 L/min; 95% CI: 0.6–1.1; $P<0.001$). There were also significant improvements in NT-proBNP level, Borg dyspnea index, and WHO FC. There were no differences noted in time to clinical worsening ($P=0.17$). There were no statistical differences noted in the occurrence of AE in the placebo and riociguat groups (Table 3). The authors concluded that riociguat significantly improved 6MWD and other clinical outcomes in the study population.[11]

A multicenter, open-label, single-group Phase IV study was conducted to assess the long-term safety and tolerability of riociguat. Of the 243 patients completing the initial Phase III study, 237 (98%) entered the extension study.[11] Patients previously receiving riociguat continued the same riociguat dose they were maintained on at the end of the initial study. Those in the placebo group received riociguat with the same dosing schematic used in the initial study.[11] The primary outcome was to assess the safety and tolerability of long-term riociguat treatment. Safety parameters included AE and laboratory variables. Exploratory efficacy end points included 6MWD, NT-proBNP, WHO FC, time to clinical worsening, and Borg dyspnea score. AEs occurred in 228 (96%) patients (Table 3). Thirteen deaths occurred during the extension study, but none were attributed to riociguat. Improvements in 6MWD in the riociguat group from the initial study were sustained at week 12 and year 1 of the extension study. In the former placebo group (n=75), an increase in 6MWD of 51±64 m was observed at week 12. In the overall population, 6MWD was 409±96 m at 1 year (n=172), compared with 351±78 m at baseline (n=237). This represented an improvement of 51±62 m in the overall population (n=172). At 1 year in the overall population, NT-proBNP changed by −416±1,321 pg/mL (n=149). At 1 year, WHO FC had improved/stabilized/worsened in 50%/45%/4% in the former riociguat group (n=117), 39%/59%/2% in the former placebo group (n=59), and 47%/50%/3% in the overall population (n=176), respectively. The proportion of patients in the overall population in WHO FC I/II/III/IV at 1 year was 14%/54%/31%/1% (n=177) compared with 1%/31%/65%/3% (n=236) at baseline, respectively. Overall, 16% of patients experienced clinical worsening during the study period. The estimated rate of clinical worsening-free survival at 1 year was 88% (95% CI: 83–92). The improvement in Borg dyspnea score seen in the former riociguat group (n=154) was maintained at week 12 (n=145) and year 1 (n=113), while patients in the former placebo group showed improved scores after the switch to riociguat at week 12 (n=75) and year 1 (n=58). The authors concluded that long-term treatment with riociguat showed a favorable benefit–risk profile in the studied population.[31]

Pharmacoeconomics

The average wholesale price (AWP) of a 30-day supply (90 tablets) of riociguat, regardless of the strength, is US$9,270 (as of October 2014).[32] The annual cost of the medication has been estimated to be US$90,000 (as of October 2013).[33] A budgetary impact analysis of adding riociguat to a US health plan's formulary for treatment of either PAH or CTEPH was conducted.[34] A decision analytic tool was developed to estimate the impact of riociguat on per-member per-month (PMPM) and per-member per-year (PMPY) bases in health care plans. Drug costs were based on 2013 AWP. In a hypothetical plan population of one million members, the model estimated that seven patients with PAH and two with CTEPH would be suitable for pharmacotherapy (based on published prevalence data). Overall, three patients were receiving riociguat in this model. The incremental cost increase to members of the health care plan to provide coverage for riociguat to three patients was US$0.27 per year and US$0.02 per month. A cost–utility analysis of bosentan and riociguat was conducted from a third-party payer perspective.[35] Bosentan was selected because it is the only other medication studied in a randomized trial fashion in the CTEPH population.[23] Data for this analysis were extrapolated from a Phase III clinical trial in the CTEPH population.[11] The economic model demonstrated that riociguat is cost-effective at a threshold of US$100,000 per quality-adjusted life-year gained after 1 year of treatment and was more cost-effective than bosentan after 2 years of therapy and beyond. While the latter two analyses are mathematical models, they both demonstrated that addition of riociguat to a health care plan had favorable financial outcomes. Both of these pharmacoeconomic analyses were conducted by personnel of the pharmaceutical company producing riociguat and the latter study was not extensively peer-reviewed.

Dosing and administration

Riociguat starting dose is 1 mg given by PO TID and is increased by 0.5 mg PO TID no more than once every 2 weeks to a maximum dose of 2.5 mg PO TID. Doses should be taken 6–8 hours apart. A lower starting dose of 0.5 mg PO TID is recommended for patients who may not tolerate the blood pressure-lowering effects of riociguat or who are taking strong cytochrome P450 (CYP) 3A4/P-glycoprotein (P-gp) inhibitors. Dose titrations may occur if SBP is >95 mmHg and there are no symptoms of hypotension. The dose of riociguat should be decreased by 0.5 mg PO TID for symptoms of hypotension.[36]

Riociguat does not cause rebound PH after sudden withdrawal but should be retitrated for dose interruptions of 3 days or longer.[36] Riociguat absorption does not exhibit significant food effects and can be administered without regard for meals.[28,36] Riociguat undergoes rapid enteral absorption but is a low solubility compound with a pKa of 4.3. Therefore, gastric acid-reducing agents significantly affect riociguat's bioavailability and should be administered at least 1 hour before or after riociguat.[28,36] Riociguat metabolism and excretion fractions demonstrate significant interpatient variability, and thus hepatic and renal impairment will have variable clinical effects between patients.[28]

Drug interactions, contraindications, and warnings

Riociguat is principally metabolized via the CYP1A1 and CYP3A4/5 isoenzymes and is a substrate of the P-gp/BCRP efflux enzymes. Potent inducers or inhibitors of these enzymes may pose clinically significant drug interactions. Strong CYP3A4/P-gp inhibitors may necessitate riociguat dose reductions. Combusted tobacco products may increase riociguat dose requirements via CYP1A1 induction.[35] Riociguat is contraindicated in patients receiving concomitant PDE5 inhibitors, nonspecific PDE inhibitors, or NO donors due to a risk of potentially fatal hypotensive complications.[35] The use of riociguat is not recommended in patients with a creatinine clearance <15 mL/min, those receiving dialysis, or with Child-Pugh C liver disease.[7] Riociguat should not be used in those with pulmonary veno-occlusive disease. In placebo-controlled trials, serious bleeding occurred more frequently in this population (2.4% vs 0%) and included one fatal case of hemoptysis.[35]

Riociguat is contraindicated in pregnancy (Category X).[35] Women of reproductive potential must enroll in a risk evaluation and mitigation strategy (REMS) program to receive the medication. This program requires monthly pregnancy testing and using two acceptable methods of contraception until 1 month after the therapy has been discontinued. Nursing mothers should not initiate or continue riociguat. Riociguat is only available through specialty pharmacies enrolled in the REMS program.

Role in therapy

Riociguat's role in the management of CTEPH will continue to evolve as more clinical experience and post-marketing data are available. Currently, it is paramount that patients with CTEPH continue to be referred early to a center with expertise in PEA for assessment of procedural candidacy.[6,14,37–40] A recent systematic review including 19 studies with 2,729 patients described outcomes after PEA.[41] Before PEA, 60%–100% of patients were WHO FC III or IV. This percentage of patients with WHO FC III or IV symptoms decreased to 0%–21% after PEA. Residual PH symptoms were present in 11%–35% of the patients after PEA. Five-year survival was in the range of 74%–89%. The median 30-day mortality after PEA was 8%. The improvement in 6MWD 2 years after PEA was 96 m.[42]

Initiation of riociguat prior to surgical assessment at a center with expertise in PEA, while shown to improve symptomatic disease, is discouraged as it has the potential to delay an often curative procedure.[14,40] One retrospective study indicated that there was no difference in outcomes with preoperative pharmacotherapy, but there was a delay in PEA in those treated with pharmacotherapy first.[43] One small randomized, controlled trial demonstrated an improvement in 6MWD by a mean of 33 m at 16 weeks when comparing preoperative pharmacotherapy with bosentan versus placebo. There is concern that this delay from diagnosis to PEA will delay the operation unnecessarily making removal of the organized thrombus more difficult.[14] Preoperative riociguat for PEA-eligible patients not assessed for PEA at a center with expertise remains an area for future research. Currently, riociguat is a novel therapeutic option in both the inoperable population and those with symptomatic disease despite PEA.[4,40]

Conclusion

PEA remains the treatment of choice for management of CTEPH for operable candidates. Riociguat represents a novel option in inoperable CTEPH and those with symptomatic disease despite PEA. Riociguat is a first-in-class oral medication that is the sole agent approved for CTEPH and which

appears to be effective at improving symptomatology and is well tolerated.

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Disclosure

The authors report no conflicts of interest in this work.

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