

Evolution of randomized, controlled studies of medical therapy in chronic thromboembolic pulmonary hypertension

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Abstract

Although pulmonary endarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH), many patients have inoperable disease, and some have persistent or recurrent pulmonary hypertension (PH) after surgery. Alternative options (balloon pulmonary angioplasty (BPA) and PH-targeted medical therapy) are, therefore, required. Studies of medical therapies for CTEPH have evolved since Aerosolized Iloprost Randomized (AIR), the first randomized, controlled study of a PH-targeted therapy (inhaled iloprost) to include patients with CTEPH. Key learnings from these studies include the need to evaluate CTEPH separately from other types of PH, the importance of prospective operability adjudication as part of the protocol, and the need for sufficient duration to allow treatment benefits to become apparent. The 16-week Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Study I (CHEST-I) study was the first to operationalize these learnings, demonstrating a significant mean improvement in 6-minute walk distance (+46 m) and improvements in hemodynamic endpoints with riociguat versus placebo. Findings from previous studies will inform the design of future studies to address key issues related to combination medical therapy. Data on combinations of macitentan with phosphodiesterase type 5 inhibitors or oral prostanoids are available from MERIT, the first study to allow such regimens. No data on combinations including riociguat, the only licensed medical therapy for CTEPH, are available. Studies are also needed for multimodality treatment, including medical therapy plus BPA, and medical therapy as a bridge to PEA in selected operable patients. To address these issues and improve patient outcomes, it is vital that we learn from current studies to improve future trial design.

Keywords

chronic thromboembolic pulmonary hypertension, pharmacological therapy, riociguat, macitentan, bosentan

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Introduction

The treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary endarterectomy (PEA). However, approximately 40% of patients are deemed to have inoperable disease, and some patients who undergo PEA will experience persistent or recurrent pulmonary hypertension (PH) after surgery.^{1,2} Alternative options are therefore needed to manage these patients. In recent years, several treatment advances have occurred for patients with CTEPH.³ For example, improvements in surgical techniques and instruments now allow PEA in selected patients with distal segmental and subsegmental disease, previously often considered inoperable.⁴ In addition, balloon pulmonary angioplasty (BPA) and PH-targeted medical therapy are evolving as important treatment options for managing patients with CTEPH who are ineligible for PEA

or who have persistent/recurrent PH after surgery. Combinations of these different treatment modalities to effectively manage CTEPH are also being explored.

The rationale for pulmonary arterial hypertension (PAH)-targeted therapy in CTEPH is partially based on the presence of PAH-like distal arteriopathy in patients with CTEPH.^{5–8} This distal arteriopathy, seen in unobstructed vascular beds, possibly in part results from shear stress caused by increased blood flow through these vessels. The resulting small-vessel changes are similar to those seen

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in PAH and are not amenable to surgery. Additionally, both patients with PAH and those with CTEPH have reduced levels of nitric oxide (NO), leading to a decreased regulation of flow-induced vasodilation in the lungs.⁹ Patients with CTEPH also have increased levels of endothelin-1 (ET-1) compared with controls,¹⁰⁻¹² which are correlated with increased disease severity and worse surgical outcomes in CTEPH.^{11,12} ET-1 is also linked with response to targeted treatment in patients with PAH.¹³ Finally, vasoreactivity is present in both PAH and CTEPH, and hemodynamic responses to inhaled prostanooids are similar in both groups of patients.¹⁴⁻¹⁶

Five classes of medical therapy, targeting the NO, prostacyclin, and ET-1 pathways (Fig. 1), are available for managing PAH and have been investigated as treatment options for CTEPH: soluble guanylate cyclase (sGC) stimulators, phosphodiesterase type 5 inhibitors (PDE5is), prostacyclin analogs (PCAs), prostacyclin receptor agonists, and endothelin receptor antagonists (ERAs).^{17,18}

This review focuses on the evolution of randomized clinical studies of medical therapy and combination modalities

in patients with inoperable CTEPH or persistent/recurrent PH after PEA. We also discuss their limitations, key learning points, and implications for future clinical trials in CTEPH.

Randomized, controlled studies in patients with inoperable CTEPH/ recurrent PH after PEA

Since the publication of the AIR (Aerosolized Iloprost Randomized) study in 2002,¹⁹ the first trial of a PH-targeted therapy to include patients with CTEPH, clinical trials in CTEPH have continued to evolve (Fig. 2).

AIR study of inhaled iloprost for severe PH

The European, multicenter AIR study included 102 patients with severe idiopathic PAH and 101 with other forms of PH (appetite-suppressant-associated PAH, $n=9$; scleroderma-associated PAH, $n=35$; CTEPH, $n=57$).¹⁹ Patients were randomized to receive inhaled iloprost, a stable PCA that

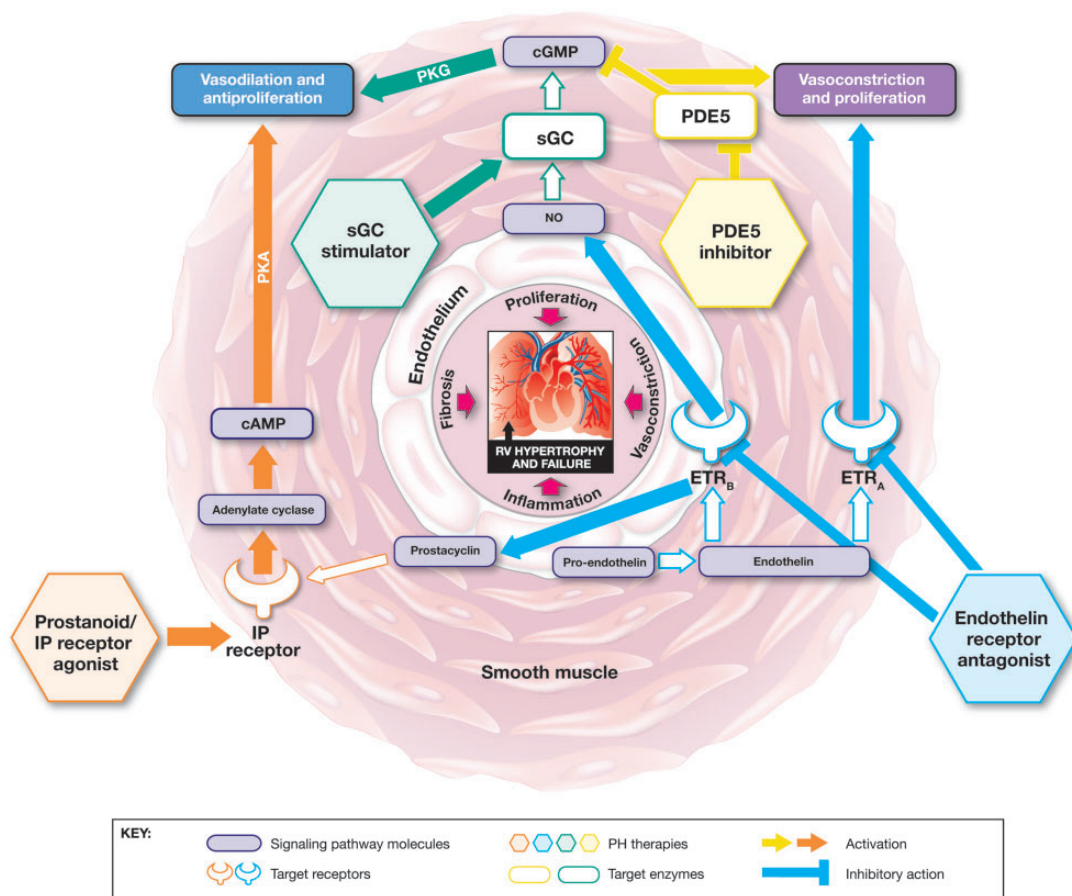


Fig. 1. Key signaling pathways targeted by medical therapies for PH.¹⁸
 cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; ETR_A: endothelin receptor A; ETR_B: endothelin receptor B; IP: prostacyclin; NO: nitric oxide; PDE5: phosphodiesterase type 5; PH: pulmonary hypertension; PKA: protein kinase A; PKG: cGMP-dependent protein kinase; RV: right ventricle; sGC: soluble guanylate cyclase.

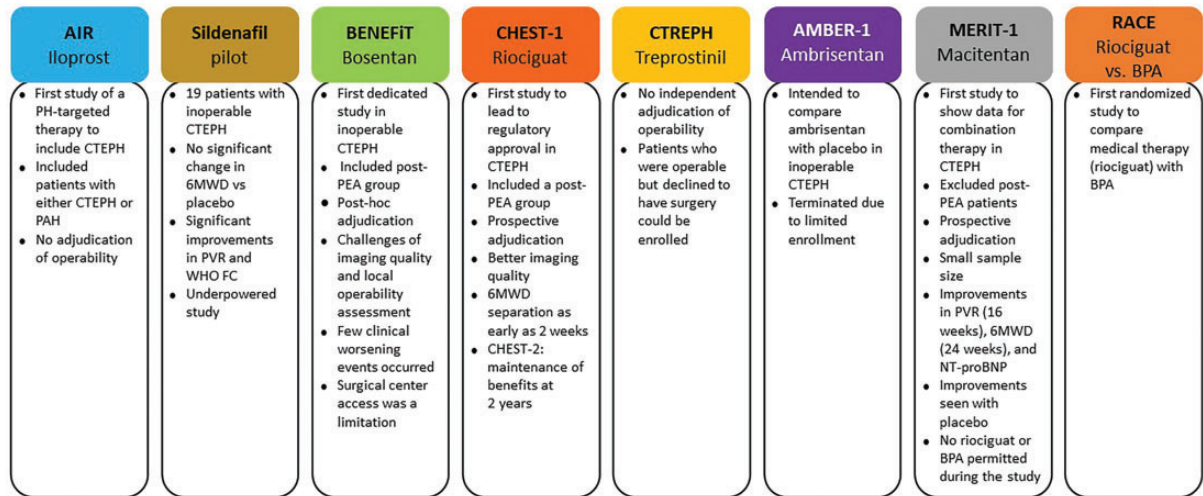


Fig. 2. Evolution over time (from left to right) of randomized, controlled studies of PH-targeted medical therapy in patients with inoperable or persistent/recurrent CTEPH.

AIR: Aerosolized Iloprost Randomized; BENEFIT: Bosentan Effects in iNoperable Forms of chronic Thromboembolic; 6MWD: 6-minute walk distance; BPA: balloon pulmonary angioplasty; CHEST: Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Study; CTEPH: chronic thromboembolic pulmonary hypertension; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAH: pulmonary arterial hypertension; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RCT: randomized controlled trial; WHO FC: World Health Organization functional class.

causes selective pulmonary vasodilatation, or placebo, for 12 weeks.

The primary endpoint in AIR was a combination of improvement in New York Heart Association (NYHA) functional class (FC), without clinical worsening or death, plus $\geq 10\%$ improvement in 6-minute walk distance (6MWD) from baseline to Week 12. In the overall population, this endpoint was reached in 16.8% of patients in the iloprost group compared with 4.9% of patients in the placebo group (estimated odds ratio, 4.0; 95% confidence interval (CI), 1.5 to 10.8; $P = 0.007$). A benefit was seen in patients with idiopathic PAH (20.8% reached the combined primary endpoint with iloprost compared with 5.5% on the placebo group) and in patients with other forms of PH (12.5% compared with 4.3%, respectively), including the 57 patients with CTEPH. A major limitation of this study was that no specific CTEPH subgroup analysis was undertaken, and it may be that the benefits of inhaled iloprost were more robust in patients with PAH than those with CTEPH. Another limitation was that the operability of CTEPH was not adjudicated as part of the study, and therefore some patients may have been eligible for PEA. Therefore, key learning points from the AIR study for future research into CTEPH included the need for separate analysis of patients with CTEPH from other forms of PH, and for adjudication of operability as part of the study protocol. Nevertheless, this study was the first to show signs that PH-targeted therapy may be beneficial in patients with CTEPH. Given the lack of data specific to CTEPH, iloprost

is not currently licensed for use in patients with CTEPH in either Europe or the USA.

Pilot study of sildenafil in inoperable CTEPH

Between 2004 and 2007, 19 patients with inoperable CTEPH recruited from a single UK center were randomized to sildenafil or placebo for 12 weeks, followed by open-label sildenafil for a total duration of 12 months.²⁰ The primary endpoint was change in 6MWD at 12 weeks, although the study was not sufficiently powered to test this endpoint, and no significant difference between the treatment groups was observed. World Health Organization (WHO) FC and pulmonary vascular resistance (PVR) were, however, significantly improved with sildenafil versus placebo at Week 12. At 12 months, patients demonstrated significant improvements in 6MWD, PVR, cardiac index, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and quality of life. No further placebo-controlled trials of sildenafil (or tadalafil) have been conducted in patients with CTEPH, and no PDE5i is currently licensed for use in CTEPH in either Europe or the USA.

BENEFIT study of bosentan for inoperable CTEPH

The BENEFIT study (Bosentan Effects in iNoperable Forms of chronic Thromboembolic PH; ClinicalTrials.gov: NCT00313222) was conducted between 2005 and 2007. This was the first multicenter, randomized, placebo-controlled trial dedicated solely to patients with CTEPH

(inoperable CTEPH or persistent PH > 6 months after PEA) and included 157 patients, 28% of whom had previously undergone PEA.²¹ Patients were deemed inoperable if they had chronic thromboembolic lesions only at the segmental and/or subsegmental levels, or if they had a high PVR compared with the level of pulmonary obstruction. Inoperability was evaluated and confirmed by a qualified surgeon or experienced physician prior to patient enrollment. Patients in BENEFiT were randomized to receive the dual ERA bosentan ($n=77$) or placebo ($n=80$) for 16 weeks.

The independent coprimary endpoints were changes from baseline to Week 16 in PVR and 6MWD. After 16 weeks of treatment, mean PVR decreased from baseline in the bosentan group and increased in the placebo group (treatment effect on PVR of -24.1% ; 95% CI: -31.5 to -16.0 ; $P < 0.0001$). However, hemodynamic improvements with bosentan did not translate into a favorable effect on exercise capacity, with a mean change from baseline to Week 16 in 6MWD of $+2.9$ m and $+0.8$ m for the bosentan and placebo groups, respectively (mean treatment effect, $+2.2$ m (95% CI: -22.5 to 26.8 ; $P = 0.5449$)). The reasons for the discrepancy between bosentan effects on these two endpoints were unclear, although the authors speculated that 16 weeks may not have been long enough for treatment effects on 6MWD to become apparent.

In the same study, a nonsignificant trend toward improvement with bosentan, compared with placebo, in WHO FC was observed (improvement in 15% of bosentan-treated and 11% of placebo-treated patients at Week 16). Moreover, patients had significant improvements in NT-proBNP levels (treatment effect of -622 ng/L in favor of bosentan; $P = 0.0034$), an important prognostic marker in patients with CTEPH.²² No statistically significant decrease in time to clinical worsening (defined as death, lung transplantation, or hospitalization due to worsening PH) was seen with treatment, although very few events occurred (three patients receiving bosentan and five patients receiving placebo). The authors suggested that this may have been due to the short duration of the study. As the BENEFiT study failed to meet its primary endpoint, bosentan has not been licensed for use in patients with CTEPH in either Europe or the USA.

Notably, the BENEFiT study included retrospective operability adjudication before unblinding by an Operability Evaluation Committee comprised of two specialized pulmonologists and two PEA surgeons. The committee judged that 11 patients (7%) were operable (7 in the bosentan group, 4 in the placebo group), leading to their exclusion from the analysis. Thus, the BENEFiT study highlighted the need for prospective operability assessment, independently adjudicated prior to enrollment, to avoid recruitment of operable patients. For this to be achieved, nonsurgical studies in inoperable CTEPH must have access

to experienced surgical centers and high-quality images for optimal adjudication of PEA eligibility.

CHEST study of riociguat for inoperable CTEPH or persistent/recurrent PH following PEA

The CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Study 1; ClinicalTrials.gov: NCT00855465) study of the sGC stimulator riociguat led to the first approval of a PH-targeted therapy in patients with inoperable CTEPH or persistent/recurrent PH following PEA.^{23,24} This large phase 3 study was conducted at 89 centers across 26 countries between 2009 and 2012.²⁵

In CHEST-1, for the first time in a nonsurgical CTEPH study, operability was adjudicated prospectively during the pretreatment phase.^{25,26} All screened patients who were initially considered inoperable ($n=312$) underwent central independent adjudication by an Operability Assessment Committee comprised of six experienced PEA surgeons, or local adjudication in collaboration with a surgeon who met predefined criteria for their level of experience in CTEPH. Operability assessment included at least a pulmonary angiogram/spiral computed tomography pulmonary angiogram supplemented by a ventilation-perfusion scan, medical history, and hemodynamic data. The overall image quality was good, but 5% were deemed not assessable, mainly due to poor quality.²⁶ After adjudication, 69 patients (22%) assessed initially as inoperable were designated operable by the adjudication committee and were excluded from the study. Of the 226 remaining patients, 189 (84%) adjudicated as inoperable and meeting CHEST-1 eligibility criteria were randomized and treated in the study, alongside 72 patients who had persistent/recurrent PH after PEA.²⁵ Patients received riociguat ($n=173$) or placebo ($n=88$) for 16 weeks, including an 8-week riociguat dose-adjustment period.

The primary endpoint of CHEST-1—change from baseline to Week 16 in 6MWD versus placebo—was met, with a treatment effect of $+46$ m (95% CI: 25 to 67 ; $P < 0.001$). Moreover, differences between riociguat and placebo were noticeable as early as Week 2 (i.e. during the riociguat dose-adjustment period). Improvements were also consistently seen across a range of secondary endpoints, including WHO FC (33% of patients improved and 5% worsened with riociguat, compared with 15% and 7%, respectively, with placebo; $P = 0.003$), NT-proBNP, and hemodynamic parameters. Clinical worsening events (defined as death, heart/lung transplantation, rescue PEA, hospitalization due to worsening PH, start of new PH-targeted treatment, decrease in 6MWD of $>15\%$ from baseline or $>30\%$ compared with the last study-related measurement, or worsening of WHO FC) occurred in 2% of riociguat patients and 6% of placebo patients. Importantly, placebo-corrected least squares mean differences in several parameters, including PVR (-246 dyn·s·cm⁻⁵), mean pulmonary artery

pressure (-5 mmHg), cardiac index (0.6 L/min/m²), and NT-proBNP (-444 ng/L), were driven by riociguat treatment and not by the deterioration of patients receiving placebo.^{25–27} Furthermore, while riociguat was effective in both the inoperable CTEPH and persistent/recurrent CTEPH subgroups, there was a trend toward greater efficacy in patients with inoperable CTEPH.²⁷ Based on the results of the CHEST-1 study, riociguat was licensed in the USA to improve exercise capacity and WHO FC in adults with persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH.²³ In Europe, riociguat is licensed to improve exercise capacity in adults in WHO FC II–III with inoperable CTEPH or persistent/recurrent CTEPH after surgical treatment.²⁴

Patients completing CHEST-1 were eligible to participate in a long-term, open-label extension study (CHEST-2; ClinicalTrials.gov: NCT00910429). In the 237 eligible patients who entered CHEST-2, improvements in efficacy parameters with riociguat were shown to persist at two years,²² with mean \pm standard deviation increases in 6MWD of 52 ± 66 m at one year and 50 ± 68 m at two years. Overall survival at two years was 93% (95% CI: 89 to 96), and clinical worsening-free survival was 82% (95% CI: 77 to 87).

By defining a prospective process to ensure that patients eligible for PEA were correctly identified and excluded before study entry, CHEST-1 set a new standard for study design in patients with CTEPH. The authors of the study suggested that the incorporation of a collaborative process to allow remote expert opinion in the absence of a local expert center permitted patients from nonreferral centers to be included.²⁶ The use of similar protocols could extend clinical study participation in the future. However, neither combination PH-targeted therapy nor the application of BPA in patients with inoperable CTEPH was assessed in CHEST-1, a limitation of the study.

AMBER-1 study of ambrisentan for inoperable CTEPH

AMBER-1, a 16-week, multicenter, randomized, double-blind, placebo-controlled phase 3 study (ClinicalTrials.gov: NCT01884675), was designed to assess the ERA ambrisentan, compared with placebo, in patients with inoperable CTEPH.²⁸ The study, conducted between 2013 and 2015, included prospective confirmation of patient operability by an expert center or central adjudication committee. However, limited enrollment (only 33 patients were randomized compared with a target of 160 patients) led to early termination of the study. The authors speculated that the unexpectedly low screening rate was due at least in part to the approval of riociguat after recruitment started, as well as the increasing use of BPA in routine practice. Patients were excluded if they had received drugs approved for PAH within 12 weeks prior to screening or had previously undergone BPA or PEA. The authors also commented that the high screening failure rate ($\sim 60\%$) was

mainly due to concerns regarding operability raised by the central adjudication committee, which may be another consideration for future studies in CTEPH. In view of the termination of the AMBER-1 study, ambrisentan is not licensed for use in patients with CTEPH in either Europe or the USA.

MERIT-1 study of macitentan for inoperable CTEPH

MERIT-1 was a multicenter, randomized, controlled, phase 2 study of the ERA macitentan versus placebo, conducted between 2014 and 2016 (ClinicalTrials.gov: NCT02021292).²⁹ Eligible patients were those with inoperable CTEPH, while patients with persistent or recurrent PH after PEA were excluded. Technical operability of CTEPH was confirmed before randomization by independent central or country-specific adjudication committees. The central adjudication committee, recommended by the steering committee and assigned by the sponsor, comprised of three experienced PEA surgeons and two PH physicians. Each country-specific adjudication committee was composed of experienced PH physicians, cardiologists, or radiologists. In total, 73 of 186 patients screened (39%) were deemed as having operable disease and therefore not randomized. After further exclusions, 80 patients were enrolled and randomized to receive macitentan ($n=40$) or placebo ($n=40$) for 24 weeks. Notably, the inclusion criteria allowed patients in WHO FC III or IV to receive PDE5i or oral/inhaled PCA provided that the doses were stable for at least one month before study entry and maintained until study end. This makes MERIT-1 the first CTEPH study allowing the inclusion of patients receiving combination PH-targeted therapy.

The primary endpoint in MERIT-1, percentage change in PVR from baseline to Week 16, was met, with a treatment effect of 0.84 (95% CI: 0.70 to 0.99; $P=0.041$) in favor of macitentan. In addition, macitentan improved 6MWD from baseline to Week 24 compared with placebo (treatment effect of $+34$ m; 95% CI: 2.9 to 65.2; $P=0.033$). The time-frame of 24 weeks for assessing 6MWD was longer than the 16-week assessment used in both BENEFiT and CHEST-1,^{21,25} recognizing that a longer treatment duration may be necessary to see differences in exercise capacity endpoints.

A limitation of MERIT-1 was not including patients receiving the CTEPH-approved medical therapy, riociguat, or patients who had previously undergone PEA or BPA. In addition, requiring just one month of stable background therapy prior to enrollment may not allow enough time for the background therapy to be truly stable.

In 2019, an application to change the license for macitentan in Europe to include CTEPH was submitted. However, the application was subsequently withdrawn by the manufacturer when the European Medicines Agency raised concerns about MERIT-1.³⁰ As a result, macitentan

is not licensed for use in CTEPH in either Europe or the USA.

CTREPH study of subcutaneous treprostinil for severe inoperable CTEPH

The phase 3 CTREPH study of the PCA treprostinil, which recruited patients between 2009 and 2016, included 105 patients with inoperable CTEPH or persistent/recurrent CTEPH after PEA (ClinicalTrials.gov: NCT01416636).³¹ Patients were randomized to receive either high-dose (~30 ng/kg per min at Week 12; $n=53$) or low-dose (~3 ng/kg per min at Week 12; $n=52$) subcutaneous treprostinil for 24 weeks. The primary endpoint, change from baseline to Week 24 in 6MWD, was met with a treatment effect of +40.7 m (95% CI: 15.9 to 65.5; $P=0.0016$). However, patient operability was not independently adjudicated in CTREPH, and the study included patients who were considered technically operable but who had declined surgery for personal reasons.

A formulation of treprostinil for intravenous infusion is licensed in Europe to improve exercise capacity in adults in WHO FC III–IV with inoperable CTEPH or persistent/recurrent CTEPH after surgical treatment.³² Treprostinil is not currently licensed in the USA for treatment of CTEPH.

Medical therapy in combination with other treatment modalities

In practice, medical therapies in CTEPH can be combined with each other in several ways, as well as with PEA and/or BPA. There are, however, limited data from controlled studies of such combinations.

Medical therapies in combination

Some indication of the effectiveness of macitentan combination therapy is available from the MERIT-1 study, which included a subgroup of patients who received macitentan in combination with either PDE5i or an inhaled or oral PCA. Results in this subgroup indicated improvements in PVR and 6MWD consistent with the findings in the overall population.²⁹ One trial that has been established specifically to investigate the efficacy of a medical therapy added to standard of care is the SELECT study (ClinicalTrials.gov: NCT03689244). This ongoing multicenter, randomized, placebo-controlled, adaptive phase 3 study will assess the efficacy and safety of selexipag, a prostacyclin receptor agonist, as add-on therapy in patients with inoperable CTEPH or persistent/recurrent PH after surgical and/or interventional treatment. The combination of riociguat and selexipag is allowed, and the use of BPA is permitted in eligible patients after study Week 26. The study endpoints in the SELECT study will include PVR at Week 20 expressed as a percentage of the baseline value. The study is currently

recruiting and is designed to recruit up to 280 eligible patients.

Medical therapy and BPA

The efficacy of BPA compared with riociguat was investigated in the multicenter, open-label, randomized, controlled RACE study, conducted between 2016 and 2019 (ClinicalTrials.gov: NCT02634203).³³ Newly diagnosed and treatment-naïve patients with CTEPH adjudicated as inoperable and with PVR > 300 dyn·s·cm⁻⁵ were randomized to receive riociguat ($n=53$) or BPA ($n=52$) and were followed for 26 weeks.³³ The primary endpoint was change in PVR from baseline to Week 26. Secondary endpoints included changes from baseline in 6MWD, WHO FC, NT-proBNP, time to clinical worsening, and medication safety. Publication of the results is awaited. RACE will provide important information on the effects of riociguat compared with BPA as first-line therapy in treatment-naïve patients with inoperable CTEPH.

Medical therapy and PEA

It has been suggested that medical therapy in patients with operable CTEPH can help to improve hemodynamic parameters before surgery, leading to reduced surgical morbidity and mortality.³⁴ Using medical therapy in this way as a “bridge to PEA” lacks evidence, however, and there is concern that the practice may delay referral for definitive surgical treatment without clinical benefit.^{2,34} The prospective, randomized, controlled phase 2 “PEA Bridging” study (ClinicalTrials.gov: NCT03273257) was intended to randomize patients with operable CTEPH and PVR > 800 dyn·s·cm⁻⁵ to receive riociguat or placebo for three months before undergoing PEA. This study would have provided evidence on the risks and benefits of bridging therapy but was terminated early because of slow recruitment and limitations imposed on the conduct of the study by the COVID-19 pandemic.

Unanswered questions in CTEPH management

Several questions relating to the management of CTEPH remain to be addressed (Table 1). Firstly, the goals and expectations of management must be clarified, given the subjectivity of operability assessment. The role of medical therapy must also be further defined. The encouraging results with BPA in inoperable patients and the emerging data for medical therapy may indicate a paradigm shift to multimodality management rather than the binary choice of operable versus nonoperable. For patients requiring medical therapy, it is unclear whether there is an optimal sequence of targeted therapies, or treatment should be tailored to center-specific variables and/or patient characteristics. The choice of endpoints in clinical trials (functional,

Table 1. Summary of unanswered questions in the management of CTEPH.

- Clarification of the goals and expectations of CTEPH treatment in the context of subjective operability assessment
- Further definition of the role of medical therapy in the BPA era, including potential paradigm shift to multimodality treatment
- Optimal sequencing of medical therapy, including combination of PH therapeutics
- Choice of endpoints in clinical trials depending on the CTEPH population of interest

BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; PH: pulmonary hypertension.

hemodynamic, coprimary endpoints, etc.) is also important and differs from PAH, which has moved on to event-driven trials. These can be influenced by considerations such as the phase of the trial, regulatory agency feedback and health-economic pressures in addition to clinical or scientific questions. Future studies of medical therapies in CTEPH will likely need to reconcile and define the role of BPA for their study population.

Summary

It is necessary to conduct randomized, controlled studies in CTEPH to expand our knowledge and treatment options, but it is imperative to ask better questions and design better studies. The evolution of CTEPH study design has resulted from earlier experience with PH-targeted medical therapies in patients with CTEPH. Despite some similarities between PAH and CTEPH, which provided the rationale for the trials discussed here, the two conditions are distinct and evidence from PAH trials cannot simply be extrapolated to CTEPH. Key learning points include the importance of prospective operability adjudication to ensure appropriate enrollment of patients with inoperable disease, sufficient study duration to allow treatment effects to become apparent, and the dedication of trials exclusively to CTEPH, recognizing the unique features of this condition and their implications for study design, execution, and interpretation. Among inoperable patients, it is important to distinguish between those with fibrotic lesions from subsegmental arteries to pulmonary arteries of 2 mm diameter that are suitable for BPA, and those with lesions in smaller vessels (<0.5 mm in diameter), similar to those seen in idiopathic PAH, which can only be treated with targeted medical therapy.

Long-term prospective studies and high-level evidence of the efficacy and safety of medical therapies in patients with CTEPH are paramount. Questions that require further investigation include combination medical therapy, medical therapy as a bridge to PEA, the efficacy and safety of medical therapy compared with BPA, and the use of these strategies in combination.

To address ongoing issues in the management of CTEPH and continue to improve outcomes for patients, it is vital to

foster basic and translational research in CTEPH, encourage collaborations in research and development, and continue to improve future study designs from accrued knowledge.

Author note

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Conflict of interest

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