Medical management of chronic thromboembolic pulmonary hypertension

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Targeted medical therapy with riociguat is beneficial for inoperable CTEPH or persistent/recurrent CTEPH after PEA http://ow.ly/pdRg3091AiF

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ABSTRACT Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of acute pulmonary emboli, organised into fibrotic material that obstructs large pulmonary arteries, and distal small-vessel arteriopathy. Pulmonary endarterectomy (PEA) is the treatment of choice for eligible patients with CTEPH; in expert centres, PEA has low in-hospital mortality rates and excellent long-term survival. Supportive medical therapy consists of lifelong anticoagulation plus diuretics and oxygen, as needed.

An important recent advance in medical therapy for CTEPH is the arrival of medical therapies for patients with inoperable disease or persistent/recurrent pulmonary hypertension after PEA. The soluble guanylate cyclase stimulator riociguat is licensed for the treatment of CTEPH in patients with inoperable disease or with recurrent/persistent pulmonary hypertension after PEA. Clinical trials of this agent have shown improvements in patients' haemodynamics and exercise capacity. Phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostanoids have been used in the treatment of CTEPH, but evidence of benefit is limited. Challenges in the future development of medical therapy for CTEPH include better understanding of the underlying pathology, end-points to monitor the condition's progress, and the optimisation of pulmonary arterial hypertension therapies in relation to diverse patient characteristics and emerging options such as balloon pulmonary angioplasty.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subclass of pulmonary hypertension. To distinguish CTEPH from subacute pulmonary embolism, diagnosis is made after ⩾3 months of therapeutic anticoagulation [1]. Diagnosis includes a mean pulmonary arterial pressure (mPAP) ⩾25 mmHg with pulmonary capillary wedge pressure (PCWP) ⩽15 mmHg, mismatched perfusion defects on lung ventilation/perfusion scan and/or specific diagnostic signs of chronic thromboembolism on angiography [1, 2].

CTEPH is considered a two-compartment disease: there is initial occlusion of the proximal major vessels by fibrotic material as a consequence of nonresolution of a single or recurrent pulmonary embolism, accompanied by a distal pulmonary arteriopathy and microvascular disease in the nonobstructed areas [3–6].

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The proximal obstructions are suitable for pulmonary endarterectomy (PEA), which is the treatment of choice for eligible patients [7, 8]. Perioperative mortality is now <5% in highly experienced surgical centres and most patients experience substantial functional improvement and near normalisation of haemodynamic parameters [6, 9–13]. Therefore, all patients should be assessed for PEA eligibility in an expert centre [6].

Not all patients with CTEPH are eligible for surgery. Patients with distal lesions are unlikely to be candidates for PEA [1, 14]. Based on international registry data, 36% of patients are considered ineligible for surgery [15]. Furthermore, ∼50% of patients will have persistent or recurrent pulmonary hypertension after surgery [9, 16] and may require further treatment. In patients with CTEPH ineligible for PEA, balloon pulmonary angioplasty (BPA) is a promising new experimental approach, but it is not yet clear which patients are best suited for this procedure; it should only be performed in experienced high-volume CTEPH centres [1].

Recently, options for the medical management of CTEPH have been widened by the application of drugs initially developed for the treatment of pulmonary arterial hypertension (PAH) and the advent of riociguat, the only targeted medical therapy currently licensed for the treatment of CTEPH.

This review discusses current medical therapies for CTEPH and emerging treatment options.

Supportive medical therapy

Optimal medical treatment for CTEPH consists of anticoagulants, plus diuretics and oxygen in cases of heart failure or hypoxaemia [1]. The aim of anticoagulation in CTEPH is to prevent *in situ* pulmonary artery thrombosis and recurrent venous thromboembolism [14]. Treatment should be continued throughout the patient's life, even after PEA [1]. Although no randomised controlled trials of anticoagulants have been conducted in patients with CTEPH, experience with vitamin K antagonists indicates that risk of recurrent pulmonary embolism or venous thromboembolism is low. Major limitations of vitamin K antagonists include their narrow therapeutic window, their interactions with food and other drugs and the need for repeated blood testing [17]. Today, many patients are receiving new oral anticoagulants, but to date there have been no clinical trials of these agents in patients with CTEPH.

PAH therapies

Rationale for use of PAH therapies in CTEPH

Drugs that target key pathways involved in the pathology of PAH are now established in the treatment of this condition [18, 19]. The similarities in pathological features between the two conditions provide a rationale for evaluating PAH therapies in patients with CTEPH [14].

Endothelin-1 is a powerful vasoconstrictor and smooth muscle mitogen synthesised and secreted by vascular endothelial cells. Levels of endothelin-1 are elevated in PAH and CTEPH [20–24], and recent evidence suggests a potential role for endothelin-1 in smooth muscle cell proliferation within the chronic clot in CTEPH, as well as in the distal arteriopathy [25]. Endothelin receptor antagonists (ERAs) act by blocking the type A endothelin receptor selectively, or both the type A and type B endothelin receptors nonselectively, preventing the vasoconstrictive and proliferative actions of endothelin-1 [18, 19, 26].

Prostacyclin, a highly potent vasodilator that can inhibit platelet aggregation and smooth muscle cell proliferation, is produced by endothelial cells [27]. Levels of prostacyclin are reduced in PAH, and thus prostanoid medications have been used [18, 19, 27].

Nitric oxide (NO), an endogenous vasodilator produced by the endothelium, inhibits platelet aggregation and growth of smooth muscle cells [28, 29]. NO activates soluble guanylate cyclase (sGC) to synthesise cyclic guanosine monophosphate (cGMP), a secondary signalling molecule that ultimately leads to decreased intracellular calcium and smooth muscle relaxation. Levels of endogenous NO synthase and NO metabolites are diminished in patients with PAH [28, 29], and thus the pathway is a key target for treatment. Inhibitors of phosphodiesterase (PDE)-5 prevent degradation of cGMP, while stimulators of sGC, such as riociguat, augment cGMP synthesis [18, 19]. There are no studies of prostacyclin or NO pathways specifically in CTEPH and the absence of an animal model greatly hampers research into the physiology of this condition. The rationale for the use of prostacyclin analogues, PDE-5 inhibitors and riociguat in CTEPH depends on its pathophysiological resemblance to PAH.

Open-label studies

Small, open-label trials of PAH therapies, including bosentan [30–32], treprostinil [33], epoprostenol [34–36] and sildenafil [37] have been conducted in patients with CTEPH. These trials are limited by their small patient cohorts, lack of randomisation and blinding, and, in many studies, by the absence of a control arm.

Randomised controlled trials

Efficacy data for randomised controlled trials of targeted therapy in patients with CTEPH [38–41] are summarised in table 1; safety results are in table 2. The efficacy and safety of the dual ERA bosentan were evaluated in the randomised, double-blind, placebo-controlled BENEFIT study [39]. Eligible patients (n=157) had symptomatic CTEPH (World Health Organization functional class (WHO FC) II–IV), 6-min walking distance (6MWD) <450 m, mPAP ⩾25 mmHg, PCWP <15 mmHg and pulmonary vascular resistance (PVR) at rest ⩾300 dyn·s·cm^{-5}. Patients were randomised to placebo or bosentan at an initial dose of 62.5 mg twice daily for 4 weeks, subsequently increased to the target dose of 125 mg twice daily (patients weighing <40 kg were maintained at 62.5 mg twice daily). After 16 weeks of treatment, mean PVR (co-primary end-point) decreased from baseline in bosentan-treated patients and increased in the placebo arm (figure 1) [39]. There was no statistically significant effect of bosentan on 6MWD, the other co-primary end-point (bosentan +2.9 m, placebo +0.8 m; mean treatment effect +2.2 m, 95% CI −22.5–26.8 m). Statistically significant improvements for bosentan over placebo on haemodynamic parameters are presented in table 1. There was no statistically significant decrease in time to clinical worsening with bosentan *versus* placebo (hazard ratio 0.63, 95% CI 0.15–2.64), with few clinical worsening

TABLE 1 Efficacy data for randomised controlled trials of targeted therapy in patients with chronic thromboembolic pulmonary hypertension

	BENEFIT [39]		Sildenafil study [41]		CHEST-1 [38]		CHEST-2 [40]	
	Bosentan	Placebo	Sildenafil	Placebo	Riociguat	Placebo	Prior riociguat	Prior placebo
Patients n	77	80	9	10	173	88	155	82
Study design	Multicentre, randomised, double-blind, placebo-controlled		Randomised, double-blind, placebo-controlled		Multicentre, randomised, double-blind, placebo-controlled		Long-term, open-label extension	
Primary end-point	Change in PVR and 6MWD after 16 weeks		Change in 6MWD after 12 weeks		Change in 6MWD after 16 weeks		None	
6MWD m	+3 (−13–19)	+1 (−18–20)	+18±34#	+0±49#	+39±79***	−6±84	+591±589	+37±69
PVR dyn·s·cm^{-5}	−146+ (−207–−85)	+30 (−25–85)	−179 (245)*	+18 (76)	−226±248***	+23±274		
mPAP mmHg			−6±7#	+0±6#	−4±7***	+1±7		
TPR dyn·s·cm^{-5}	+							
PAOP mmHg			+0±3#	−0±3#				
mRAP mmHg			−0±5#	−1±6#	−1±5	−1±5		
PCWP mmHg					+1±4	+0±4		
mP_a mmHg					−9±12***	−0±12		
Cardiac output L·min^{-1}					+1±1***	−0±1		
Cardiac index L·min^{-1}·m^{-2}	***		−0±1#	−0±0#				
$S_{v}O_2$ %								
$S_{a}O_2$ %					−2±4	−3±8		
$P_{a}O_2$ mmHg					−3±15	−5±12		
Heart rate beats·min^{-1}					+2±12	+1±12		
NT-proBNP pg·mL^{-1}	−200**,¶	+400¶	−355±648#	−77±130#	−291±1717***	+76±1447	−375±1182	−505±1591
WHO FC %								
Improved	14	11	44	0	33	15	50	39
No change	83	80	56	80	62	78	45	59
Worsened	3	9	0	20	5	7	4	2
Clinical worsening events %	4	6			2	6	16	
Borg dyspnoea score	−0 (−1–0)*	+0 (−0–1)	−1±1#	+0±2#	−1±2**	+0±2	−1±2	−1±2
EQ-5D score					+0.06±0.28	−0.08±0.34	+0.12±0.29	+0.01±0.30
LPH score					−7±19	−2±19		
CAMPHOR score								
Symptoms			−2±5#	−0±3#				
Activity			−3±2#	−1±3#				
Quality of life			−2±7#	−0±4#				

Data are presented as mean±SD or mean (95% CI), unless otherwise stated. Data represent change from baseline at 16 weeks (CHEST-1 and BENEFIT), 12 weeks (sildenafil study) or 1 year (CHEST-2). 6MWD: 6-min walking distance; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; TPR: total pulmonary resistance; PAOP: pulmonary artery occlusion pressure; mRAP: mean right atrial pressure; PCWP: pulmonary capillary wedge pressure; mP_a: mean arterial pressure; $S_{v}O_2$: mixed venous oxygen saturation; $S_{a}O_2$: arterial oxygen saturation; $P_{a}O_2$: arterial oxygen tension; NT-proBNP: *N*-terminal of the pro-brain natriuretic peptide; WHO FC: World Health Organization functional class; EQ-5D: EuroQoL 5-dimensions quality-of-life questionnaire; LPH: Living with Pulmonary Hypertension questionnaire; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review. #: mean±SE; ¶: estimated from graph. *: p<0.05; **: p<0.01; ***: p<0.001; +: p<0.0001 *versus* placebo.

TABLE 2 Adverse-event data for randomised controlled trials of targeted therapy in patients with chronic thromboembolic pulmonary hypertension

	BENEFIT [39]		Sildenafil study [41]		CHEST-1 [38]		CHEST-2 [40]	
	Bosentan	Placebo	Sildenafil	Placebo	Riociguat	Placebo	Prior riociguat	Prior placebo
Patients n	77	80	9	10	173	88	155	82
All adverse events [#]								
Headache	7	1	22	10	25	14		
Dizziness/vertigo	5.2	1.3			23	12	19	20
Dyspepsia	<5	<5	33	10	18	8		
Peripheral oedema	13	8			16	20	15	23
Nasopharyngitis	5	3			15	9	24	22
Alanine aminotransferase increase[¶]	14	4						
Diarrhoea					10	5	14	15
Cough					5	18	13	15
Dyspnoea					5	14	12	11
Upper respiratory tract infection					6	5	12	10
Serious adverse events[+]								
Right ventricular failure	3	4	0	0	3	3		
Syncope			0	0	2	3		
Haemoptysis			0	0	2	0	4 (2)	
Worsening pulmonary hypertension	3	1	0	0				
Urticarial rash			11	0				

Data are presented as % of patients (rounded to nearest whole number unless otherwise stated) or n (%). [#]: adverse events occurring in ⩾10% of patients in the active treatment arm in any study; [¶]: three times the upper limit of normal; [+]: "most frequent serious adverse events", as presented in the respective publications.

events in either treatment group (bosentan n=5 (6%), placebo n=3 (4%)). The most frequent adverse events in the bosentan arm were peripheral oedema, abnormal liver function test, headache, right ventricular failure, nasopharyngitis, vertigo and palpitations (table 2). Two patients (3%) in the bosentan group and four (5%) in the placebo group withdrew as a result of adverse events, and one death occurred in each treatment arm (both judged to be unrelated to study treatment).

The ERA macitentan (10 mg·day^{-1}) is currently under investigation in the randomised, double-blind, placebo-controlled MERIT-1 study, which plans to enrol 78 patients with surgically inoperable CTEPH and is expected to report in the near future (ClinicalTrials.gov NCT02021292). The primary outcome is

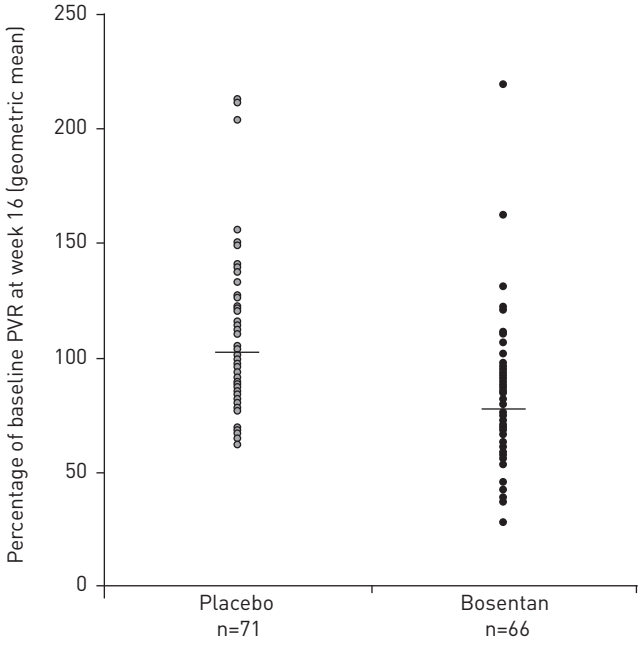

FIGURE 1 Percentage of baseline pulmonary vascular resistance (PVR) at week 16 in patients receiving bosentan or placebo in the BENEFIT study [39]. Reproduced and modified from [39] with permission.

PVR at week 16. The results from this trial are expected soon. The study will be followed by an open-label extension, MERIT-2, which concentrates on safety and is expected to complete in 2018 (ClinicalTrials.gov NCT02060721). The ERA ambrisentan (5 mg·day^{-1}) was to have been investigated in patients with inoperable CTEPH in the AMBER-I study (ClinicalTrials.gov NCT01884675) and its open-label follow-up, AMBER-II (ClinicalTrials.gov NCT01894022), but only 33 out of 160 planned patients were enrolled (ambrisentan n=17, placebo n=16). The available data from AMBER-I have been published on the ClinicalTrials.gov website, showing a median change in 6MWD at 16 weeks (primary end-point) of +25 m in the ambrisentan arm *versus* −10 m in the placebo arm (outcome 1). Median change from baseline in PVR was −130 dyn·s·cm^{-5} with ambrisentan and −103 dyn·s·cm^{-5} with placebo (outcome 2).

Sildenafil, a PDE-5 inhibitor, was evaluated in a randomised, placebo-controlled pilot study in 19 patients with inoperable or persistent CTEPH (WHO FC II/III) and a 6MWD of 100–450 m [41]. Patients were randomised to sildenafil 40 mg three times daily or placebo for 12 weeks, at which time all placebo patients were switched to sildenafil, with a repeat assessment after 1 year. At 12 weeks the change from baseline in 6MWD (primary end-point) did not differ significantly between the sildenafil and placebo arms, but an improvement in PVR was seen (table 1). At 1 year (n=17), there were significant improvements from baseline in the sildenafil arm for 6MWD (+36 m, 95% CI 8–64 m; p=0.014) and PVR (−149 dyn·s·cm^{-5}, 95% CI −228–−71 dyn·s·cm^{-5}; p<0.001). It should be noted that the overall severity of CTEPH at baseline was lower in the placebo arm than in the sildenafil arm.

The Aerosolized Iloprost Randomized Study included 203 patients with severe pulmonary hypertension, including 57 with CTEPH, randomised to receive inhaled iloprost or placebo [42]. The study reported an overall positive treatment effect, but the subgroup analyses described results for primary pulmonary hypertension and a "nonprimary" population that included CTEPH, collagen vascular disease and use of appetite suppressants. The implications of this trial for CTEPH are unclear, because the results for CTEPH patients alone were not reported.

Real-world data

Single centres and registries have described the management of CTEPH: examples are summarised in table 3 [10, 43–48]. The patients reported may be postoperative, technically inoperable, those who refuse surgery and those with operable disease but who are not suitable for PEA because of comorbid conditions. Drug use, effectiveness and outcomes can be expected to vary between these groups. The national centre for PEA surgery in the UK [44], an international registry [10, 11] and several national pulmonary hypertension registries [43, 45–48] indicate that targeted medical therapy is used in both nonoperated and operated patients, but more frequently in the former. ERAs (particularly bosentan) are the most frequently used targeted therapy, the exception being in Latvia, where 90% of patients receive sildenafil [48]. Most patients receiving targeted therapy are treated with a single agent, particularly when treatment is initiated, although some receive combination therapy during the course of the disease [10, 43, 45–47]. The coadministration of riociguat with PDE-5 inhibitors is contraindicated, because excessive reductions of systemic blood pressure can occur with this combination [49]. Published outcomes data from registries are limited, but the most recent results show that 1-year survival with medical treatment for nonoperated patients with CTEPH is ⩾88% (table 3). Recent data from the international CTEPH registry show that nonoperated patients who received targeted therapy had more severe disease at baseline, in terms of a shorter time from symptoms to diagnosis, a higher frequency of WHO FC III/IV, shorter 6MWD and a more severe haemodynamic profile (higher mPAP and PVR; lower cardiac output and PCWP) [10]. Survival is consistently worse among nonoperated than operated patients. Interpretation of this finding should consider differences in baseline characteristics and the diverse reasons for a patient being considered inoperable (*e.g.* comorbidity or distal disease).

CTEPH-targeted medical therapy

The CHEST-1 study

The efficacy and safety of the dual-action sGC stimulator riociguat were assessed in CHEST-1, a phase III, multicentre, randomised, double-blind, placebo-controlled study [38]. Patients (n=261) had inoperable CTEPH, as assessed prospectively by an adjudication committee of experienced PEA surgeons, or persistent/recurrent pulmonary hypertension after PEA, with a 6MWD of 150–450 m, PVR >300 dyn·s·cm^{-5} and mPAP ⩾25 mmHg. Eligible patients were randomised to receive placebo or riociguat at an initial dose of 1 mg three times daily. In the first 8 weeks of the study, the dose was adjusted according to systolic systemic arterial pressure and signs/symptoms of hypotension to a final individualised dose of up to 2.5 mg three times daily. Patients then received their individualised dose for a further 8 weeks. At week 16, 77% of patients still participating in the study were taking the maximal riociguat dose of 2.5 mg three times daily. During the study, the dose of the study drug was decreased in 18 patients (10%) in the riociguat group compared with three (3%) in the placebo group. At week 16, 6MWD (the primary end-point) had increased from baseline by

a mean of 39 m in riociguat-treated patients compared with a 6 m decrease in the placebo arm (least-squares mean difference 46 m, 95% CI 25–67 m; p<0.001). In addition, significantly more patients experienced improvement/stabilisation of their WHO FC in the riociguat arm (33%/62%, respectively) compared with the placebo arm (15%/78%, respectively; p=0.003), although there was no statistically significant difference in the incidence of clinical worsening events between the two arms (riociguat 2%, placebo 6%). Significant benefits

TABLE 3 Published registry data for pulmonary arterial hypertension therapies in patients with chronic thromboembolic pulmonary hypertension (CTEPH)

Country (year) [ref.]	Functional class	Therapies		Main outcomes
UK (2008)# [44]	WHO II–IV	**Surgical** n=321¶ Targeted therapy 65	**Nonsurgical** n=148¶ Targeted therapy 90 ERA 56 PDE-5 inhibitor 33 Prostanoid 11	Survival at 1 and 3 years+: 88% and 76%, respectively, for surgical patients; 82% and 70%, respectively for nonsurgical patients (p=0.023)
International (2016) [10]	NYHA I–IV	**Operated** n=404 Overall 29 ERA 13 PDE-5 inhibitor 15 Prostanoid 1	**Nonoperated** n=275 Overall 61 ERA§ 24 PDE-5 inhibitor 17 ERA + PDE-5 inhibitor 18 Prostanoid 2	Estimated survival at 1, 2 and 3 years **Operated** 93% (95% CI 90–95%), 91% (87–93%), and 89% (86–92%), respectively **Nonoperated** 88% (95% CI 83–91%), 79% (74–83%) and 70% (64–76%), respectively
Latvia (2016) [48]	NYHA II–IV	**Overall** n=31 Sildenafil 90 Ambrisentan 7 Bosentan 1		Cross-sectional analysis only
Portugal (2013) [43]	WHO II–IV	**Overall** n=33 Any 67 Monotherapy 36 Two drugs 15 Three drugs 7 Clinical trial 3 ERA 52 Sildenafil 39 Prostanoid 6		Overall Kaplan–Meier survival estimate at 1 year 94%; nonoperated 92.9%; PEA 100%
Spain (2016) [45]	WHO I–IV	**PEA** n=122 Any 43	**Non-PEA** n=269 Any 82 ERA 38 PDE-5 inhibitor 31 ERA/PDE-5 inhibitor 8 Prostanoid (oral) 3 Prostanoid (*i.v.*) 1 Prostanoid (inhaled) <1	1-, 3- and 5-year survival: nonoperated 93%, 81% and 65%, respectively, and operated 97%, 91% and 86%, respectively (p=0.003) In nonoperated patients at 1 year: 39% improved WHO FC; 6MWD increased by 28±92 m; mPAP decreased by 1.1±11.8 mmHg; PVR decreased by 3.5±4.6 Wood units
Switzerland (2008) [46]	NYHA II–IV	**Baseline** n=70 Any 31 Iloprost (inhaled) 22 Bosentan 5 Bosentan/sildenafil 1 Iloprost (*i.v.*) 1 **Last visit** n=46 Any 81 Iloprost (inhaled) 24 Bosentan 21 Sildenafil 7 Bosentan/iloprost 6 Sildenafil/iloprost 11 Bosentan/sildenafil 6 ⩾3 drugs 2		Significant increase in 6MWD from baseline (377 m) to best response (436 m; p<0.001) At last assessment, 6MWD was significantly lower than best response (380 m; p<0.001) Functional class distribution (I/II/III/IV) improved from 0/14/60/26% at baseline to 6/20/40/34% at best 6MWD response and 4/14/44/38% at last assessment

Continued

TABLE 3 Continued

Country (year) [ref.]	Functional class	Therapies	Main outcomes
Switzerland (2015) [47]	NYHA 3.0±0.7	**Overall** (n=100)[f] **Started within 3 months** Any 74 Monotherapy 64 Two drugs 9 Three drugs 0 ERA 63 PDE-5 inhibitor 20 Prostanoid 0 **Maximal therapy** Any 82 Monotherapy 49 Two drugs 30 Three drugs 2	Overall 1-, 2-, 3- and 4-year transplant-free survival in patients with nonoperated CTEPH was 91%, 84%, 77% and 73%, respectively Survival was significantly better in patients treated after 2004 (p<0.05)

Data are presented as % or mean±SD, unless otherwise stated. WHO: World Health Organization; ERA: endothelin receptor antagonist; PDE: phosphodiesterase; New York Heart Association; PEA: pulmonary endarterectomy; 6MWD: 6-min walking distance; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance. [#]: study from UK national PEA surgery centre; [¶]: data from 2003 onward; [+]: data from 2001 onward; [§]: mostly bosentan, with some sitaxsentan; [f]: data for 2009–2012.

for riociguat *versus* placebo on key efficacy parameters are shown in table 1. The most frequently occurring adverse events in the riociguat arm were headache, dizziness, dyspepsia, peripheral oedema and nasopharyngitis (table 2). The most frequently occurring serious adverse events were right ventricular failure, syncope and haemoptysis (table 2). Deaths related to adverse events occurred in two patients (1%) in the riociguat group (heart failure n=1 and acute renal failure n=1) and in three patients (3%) in the placebo group (respiratory insufficiency n=1, circulatory arrest n=1 and cardiac arrest n=1). With 89% of patients receiving the higher doses of 2.5 and 2.0 mg three times daily at week 16, dose-dependent efficacy and safety have not been analysed.

Based on the results of the CHEST-1 trial, riociguat was licensed in Europe for the treatment of adult patients with WHO FC II/III and inoperable CTEPH or persistent/recurrent pulmonary hypertension after surgical treatment [49]. The adjudication committee excluded 164 (37%) out of the 446 patients screened for CHEST-1 because they were considered "operable" in terms of disease distribution. This observation illustrates the importance of thorough evaluation of CTEPH patients and the use of pharmacological therapy only in patients not eligible for PEA.

Riociguat responder analysis

For patients with PAH, several parameters that indicate response to treatment have been identified, and threshold values for these parameters which correlate with survival have been defined. These "responder thresholds" form part of treatment goals for patients with PAH [1, 50, 51]. These values include 6MWD ⩾380 m, WHO FC I/II, cardiac index ⩾2.5 $L \cdot min^{-1} \cdot m^{-2}$, mixed venous oxygen saturation (S_{vO_2}) ⩾65% and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) <1800 $pg \cdot mL^{-1}$.

An exploratory analysis from CHEST-1 examined the proportion of patients who achieved the responder thresholds described earlier at baseline and at the end of the study [52]. In addition, the analysis examined the proportions of patients achieving PVR <500 $dyn \cdot s \cdot cm^{-5}$ because values above this level are strongly correlated with increased mortality in patients with CTEPH [53]. Riociguat increased the proportion of patients with 6MWD ⩾380 m, WHO FC I/II and PVR <500 $dyn \cdot s \cdot cm^{-5}$ from 37%, 34% and 25%, respectively, at baseline to 58%, 57% and 50%, respectively, at week 16, whereas there was little change in placebo-treated patients. Similar changes were observed for thresholds for cardiac index, S_{vO_2}, NT-proBNP level and right atrial pressure. Additionally, riociguat was associated with an increase in the proportion of patients meeting the combination of response criteria for 6MWD, WHO FC, cardiac index, S_{vO_2} and NT-proBNP level. These results suggest that riociguat increased the proportion of patients achieving criteria defining a positive response to therapy.

Riociguat long-term data

Patients who completed CHEST-1 were eligible to enter a long-term open-label extension study (CHEST-2) [40, 54]. Overall, 237 patients (98%) entered CHEST-2 and received riociguat (patients who

received placebo in CHEST-1 were initiated at a dose of 1 mg three times daily and adjusted to an individual dose as in the CHEST-1 study). The primary objective of CHEST-2 was to evaluate the long-term safety of riociguat (mean treatment duration was 83 weeks, median 75 weeks). Of 157 patients treated for 1 year in CHEST-2, 12 (8%) were receiving additional PAH therapies (ERAs n=8, prostanoids n=4). The most common adverse events in the extension study were nasopharyngitis (23%), dizziness (19%), peripheral oedema (18%) and diarrhoea (14%). For adverse events of special interest, hypotension was reported in 6% of patients and syncope in 7%. Overall, exposure-adjusted rates of adverse events were lower in CHEST-2 than in CHEST-1. The most common drug-related serious adverse events were syncope (2%) and hypotension (1%), which resolved in all cases. Exploratory efficacy analyses showed that the increase in 6MWD seen in patients originally randomised to riociguat was maintained, and 6MWD also increased in patients originally randomised to placebo, to an extent comparable to the former group. The estimated rate of clinical worsening-free survival at 1 year was 88% (95% CI 83–92%), with an estimated overall survival rate at 1 year of 97% (95% CI 93–98%). 2-year data from CHEST-2 have recently been published. The mean±SD change from baseline in 6MWD was +52±66 m at 1 year (n=209) and +50±68 m at 2 years (n=162) [54]. The estimated survival rate was 93% (95% CI 89–96%) at 2 years (figure 2) [54], with no new safety signals detected with the additional duration of treatment.

Other potential uses of medical therapy in CTEPH

Bridging therapy

One potential use of medical therapy in CTEPH is as a bridge to PEA [14, 55]. Registry data show that a substantial proportion of operable patients receive such therapy (table 3), but no randomised trials have been performed in this patient population. The first report of bridging therapy was from 12 patients with severe CTEPH (PVR >1200 dyn·s·cm^{-5}) who received continuous *i.v.* prostacyclin before undergoing PEA [35]. Treatment was associated with a 28% decrease in mean PVR (from 1510 to 1088 dyn·s·cm^{-5}; p<0.001) and a marked decrease in plasma BNP level (from 547 to 188 pg·mL^{-1}; p<0.01). Operative mortality was 8%. In a retrospective analysis of nine patients who received continuous *i.v.* epoprostenol before PEA, six patients experienced either clinical stability or improvement, with a mean reduction in PVR of 28%, and three experienced clinical deterioration [56]. In contrast, in a study of inhaled iloprost before PEA, there were no significant changes in mPAP, cardiac index or PVR; the authors concluded that bridging therapy may have detrimental effects on systemic haemodynamics [57].

In a single-blind randomised study, 25 patients with CTEPH were randomised to standard of care with or without bosentan for 16 weeks before surgery [58]. After 16 weeks, there were statistically significant benefits in favour of bosentan in total pulmonary resistance (–299 dyn·s·cm^{-5}; p=0.004), 6MWD (+33 m; p=0.014) and mPAP (−11 mmHg; p=0.005). Postoperative mortality was four (31%) out of 13 patients who received bosentan *versus* three (25%) out of 12 patients who did not.

A retrospective analysis compared 111 patients with CTEPH who received targeted therapy, including bosentan, sildenafil, epoprostenol and combination therapy, before undergoing PEA with 244 patients who did not receive targeted therapy [59]. Patients receiving medical therapy had little or no improvement in haemodynamic or post surgical outcomes, and referral of operable patients for PEA was delayed compared with patients who did not receive medical therapy. In the international CTEPH registry there were no differences in PEA complications between operated patients who received bridging therapy compared with those who did not, but multivariable analysis indicated that bridging therapy was associated with increased mortality (hazard ratio 2.62, 95% CI 1.30–5.28; p=0.0072) [10].

At present there is no evidence to recommend bridging therapy before PEA, and all eligible patients should proceed to surgery without delay.

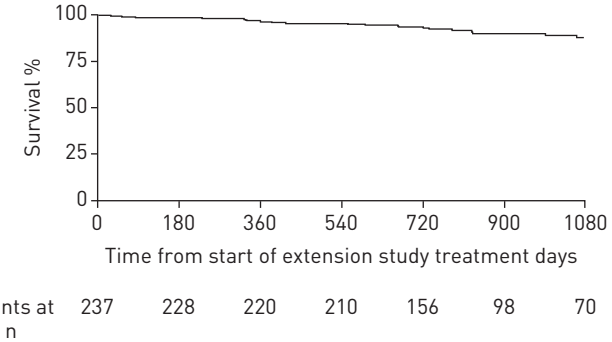

FIGURE 2 Kaplan–Meier analysis of survival over 2 years of treatment with riociguat in the CHEST-2 study [54]. Overall survival was 97% (95% CI 93–98%) at 1 year and 93% (95% CI 89–96%) at 2 years. If the worst-case scenario was assumed, in which patients who dropped out were assumed to have died, survival was 92% (95% CI 88–95%) at 1 year and 87% (95% CI 82–91%) at 2 years. Reproduced and modified from [54] with permission.

Operable patients not undergoing surgery

Medical treatment may be appropriate for patients who are technically operable in terms of disease distribution, but for whom surgery is refused or is considered to be too high risk because of comorbid conditions. Their risk–benefit ratio may be unacceptable because of an excessive surgical risk or because the anticipated benefit is small, as in patients with mild symptoms and good functional capacity: the effects of medical therapy may differ greatly between these populations. There are no robust data in this population, and treatment is based on anecdotal evidence and consensus. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines state that "Medical treatment of CTEPH with targeted therapy may be justified […] in the presence of an unacceptable surgical risk–benefit ratio" [1]. Other authors affirm that all operable patients should proceed to PEA without delay [55].

Patients receiving BPA

Studies, mainly undertaken in Japan, have described use of targeted medical therapy for "bridging" prior to BPA or in patients whose haemodynamic parameters did not normalise after BPA [60–68]. The implications for the use of targeted PAH therapies are difficult to assess in patients undergoing a series of BPA procedures. These studies were uncontrolled, and in European practice, patients in the Japanese cohorts would have been referred for PEA assessment first rather than medical therapy or BPA.

Summary and future directions

The development of further medical therapies for CTEPH depends on improving our understanding of the pathological mechanisms of this disease, including the pathways involved in progression of an acute thrombus into an obstructive fibrous mass, and how the additional distal arterial vasculopathy develops. The lack of an animal model for CTEPH is a barrier to research in this area.

The 2015 ESC/ERS guidelines for the treatment of pulmonary hypertension state that targeted medical therapy may be justified in technically nonoperable patients or those with persistent or recurrent pulmonary hypertension after PEA [1], but the optimal use and benefits of most therapies are unclear, and randomised controlled trials and/or consensus are needed. Riociguat is currently the only targeted medical therapy licensed for the treatment of adults with inoperable or persistent/recurrent CTEPH and recommended by ESC/ERS guidelines [1, 49].

There has been no "head to head" clinical trial to compare efficacy of the PAH therapies either in PAH or CTEPH. With this limitation, the short-term haemodynamic effects of riociguat, bosentan and sildenafil in CTEPH are similar (table 1), but their effects on 6MWD are different [38, 39, 41]. In contrast, in PAH the three classes have similar effects on haemodynamic parameters and exercise capacity [69–71]. The poor correlation between haemodynamic and functional outcomes highlights the need to improve study design and end-points in CTEPH. A recent study reported that patients with inoperable CTEPH (which might be considered "more PAH-like") experienced significant improvements in peak oxygen uptake and gas exchange after treatment with PAH drugs, but there were no such effects in patients with operable CTEPH (which might be considered "less PAH-like") [72]. The authors concluded that drug effects on exercise function in inoperable CTEPH cannot be translated to all forms of the condition. In addition, further studies are required to confirm the role of targeted medical therapies before and after BPA and to characterise the patient populations suitable for the two options. The RACE study (ClinicalTrials.gov NCT02634203), in which patients with CTEPH who are not eligible for PEA will be randomised to riociguat or BPA, may throw light on this question.

With the excellent results now achieved in expert centres, PEA remains the treatment of choice for CTEPH, and all patients should be managed at an expert centre in which the assessment of operability should be made. Riociguat, PAH-targeted therapy or BPA should only be offered to patients ineligible for PEA or with persistent/recurrent CTEPH after surgery [73, 74]. Future developments in targeted medical therapy may demand more refined definitions of CTEPH (*e.g.* distribution of disease, operability or eligibility for medical therapy) so that treatments can be individualised to provide the most appropriate treatment and the best possible outcome.

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