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Advances in targeted therapy for chronic thromboembolic pulmonary hypertension

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Abstract
Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by unresolved thrombi in the pulmonary arteries and microvasculopathy in nonoccluded areas. If left untreated, progressive pulmonary hypertension will induce right heart failure and, finally, death. Currently, pulmonary endarterectomy (PEA) remains the only method that has the potential to cure CTEPH. Unfortunately, up to 40% of patients are ineligible for this procedure for various reasons. In recent years, refined balloon pulmonary angioplasty (BPA) has become an alternative option for inoperable CTEPH patients, and it may be another curative treatment in the future, particularly in combination with prior PEA. Nevertheless, 23% of patients still suffer from persistent PH after BPA. Given that CTEPH shares many similarities with idiopathic pulmonary arterial hypertension (PAH), targeted drugs developed for PAH are also attractive options for CTEPH, especially for inoperable or persistent/recurrent CTEPH patients. To date, riociguat, macitentan, and subcutaneous treprostinil are the only drugs proven by randomized control trials to be capable of improving the exercise capacity (6-min walking distance) of CTEPH patients. In this review, we summarize the achievements and unresolved problems of PAH-targeted therapy for CTEPH over the last decade.

Keywords Chronic thromboembolic pulmonary hypertension · Pulmonary arterial hypertension-targeted therapy · Combination therapy · Bridging therapy

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease with a poor prognosis. The 5-year survival rate is only 10% for CTEPH patients with a mean pulmonary artery pressure (mPAP) ≥ 50 mmHg [1]. CTEPH is usually considered to be the result of a single or recurrent pulmonary embolism. A recent meta-analysis showed that the incidences of CTEPH in all comers with pulmonary embolism, survivors of pulmonary embolism, and survivors without major comorbidities were 0.56, 3.2, and 2.8%, respectively [2]. CTEPH is characterized by the nonresolution of organized thrombi in proximal or distal pulmonary arteries and microvasculopathy in nonoccluded areas, leading to elevated pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and finally, right heart failure [3].

A diagnosis of CTEPH is based on the presence of precapillary PH measured by right heart catheterization, in combination with chronic flow-limiting thrombi within pulmonary arteries after at least 3 months of effective anticoagulation. Precapillary PH is defined as mPAP ≥ 25 mmHg and a mean pulmonary arterial wedge pressure ≤ 15 mmHg [4]. According to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines on PH [5], CTEPH is classified as group 4 PH, the only subtype of PH that is potentially curable.

Currently, pulmonary endarterectomy (PEA) is the only treatment that has the potential to cure CTEPH [5]. The majority of operated patients experience almost complete normalization of hemodynamics and improvements in symptoms. However, up to 40% of CTEPH patients are ineligible for PEA for various reasons, such as distal lesions, severe comorbidities, and surgeon expertise [5, 6]. Furthermore, 17 to 31% of operated patients will develop persistent or recurrent PH [6].

For such inoperable patients, refined balloon pulmonary angioplasty (BPA) is a new alternative option, and it may be

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another curative treatment in the future, particularly in combination with prior PEA. Since 2012, numerous studies have demonstrated that BPA can improve exercise capacity, heart function, and hemodynamics [7, 8]. Nevertheless, 23% of patients still suffer from persistent PH after BPA [9].

Pulmonary arterial hypertension (PAH), group 1 PH, is inoperable and mainly treated with medication [5]. The value of targeted therapy in PAH has been widely acknowledged. Given that CTEPH shares many similarities with idiopathic PAH [10, 11], PAH-targeted therapy is also an attractive option for CTEPH, especially for inoperable or persistent/recurrent CTEPH patients. In this review, we summarize the achievements and unresolved problems of PAH-targeted therapy for CTEPH over the last decade.

Pathophysiology of CTEPH and rationale for using PAH-targeted drugs

Previous publications have summarized the current understanding of the pathogenesis of CTEPH [12]. The key points are as follows. First, inherited thrombophilia does not seem to contribute to the development of CTEPH, whereas acquired hypercoagulable states, such as antiphospholipid syndrome, are more common in CTEPH than in PAH and may lead to CTEPH in these patients. Second, increased factor VIII levels are observed in a proportion of CTEPH patients, but it remains unclear whether increased factor VIII levels are the cause or consequence of CTEPH. Third, there is no strong causal link between the development of CTEPH and tissue plasminogen activator/plasminogen activator inhibitor-1 system. On the other hand, Satoh et al. [13] reported that activated thrombin-activatable fibrinolysis inhibitor played a key role in the development of CTEPH. Fourth, abnormal fibrin may also contribute to the development of CTEPH in some patients. Fifth, excessive inflammation and deficient angiogenesis may negatively affect thrombus resolution. Sixth, thrombi in distal pulmonary arteries and arteriopathy in nonoccluded areas are thought to be responsible for persistent or recurrent PH after PEA. Seventh, in situ thrombosis may also contribute to the development and progression of CTEPH.

The rationale for administering PAH-targeted drugs to CTEPH patients has also been previously described in detail [10, 11]. In general, CTEPH shares many similarities with idiopathic PAH, including histological changes in small pulmonary vessels, thrombosis in large pulmonary vessels, and clinical manifestations. The efficacy of PAH-targeted therapies in CTEPH has also been demonstrated in current clinical practice [14].

PAH-targeted therapies for CTEPH

Soluble guanylate cyclase stimulators

Riociguat is a soluble guanylate cyclase (sGC) stimulator [15] and is the first and only therapy that has been approved for CTEPH. It has a direct stimulating effect on sGC, which is independent of nitric oxide (NO). Meanwhile, it also increases the sensitivity of sGC to NO [16]. These two effects increase the level of cyclic guanosine monophosphate (cGMP), which induces vasodilation and suppresses vascular remodeling, inflammation, and platelet aggregation [15]. A summary of studies regarding riociguat for the treatment of CTEPH is presented in Table 1.

The CHEST-1 study, the first randomized controlled trial (RCT) of riociguat, confirmed the satisfactory tolerability and efficacy of riociguat for inoperable or persistent/recurrent CTEPH [17]. This 16-week trial included 261 participants. A total of 173 patients were randomly assigned to the riociguat group, and 88 patients were assigned to the placebo group, with a maximum dose of 7.5 mg per day. The primary end point was the change of the 6-min walking distance (6MWD) after 16 weeks of treatment. At week 16, the 6MWD was increased by 39 m in the riociguat group, while it was decreased by 6 m in the control group. Significant improvements in secondary end points, including PVR, mPAP, cardiac output (CO), N-terminal pro-brain natriuretic peptide (NT-proBNP), and WHO functional class (WHO FC), were also observed. The incidence of clinical worsening events was comparable between the two groups. Most adverse events (AEs) were mild or moderate, such as headache, dizziness, peripheral edema, and cough. The incidence of serious AEs (e.g., right ventricular failure, syncope, and hemoptysis) was no more than 3% in both groups.

Several prognostic predictors and their threshold values for the long-term outcomes of PAH have been determined and have become important treatment goals [18–21]. Based on the results of the CHEST-1 study [17], D'Armini et al. [22] selected a series of these predictor thresholds and compared the percentage of patients achieving these thresholds at baseline with that percentage at the end of the CHEST-1 study in both the riociguat and placebo groups; these thresholds included 6MWD $\geq$ 380 m, cardiac index $\geq$ 2.5 L/min/m^2, PVR $<$ 500 dyn·s·cm^{-5}, mixed venous oxygen saturation $\geq$ 65%, WHO FC I/II, NT-proBNP $<$ 1800 pg/mL, and right atrial pressure $<$ 8 mmHg. At 16 weeks, the riociguat group had a greater proportion in every threshold compared with baseline, whereas the placebo group had an unchanged or decreased proportion in every threshold except for right atrial pressure and WHO FC. The authors also analyzed the proportion of patients achieving a combined predictor end point including all selected predictors. The results showed that the riociguat group had a greater proportion of patients achieving a

Table 1 Studies related to riociguat for the treatment of CTEPH

Study	Design	Patient	Duration	Main findings
CHEST-1 [17]	RCT	189 inoperable and 72 persistent/recurrent CTEPH patients	16 weeks	Significant improvement in 6MWD; significant improvements in secondary end points, including PVR, mPAP, WHO FC
D'Armini et al. [22]	RCT	189 inoperable and 72 persistent/recurrent CTEPH patients	16 weeks	Increase in the percentage of patients achieving predictor thresholds developed for PAH
CHEST-2 [6]	Open-label	155 riociguat-treated and 82 placebo-treated CTEPH patients from CHEST-1	75 weeks (median)	Favorable safety and tolerability profiles of long-term riociguat therapy; improvements in 6MWD and WHO FC achieved in CHEST-1 sustained for up to 1 year
Simonneau et al. [23]	Open-label	155 riociguat-treated and 82 placebo-treated CTEPH patients from CHEST-1	116 weeks (median)	Patients achieving the median for NT-proBNP or 6MWD at baseline and follow-up and those achieving the median for increase in 6MWD had better survival rates
Benza et al. [24]	RCT	155 riociguat-treated and 82 placebo-treated CTEPH patients from CHEST-1	116 weeks (median)	Significant improvement in RRS at 16 weeks in CHEST-1 and 12 weeks in CHEST-2; RRS at baseline, 16 weeks in CHEST-1 and its changes from baseline to 16 weeks were predictors of long-term survival
Halank et al. [28]	Open-label	41 inoperable CTEPH patients and 27 PAH patients	77 months (median)	Favorable safety and tolerability profiles of long-term riociguat therapy; improvements in 6MWD and WHO FC observed in the initial stage were maintained for up to 48 months
CTEPH EAS [29]	Open-label	216 inoperable and 84 persistent/recurrent CTEPH patients	47 weeks (median)	Safety, tolerability, and improvements in 6MWD and WHO FC were comparable between switched and treatment-naïve patients; no apparent safety events during the washout period
CAPTURE [30]	Retrospective	82 CTEPH patients and 40 PAH patients	–	Switching patients from insufficient PAH-targeted therapies to riociguat treatment may be feasible in clinical practice
Marra et al. [37]	Prospective	18 CTEPH patients and 21 PAH patients	12 months	Significant improvement in right heart size and function
Ahmadi et al. [38]	Prospective	5 inoperable patients and 1 persistent CTEPH patient	6 months	Significant improvement in RVSVI; there were trends toward improved right ventricular fibrosis and metabolism–flow relationships
Weir et al. [39]	Case series	6 sickle cell-related CTEPH patients	–	Significant improvements in WHO FC, 6MWD, NT-proBNP and right ventricular systolic pressure

CTEPH, chronic thromboembolic pulmonary hypertension; *RCT*, randomized controlled trial; *6MWD*, 6-min walking distance; *PVR*, pulmonary vascular resistance; *mPAP*, mean pulmonary arterial pressure; *WHO FC*, World Health Organization functional class; *PAH*, pulmonary arterial hypertension; *NT-proBNP*, N-terminal pro-brain natriuretic peptide; *RRS*, REVEAL risk score; *RVSVI*, right ventricular stroke volume index

Table 2 Studies related to sildenafil for the treatment of CTEPH

Study	Design	Patient	Duration	Main findings
Suntharalingam et al. [41]	Prospective	9 inoperable and 9 persistent CTEPH patients	–	Acute improvements in hemodynamics; hemodynamic responses to intravenous sildenafil correlated with inhaled nitric oxide
Reichenberger et al. [42]	Open-label	104 inoperable CTEPH patients	12 months	Sustained improvements in 6MWD, PVR, and WHO FC; acute hemodynamic responses to oral sildenafil were not associated with long-term outcome
Suntharalingam et al. [43]	RCT	19 inoperable CTEPH patients	12 weeks	No significant changes in 6MWD (primary end point); improvements in PVR, mPAP, and WHO FC were observed
Suntharalingam et al. [43]	Open-label	18 inoperable CTEPH patients	12 months	Significant improvements in 6MWD, PVR, cardiac index, and NT-proBNP
Toshner et al. [44]	Open-label	18 inoperable CTEPH patients	12 months	The relative area change of the proximal pulmonary artery was correlated with improvements in 6MWD and NT-proBNP at 1 year
Sekine et al. [45]	Retrospective	40 CTEPH patients and 19 PAH patients	–	CTEPH patients with TT genotype tended to have better 3-year clinical worsening-free survival; in the overall population, the TT genotype correlated with better post-sildenafil WHO FC
Nishimura et al. [46]	Prospective	58 CTEPH patients and 32 PAH patients	–	CTEPH patients with II/TT genotypes had lower post-sildenafil BNP levels and better 5-year clinical progression-free survival
Claessen et al. [47]	Prospective	14 CTEPH patients and 7 healthy controls	–	Acute improvements in mPAP/CO slope, RVEF and SVi; total PVR was negatively correlated with peak exercise RVEF/SVi

CTEPH, chronic thromboembolic pulmonary hypertension; *6MWD*, 6-min walking distance; *PVR*, pulmonary vascular resistance; *WHO FC*, World Health Organization functional class; *RCT*, randomized controlled trial; *mPAP*, mean pulmonary arterial pressure; *NT-proBNP*, N-terminal pro-brain natriuretic peptide; *CO*, cardiac output; *RVEF*, right ventricular ejection fraction; *SVi*, stroke volume index

combined predictor end point than the placebo group did (OR = 4.98, 95% CI = 1.68–14.77). However, whether these predictor thresholds developed for PAH remain valid in CTEPH needs further study.

The CHEST-2 study focused on the long-term safety and tolerability of riociguat [6]. This open-label study included 155 riociguat-treated and 82 placebo-treated participants from the CHEST-1 study. The median treatment duration was 75 weeks. At 1 year, 90% of participants were still receiving riociguat at 7.5 mg a day, supporting the long-term tolerability of riociguat. Only 3% of participants discontinued riociguat treatment due to AEs. Serious AEs were reported in 5% of participants; among these AEs, the most common were syncope and hypotension (2 and 1%, respectively), both of which were properly handled in all cases. Hemoptysis or pulmonary hemorrhage was found in 3% of participants, and the authors advised clinicians to regularly evaluate the patient's risk of pulmonary bleeding during riociguat therapy. No riociguat-related deaths were reported. Moreover, the former riociguat group showed better improvements in the 6MWD and WHO FC than the former placebo group, which supports the early administration of riociguat.

Based on the results of the CHEST-2 study, Simonneau et al. [23] partially answered the question raised by the work of D'Armini et al. [22]. The authors reported that patients achieving 6MWD increase ≥ 43 m ($p = 0.0047$), 6MWD ≥ 366 m at baseline ($p = 0.0199$), or 6MWD ≥ 406 m at follow-up ($p = 0.0385$) had better survival rates than those who failed to achieve these thresholds. Similar results were also observed for the NT-proBNP concentration (NT-proBNP < 938 pg/mL at baseline, $p < 0.0183$; NT-proBNP < 475 pg/mL at follow-up, $p < 0.0068$). However, an association between WHO FC and overall survival was not observed. Thus, these thresholds may be used as treatment goals for clinicians treating CTEPH patients with riociguat.

Based on the CHEST-1 and CHEST-2 studies [6, 17], Benza et al. [24] performed further work. The predictive value of the REVEAL risk score (RRS) has been validated in PAH [25]. Benza et al. selected 9 of the 12 RRS variables to establish a risk prediction model for CTEPH patients. It should be noted that only 7 of the 12 variables are needed to maintain the predictive power of the RRS [26, 27]. Compared with baseline, the RRS was decreased at 16 weeks in the CHEST-1 and 12 weeks in the CHEST-2 study. In addition, the percentage of patients in the low-risk stratum (RRS ≤ 7) was increased. A one-point decrease in the RRS at baseline or at 16 weeks in the CHEST-1 study led to a 30% reduction in the relative risk of death in the CHEST-2 study. A one-point decrease in the RRS from baseline to 16 weeks in the CHEST-1 study led to a 32% reduction in the relative risk of death in the CHEST-2 study. Similar patterns were also observed in the relationship between the risk stratum and long-term outcomes. Therefore,

the RRS may be an effective tool for predicting the long-term outcomes of CTEPH in the context of riociguat treatment.

A phase II long-term extension study sharing similar objectives with the CHEST-2 study included 41 inoperable CTEPH patients and 27 PAH patients [28]. In contrast to 75 weeks in the CHEST-2 study [6], the median treatment duration was 77 months in this study. At the final data cutoff point, 56% of the CTEPH patients and 48% of the PAH patients remained on the treatment regimen. The safety profiles were similar to those in the CHEST studies [6, 17]. Improvements in the 6MWD and WHO FC observed in the initial stage of this study (3 months) were maintained for up to 48 months.

The phase IIIb CTEPH early access study (CTEPH EAS) also shared similar objectives with the CHEST-2 study and included 300 inoperable or persistent/recurrent CTEPH patients [29]. Eighty-four of those patients had previously received PAH-targeted therapies, and the rest were treatment naïve. The safety profile of the CTEPH EAS was consistent with that of the CHEST-1 and CHEST-2 studies [6, 17]. Interestingly, the study also reported that the safety, tolerability, and improvements in the 6MWD and WHO FC were comparable between switched and treatment-naïve patients. Moreover, no apparent safety events occurred during the washout period (median duration 4 days, range 3–74 days).

The CAPTURE study, a multicenter retrospective chart review, was designed to determine how clinicians switched CTEPH patients from nonsatisfactory PAH-targeted therapies to riociguat treatment in clinical practice [30]. This study included 82 CTEPH patients and 40 PAH patients; 52% of the CTEPH patients had received phosphodiesterase type 5 (PDE-5) inhibitors before, and 71% of them were switched to riociguat monotherapy, similar to the CTEPH EAS [29]. The median duration of the washout period was 0 days (range 24–51 days). Two of the 82 CTEPH patients experienced AEs during the washout period. The study only reported a mixed incidence of AEs during the dose-adjustment period, involving both CTEPH and PAH patients. During this period, 41% of these patients experienced AEs, most of which were mild or moderate. Two (2%) patients experienced serious drug-related AEs. The percentage of patients who reached the maximum dose in the CAPTURE study was similar to that in the CHEST-1 study [17]. These studies suggest that switching patients from insufficient PAH-targeted therapies to riociguat treatment may be feasible in most patients.

In the CHEST-1 and CHEST-2 studies and the CTEPH EAS, the patients were titrated as much as possible to the maximum dose of 7.5 mg per day [6, 17, 29]. However, some CTEPH patients may also have conditions that could increase their exposure to riociguat, such as right heart failure and renal impairment. For these patients, doses lower than 7.5 mg per day may have an efficacy similar to that of the maximum dose [31–34].

Right heart failure is one of the main causes of death in CTEPH [35, 36]. Marra et al. [37] assessed the effects of riociguat on right heart size and function by echocardiography. Twenty-one PAH and 18 CTEPH patients were enrolled in this study. After 12 months of riociguat therapy, the mean right ventricular (RV) area, right atrial area, and RV free wall thickness decreased by 5.9 cm^2 ($p < 0.001$), 3.5 cm^2 ($p < 0.001$), and 1.9 mm ($p < 0.01$), respectively. Tricuspid annular plane systolic excursion and tricuspid annular velocity increased by 3.6 mm ($p = 0.002$) and 1.7 mm/s ($p = 0.006$), respectively. A prospective study was designed to investigate the effects of riociguat on RV remodeling, metabolism, and perfusion and ultimately included six patients [38]. By cardiac magnetic resonance (CMR), late gadolinium enhancement (LGE) was used to detect RV fibrosis. By positron emission tomography, ^{18}F-fluorodeoxyglucose uptake and ^{13}N-ammonia were used to assess RV metabolism and perfusion, respectively. After 6 months of riociguat treatment, the RV stroke volume index and RV ejection fraction (RVEF) increased by 13.5 mL/m^2 ($p = 0.03$) and 4.9% ($p = 0.09$), respectively. A reduction in the total myocardial LGE was observed in five patients ($p = 0.09$). Decreased septal LGE was observed in three patients ($p = 0.68$). Although riociguat had no significant effects on RV metabolism or perfusion ($p = 1$ and $p = 0.84$, respectively), improvement was observed in the ratio of myocardial metabolism to blood flow ($p = 0.62$). Due to the small sample size of this study, further in-depth work is needed to confirm whether riociguat decreases RV fibrosis and improves metabolism and perfusion.

A case series including six patients revealed that riociguat may also be suitable for the treatment of sickle cell-related CTEPH [39]. After riociguat treatment, improvements in the WHO FC, 6MWD, NT-proBNP level, and RV systolic pressure were observed. Further studies are needed to determine the role of riociguat in the management of sickle cell-related CTEPH.

PDE-5 inhibitors

As mentioned above, cGMP is an important mediator in the NO pathway, which induces pulmonary vasodilation. PDE-5, an enzyme capable of degrading cGMP, is abundantly expressed in lung tissue [40]. Thus, several studies have explored the efficacy of sildenafil, an inhibitor of PDE-5, in CTEPH. A summary of these studies is presented in Table 2.

Suntharalingam et al. [41] recruited 18 CTEPH patients to examine the acute effects of sildenafil on hemodynamics. After a 100 ng/L dose of intravenous sildenafil, the mPAP and PVR decreased by 16.9% ($p = 0.001$) and 25.1% ($p = 0.001$), respectively. The ratio of PVR to systemic vascular resistance also decreased by 0.06 ($p = 0.06$), indicating that sildenafil selectively affected the pulmonary circulation. The authors also reported a correlation between invasive acute

vasoreactivity testing and responses to sildenafil treatment with respect to the mPAP and CO ($r = 0.74$, $p < 0.001$; $r = 0.82$, $p < 0.001$, respectively).

In an open-label trial that included 104 inoperable CTEPH patients, Reichenberger et al. [42] studied the long-term effects of sildenafil on inoperable patients. After 3 months of sildenafil treatment, the 6MWD increased from 310 to 361 m ($p = 0.0001$), the PVR decreased from 863 to 759 dyn·s·cm^{-5} ($p = 0.0002$) and the WHO FC improved ($p = 0.01$). Moreover, improvements in the 6MWD and WHO FC were sustained over 12 months. However, acute effects induced by 50 mg of oral sildenafil (equivalent to 300 ng/L of intravenous sildenafil) were not associated with the long-term outcomes. In a randomized, double-blind, placebo-controlled study of sildenafil, Suntharalingam et al. [43] recruited 19 inoperable CTEPH patients. After 12 weeks of treatment, changes in the 6MWD (the primary end point) were comparable between the sildenafil and placebo groups. However, significant improvements in the secondary end points, including the PVR, mPAP, and WHO FC, were observed. Eighteen patients in this study were then transferred to an open-label stage of 9 months of sildenafil treatment. The results showed that the 6MWD increased by 36 m ($p = 0.014$). The PVR, cardiac index, and NT-proBNP level also significantly improved (− 149 dyn·s·cm^5, + 0.2 L/min/m^2, − 189 pg/mL, respectively). Sildenafil was well tolerated, except one patient experienced urticaria and one patient died due to disease progression. Based on the results of Suntharalingam et al. [43], Toshner et al. [44] found that the relative area change (RAC) of the proximal pulmonary artery, as measured by MRI, had potential as a noninvasive tool for predicting individual responses to sildenafil treatment. The pre-sildenafil RAC was correlated with improvements in the 6MWD and NT-proBNP level at 1 year ($r = 0.70$, $p = 0.006$; $r = 0.59$, $p = 0.03$), whereas it was not associated with changes in the mPAP or CO.

Sekine et al. [45] investigated the association between the C825T polymorphism of the G-protein β3 subunit gene (GNB3) and the efficacy of sildenafil treatment in PH patients; 19 PAH and 40 CTEPH patients were retrospectively enrolled. In the CTEPH group, there was a trend showing that patients with the TT genotype had better 3-year clinical progression-free survival than those with the CT/CC genotypes ($p = 0.093$). In a mixed group of CTEPH and PAH patients, patients with the TT genotype had a better post-sildenafil WHO FC and tended to have a greater improvement in the 6MWD ($p = 0.03$ and $p = 0.05$, respectively). However, no significant effects of the TT genotype on hemodynamics were observed. A recent study further examined whether the combined angiotensin-converting enzyme (ACE)/GNB3 polymorphism was associated with the efficacy of sildenafil treatment in PH patients; 32 PAH and 58 CTEPH patients were enrolled [46]. In the CTEPH group, patients with the II/TT genotypes had lower post-sildenafil BNP levels and better 5-year clinical progression-free survival rates than those with non-II/TT genotypes (115 vs. 275 pg/mL, $p = 0.02$; 100 vs. 45.5%, $p = 0.03$, respectively). In contrast to the results of Sekine et al. [45], there was no difference in the WHO FC between the II/TT and non-II/TT genotypes in a mixed group of CTEPH and PAH patients; however, combined ACE/GNB3 polymorphisms did not improve hemodynamics either. The mechanisms by which these two gene polymorphisms affect the sildenafil response remain unclear.

Claessen et al. [47] investigated how sildenafil affected exercise capacity in CTEPH by studying 14 CTEPH patients and 7 healthy control subjects. It is worth noting that RV performance during exercise was measured by real-time CMR in this study. During incremental exercise without sildenafil administration, the mPAP/CO slope was greater in the CTEPH group than in the control group (6.7 vs. 0.94 mmHg/L/min, $p < 0.001$), while the healthy controls showed an increased stroke volume index (SVi) and RVEF ($p = 0.002$ and $p < 0.01$, respectively), which was not observed in the CTEPH patients. After a single dose of sildenafil (50 mg, oral), the mPAP/CO slope decreased by 3.2 mmHg/L/min ($p = 0.020$), while both the RVEF and SVi at rest and at peak exercise increased ($p < 0.05$). Sildenafil did not affect these three parameters in healthy controls. More importantly, there was a strong inverse correlation between the total PVR and the peak exercise RVEF/SVi ($r = -0.65$, $p = 0.016$; $r = -0.80$, $p = 0.001$, respectively), indicating that exercise CMR could be used as a noninvasive tool for assessing the effects of other PAH-targeted drugs on exercise hemodynamics in CTEPH patients.

Tadalafil is another PDE-5 inhibitor. In an in vitro experiment, Yamamura et al. [48] found that tadalafil could promote apoptosis, downregulate the expression of PDE-5, and inhibit cell proliferation in pulmonary arterial smooth muscle cells (PASMCs) from patients with idiopathic PAH, while similar phenomena were not observed in PASMCs from CTEPH patients. These results indicate that idiopathic PAH and CTEPH are in fact two distinct conditions, which might undermine the rationale for the use of PDE-5 inhibitors in CTEPH.

Endothelin receptor antagonists

The important role of endothelin (ET)-1 in the development of CTEPH has been determined [49–51]. Bosentan is an endothelin receptor antagonist that can block both ET_A and ET_B receptors. Studies relevant to bosentan for the treatment of CTEPH are summarized in Table 3.

The double-blind, randomized, placebo-controlled BENEFiT study included 157 patients and investigated the efficacy of bosentan in CTEPH with the 6MWD and PVR as coprimary end points [52]. After 16 weeks of treatment, the mean treatment effects were a 24% ($p < 0.0001$) decrease in the PVR and a 2.2 m ($p = 0.5449$) increase in the 6MWD, with satisfactory safety and tolerability profiles. Nishikawa-

Table 3 Studies related to bosentan for the treatment of CTEPH

Study	Design	Patient	Duration	Main findings
BENEFiT [52]	RCT	157 inoperable or persistent/recurrent CTEPH patients	16 weeks	Significant improvement was observed in PVR, but not in 6MWD (coprimary end points)
Nishikawa-Takahashi et al. [53]	Retrospective	7 inoperable CTEPH patients	More than 2 years	Significant improvement was observed in PVR, but not in 6MWD
Post et al. [54]	Retrospective	18 inoperable CTEPH patients	31 months (median)	Improvements in 6MWD persisted for up to 24 months
BOCTEPH study [55]	Open-label	15 inoperable CTEPH patients	6 months	Significant improvements in PVR (primary end point) and 6MWD (secondary end point)
Vassallo et al. [56]	Open-label	34 inoperable CTEPH patients	12 months	Significant improvement in 6MWD (primary end point)
Becattini et al. [57]	Systematic review	–	–	Bosentan group had a slightly longer 6MWD than the placebo group after 3–6 months of treatment
Chen et al. [58]	Systematic review	–	–	6MWD did not differ between bosentan and placebo groups
Nishimura et al. [46]	Prospective	58 CTEPH and 32 PAH patients	–	Polymorphisms of ACE/GNB3 did not affect the efficacy of bosentan treatment in CTEPH
Hirashiki et al. [59]	Prospective	8 CTEPH and 18 PAH patients	3 months	Increase in flow-mediated vasodilation was observed in the PAH group, but not in the CTEPH group

CTEPH, chronic thromboembolic pulmonary hypertension; *RCT*, randomized controlled trial; *PVR*, pulmonary vascular resistance; *6MWD*, 6-min walking distance; *PAH*, pulmonary arterial hypertension; *ACE*, angiotensin-converting enzyme; *GNB3*, G-protein β3 subunit

Takahashi et al. [53] retrospectively analyzed the clinical characteristics of seven inoperable CTEPH patients who had received bosentan treatment for over 2 years. In line with the BENEFiT study [52], a great reduction in the PVR ($p < 0.05$) was reported, while no significant improvement in the 6MWD was achieved. A retrospective study also assessed the long-term efficacy of bosentan in inoperable CTEPH patients over a median treatment period of 31 months [54]. The results revealed a significant improvement in the 6MWD that was sustained for up to 24 months. However, this improvement failed to remain statistically significant during long-term follow-up (defined as more than 24 months), which is consistent with the work reported by Nishikawa-Takahashi et al. [53].

The BOCTEPH study was an open-label study of the effects of bosentan on 15 inoperable CTEPH patients [55]. After 6 months of treatment, the PVR (primary end point) significantly decreased from 852 to 657 dyn·s·cm^{-5} ($p = 0.02$) and the 6MWD (secondary end point) significantly increased from 389 to 443 m ($p = 0.005$). Improvements in other secondary end points were also observed, including quality of life, WHO FC, and serum uric acid. Based on the BOCTEPH study [55], another open-label, nonrandomized study conducted further research by setting controls [56]. The authors equally divided 34 inoperable CTEPH patients into two groups: standard therapy and standard therapy plus bosentan. After 1 year of treatment, the 6MWD (primary end point) increased by 57 m ($p = 0.023$) and the systolic pulmonary artery pressure (secondary end point) remained stable ($p = 0.221$) compared with baseline, while both of these parameters deteriorated in the controls.

In a systematic review, Becattini et al. [57] reported that while the 6MWD in the bosentan-treated group was 2.11 m (95% CI = 1.84–2.39) longer than that in the placebo-treated group after 3–6 months of treatment, the heterogeneity among studies was significant (I^2 98%). The authors stressed that the improvement in the 6MWD was mainly driven by the data from open-label studies. However, a recent systematic review reported that 6MWD, WHO FC, and clinical worsening did not differ between the bosentan and placebo groups, with the exception of certain hemodynamic parameters [58]. Thus, whether bosentan could improve exercise capacity remains controversial. Another unanswered question is whether improvements in hemodynamics induced by bosentan or sildenafil treatment correlate with clinical outcomes, like the RRS in riociguat treatment discussed above [24, 25].

Unlike sildenafil, polymorphisms of ACE/GNB3 do not affect the efficacy of bosentan treatment in CTEPH [46]. Hirashiki et al. [59] evaluated the effects of bosentan on peripheral endothelial dysfunction in PAH and CTEPH patients. After 3 months of bosentan therapy, flow-mediated vasodilation increased from 6.01 to 8.07% ($p < 0.0001$) in the PAH group, whereas no significant change was observed in the CTEPH group. This finding also indicates that PAH and CTEPH are two distinct conditions.

Macitentan is also a dual endothelin receptor antagonist, characterized by sustained receptor binding [60]. The double-blind, randomized, placebo-controlled MERIT-1 study was carried out to evaluate the effects of macitentan on inoperable CTEPH patients [61]. At 16 weeks, the macitentan group had a greater reduction in PVR (primary end point) than

the controls (23 vs. 12.8%, $p = 0.041$). In contrast with the BENEFiT study [52], the improvement in the 6MWD was 34 m ($p = 0.033$) longer in the macitentan group than that in the control group at 24 weeks.

Prostacyclin analogues

Prostacyclin analogues (e.g., iloprost, beraprost, treprostinil) exert vasodilative, antiproliferative, and antithrombotic effects through binding to prostanoid receptors and elevating intracellular cyclic adenosine monophosphate (cAMP) levels [62]. A summary of studies related to prostacyclin analogues for the treatment of CTEPH is presented in Table 4.

Scelsi et al. [63] investigated the efficacy of epoprostenol (synthetic prostacyclin) in CTEPH; 11 inoperable CTEPH patients and 16 PAH patients were enrolled. After a median treatment duration of 12.4 months, intravenous epoprostenol significantly improved the WHO FC and 6MWD and alleviated the clinical symptoms of right heart failure in the CTEPH group. Cabrol et al. [64] retrospectively analyzed 27 inoperable CTEPH patients who had received epoprostenol infusion for over 3 months. Compared with baseline, significant improvements were observed in not only the mPAP, PVR, and cardiac index but also the 6MWD (346 vs. 280 m, $p < 0.005$). In a case series, Ikari et al. [65] reported that prostaglandin I_2 may lead to isolated ACTH deficiency in CTEPH patients.

Olschewski et al. [66] assessed the efficacy of inhaled iloprost in PH in a randomized, placebo-controlled study. A total of 203 PH patients were recruited, including 33 CTEPH patients in the iloprost group. Although the authors reported that the iloprost group showed greater improvements in exercise capacity and WHO FC than the placebo group, no subgroup analysis of CTEPH patients was performed. In a prospective study, Krug et al. [67] evaluated the acute effects of inhaled iloprost on 6 operable and 14 inoperable CTEPH patients. After the inhalation of iloprost, the PVR decreased from 1057 to 821.3 dyn·s·cm^{-5} ($p < 0.0001$), the mPAP decreased from 50.55 to 45.75 mmHg ($p = 0.0002$), and the CO increased from 3.66 to 4.05 L/min ($p < 0.0106$). Ulrich et al. [68] compared acute vasoreactivity to inhaled iloprost between PAH and CTEPH patients. In the CTEPH group, inhaled iloprost led to a reduction of 16.3% ($p < 0.01$) and 8.3% ($p < 0.01$) in the PVR and mPAP, respectively. The responses to inhaled iloprost were comparable between the PAH and CTEPH groups, while the acute vasodilator responses were not correlated with an improvement in the 6MWD in either group. Reichenberger et al. [69] investigated the effects of inhaled iloprost on pulmonary gas change and pulmonary function in PH patients. In the CTEPH subgroup, 3 months of treatment with inhaled iloprost did not negatively affect pulmonary gas change or function, and an improvement in the 6MWD was observed.

Lang et al. [70] retrospectively analyzed the long-term efficacy of subcutaneously infused treprostinil in 122 PH patients, of whom 23 were CTEPH patients. In the whole population, significant improvements in the 6MWD and WHO FC were observed after 1 year and were maintained up to 3 years. The 4-year survival rates were comparable between the idiopathic PAH and CTEPH groups. In an open-label study sharing similar objectives with the work reported by Lang et al. [70], 25 severe inoperable CTEPH patients were exclusively enrolled [71]. The mean follow-up period was 24 months. Significant improvements in the WHO FC ($p = 0.001$), 6MWD ($p = 0.01$), PVR ($p = 0.01$), BNP level ($p = 0.02$), and CO ($p = 0.007$) were observed. Moreover, the 5-year survival rate was better in the treprostinil group than in the control group (53 vs. 16%, $p = 0.02$). The CTREPH study is the first RCT designed to examine the efficacy of subcutaneous treprostinil for CTEPH [72]. A total of 105 inoperable or persistent/recurrent CTEPH patients were recruited and randomly assigned in a 1:1 ratio to high-dose (30 ng/kg per min) or low-dose (3 ng/kg per min) subcutaneous treprostinil group. The primary end point was the change of the 6MWD after 24 weeks treatment. At week 12, improvements in 6MWD were comparable between the high-dose group and the low-dose group (32.7 vs. 27.3 m, $p = 0.27$). It should be noted that it took 12 weeks for the high-dose group to reach the target dose. At week 24, the high-dose group had a greater increase in 6MWD than the low-dose group did (44.98 vs. 4.29 m; treatment effect 40.69 m, $p = 0.0016$). The high-dose group also had better improvements in WHO FC, NT-proBNP, and hemodynamics. The most common adverse events were infusion site pain and other infusion site reactions, the frequency of which were similar between the two groups.

Ono et al. [73] examined the efficacy of beraprost in inoperable CTEPH. After a mean treatment duration of 2 months, the mPAP decreased by 11% ($p < 0.05$) and the PVR decreased by 18% ($p < 0.05$) in the beraprost group. Compared with conventional therapy, beraprost also greatly improved the 5-year survival rate (76 vs. 46%, $p < 0.05$). Nagaya et al. [74] assessed the effects of beraprost on the cardiopulmonary exercise test (CPET) results of patients with PAH and CTEPH. A subanalysis of the CTEPH group showed that beraprost caused a 9% increase in the peak oxygen consumption ($p < 0.05$), a 7% decrease in carbon dioxide production ($p < 0.05$), and an increase in the peak workload from 88 to 98 W ($p < 0.05$). The authors also reported that the response of the CPET results to beraprost was comparable between the PAH and CTEPH groups. Vizza et al. [75] also compared the effects of beraprost on exercise capacity between PAH and CTEPH patients. After 6 months of beraprost therapy, the 6MWD increased from 312 to 373 m ($p = 0.0003$) and

Table 4 Studies related to prostacyclin/prostacyclin analogues for the treatment of CTEPH

Study	Drug	Design	Patient	Duration	Main findings
Scelsi et al. [63]	Epoprostenol	Prospective	11 inoperable CTEPH patients and 16 PAH patients	12.4 months (median)	Significant improvements in WHO FC, 6MWD, and clinical symptoms of right heart failure
Cabrol et al. [64]	Epoprostenol	Retrospective	27 inoperable CTEPH patients	More than 3 months	Significant improvements in mPAP, PVR, cardiac index, and 6MWD
Ikari et al. [65]	Prostaglandin I_2	Case series	2 CTEPH patients	–	Prostaglandin I_2 may lead to isolated ACTH deficiency in CTEPH patients
Olschewski et al. [66]	Iloprost	RCT	57 CTEPH patients and 146 PAH patients	12 weeks	In the overall population, exercise capacity and WHO FC improved
Krug et al. [67]	Iloprost	Prospective	6 operable and 14 inoperable CTEPH patients	–	Inhaled iloprost induced acute improvements in PVR, mPAP, and cardiac output
Ulrich et al. [68]	Iloprost	Prospective	22 CTEPH patients and 35 PAH patients	–	Acute hemodynamic responses to inhaled iloprost were comparable between PAH and CTEPH groups
Reichenberger et al. [69]	Iloprost	Prospective	15 CTEPH patients and 48 other forms of PH patients	3 months	Inhaled iloprost did not negatively affect pulmonary gas change or pulmonary function test; improvement in 6MWD
Lang et al. [70]	Treprostinil	Retrospective	23 CTEPH patients and 99 PAH patients	26.2 months (mean)	In the whole population, 6MWD and WHO FC improved; 4-year survival was comparable between the PAH and CTEPH groups
Skoro-Sajer et al. [71]	Treprostinil	Open-label	17 inoperable and 8 persistent/recurrent CTEPH patients	24 months (mean)	Significant improvements in WHO FC, 6MWD, PVR, BNP, cardiac output, and 5-year survival
CTREPH [72]	Treprostinil	RCT	105 inoperable CTEPH patients	24 weeks	Significant improvements in 6MWD, WHO FC, NT-proBNP, and hemodynamics
Ono et al. [73]	Beraprost	Retrospective	43 inoperable CTEPH patients	36 months (mean)	Significant improvements in mPAP, PVR, and 5-year survival
Nagaya et al. [74]	Beraprost	Prospective	16 CTEPH patients and 14 PAH patients	3 months	Significant improvements in exercise tolerance and ventilatory efficiency
Vizza et al. [75]	Beraprost	Prospective	8 CTEPH patients and 8 PAH patients	6 months	Significant improvements in 6MWD and WHO FC
Holmboe et al. [76]	Iloprost, treprostinil, epoprostenol, and MRE-269	In vitro	Right atrial trabeculae from CTEPH patients and controls	–	These 4 drugs had no direct inotropic effects on pressure-overloaded or on normal right atria

CTEPH, chronic thromboembolic pulmonary hypertension; *PAH*, pulmonary arterial hypertension; *WHO FC*, World Health Organization functional class; *6MWD*, 6-min walking distance; *mPAP*, mean pulmonary arterial pressure; *PVR*, pulmonary vascular resistance; *RCT*, randomized controlled trial; *BNP*, B-type brain natriuretic peptide; *NT-proBNP*, N-terminal pro-brain natriuretic peptide

the WHO FC increased from 2.7 to 2 ($p < 0.05$) in the CTEPH group, and the PAH group showed similar results.

In an in vitro experiment, Holmboe et al. [76] investigated the direct effects of prostacyclins (iloprost, treprostinil, epoprostenol, and MRE-269) on right atrial trabeculae from CTEPH patients and patients with other cardiovascular diseases without right heart pressure overload. The results showed that these four drugs had no direct inotropic effects on either the pressure-overloaded right atrium or the normal right atrium. Thus, the mechanisms through which prostacyclins improve right heart function cannot be explained by their direct effects on cardiomyocytes.

Selexipag is a selective prostacyclin IP receptor agonist that has been approved for PAH [77]. The first and only set of data about the use of selexipag in CTEPH was reported by Thurber et al. [78]. The CTEPH patient was a 42-year-old man in functional class IV. Due to the requirement of the patient, intravenous treprostinil therapy was successfully transferred into oral selexipag (1600 mcg twice daily) over a 6-day transition. The patient remained stable for 14 days and then was rehospitalized due to complications unrelated to selexipag. After 2 to 3 days, selexipag therapy was restored but was discontinued approximately 1 month later due to volume overload and dyspnea.

Combination therapies

Combination therapy strategies for PAH have been well established. However, there is no consensus on such therapies for CTEPH at present, and publications relevant to this topic are very limited. An international study showed that 58–73% of CTEPH patients received monotherapy, 24–30% of them received dual therapy, and 2–15% of them received combination therapy with three or more drugs [79].

Prostacyclin analogues added to sildenafil

In an open-label, randomized, controlled study, Ghofrani et al. [80] compared the efficacy of sildenafil alone with sildenafil plus inhaled iloprost. Thirty patients were enrolled, 16 with PAH, and 13 with CTEPH. The overall hemodynamic response was measured by the area under the curve (AUC) of the PVR reduction. In the whole population, the authors reported that the addition of inhaled iloprost to sildenafil further improved the PVR and cardiac index, for which the AUC was greater than the summed AUCs for sildenafil alone and inhaled iloprost alone ($p < 0.001$). Vasodilation caused by combination therapy showed pulmonary selectivity, with no AEs. A subgroup analysis showed that the etiology of PH had no significant effect on the hemodynamic response, which supports the utilization of this combination therapy in CTEPH. Voswinckel et al. [81] investigated the acute effects of inhaled treprostinil added to oral sildenafil in 50 PH patients. The results showed that inhaled treprostinil following oral sildenafil further decreased the PVR, with a minor decrease in the systemic vascular resistance and mean arterial pressure. Acute hemodynamic responses similar to those were observed in both the PAH and CTEPH groups. Horng et al. [82] described that the hemodynamics of a 25-year-old pregnant woman with CTEPH were successfully stabilized by the sequential combination of sildenafil and inhaled iloprost. More importantly, this therapy had no serious adverse effects on either the patient or the newborn.

Riociguat added to treprostinil

In a case report, Swisher et al. [83] described their experience in combination therapy for CTEPH. By the time sildenafil was initiated, a 77-year-old female was in a condition of WHO FC IV with a pulmonary arterial pressure of 91 mmHg. After 24 months of sildenafil treatment, inhaled treprostinil was added to sildenafil due to hemodynamic deterioration. Thirty months later, sildenafil was replaced by riociguat due to WHO FC deterioration. Although sildenafil plus treprostinil temporarily improved the patient's WHO FC, her hemodynamics remained unchanged. In contrast, riociguat plus treprostinil improved the hemodynamics, WHO FC, and 6MWD after 12 months of treatment.

Macitentan added to PDE-5 inhibitors

Sixty-one percent of the patients recruited to participate in the MERIT-1 study were also receiving background PAH-targeted therapy (predominantly PDE-5 inhibitors) [61]. After 16 weeks of macitentan treatment, the improvement in PVR was consistent in patients already receiving PAH-targeted therapy and in patients receiving no other PAH-targeted therapy. A similar phenomenon was also observed in the 6MWD at 24 weeks. These results indicate that patients may benefit from a strategy combining macitentan and other PAH-targeted drugs. Thus, it is of great interest to explore the treatment effects of the initial or sequential combination of riociguat/subcutaneous treprostinil and macitentan.

Bridging therapy

The preoperative PVR has been shown to be a predictor of postoperative mortality at 1 month, 1 year, and 3 years [84]. CTEPH patients with a preoperative PVR of no more than 800 dyn·s·cm^{-5} had a better survival probability than those who failed to reach the threshold [84]. Currently, there is no convincing evidence supporting the use of PAH-targeted drugs as bridging therapy to PEA or BPA [5]. An international prospective registry study showed that 29% of operated

CTEPH patients received PAH-targeted therapy and that the most commonly used drugs were sildenafil and bosentan [35].

Prior to PEA

In a retrospective study, Nagaya et al. [85] investigated the efficacy of intravenous prostacyclin in 33 operable CTEPH patients. It should be noted that the prostacyclin group had higher pretreatment PVR and BNP levels than the controls (1631 vs. 893 dyn·s·cm^{-5}, $p < 0.001$; 547 vs. 153 pg/mL, $p < 0.05$, respectively) at baseline. After a mean treatment period of 46 days, prostacyclin caused a 28% reduction in PVR, while PVR remained unchanged in the controls. The BNP level also decreased to a degree comparable to that in the controls. Although the hemodynamics in the prostacyclin group were more unfavorable, the postoperative PVR and BNP levels were comparable in the two groups, suggesting that high-risk patients may benefit more from bridging therapy. In a single-blind, randomized, controlled trial, Reesink et al. [86] reported their experience using bosentan as a bridge to PEA in 25 patients. After 16 weeks of treatment, the bosentan group showed greater improvements in the total pulmonary resistance (TPR, $p = 0.004$), 6MWD ($p = 0.014$), and mPAP ($p = 0.005$) than the controls. After PEA, there was a trend showing that the bosentan group had a lower mPAP ($p = 0.09$) and TPR ($p = 0.08$) than the controls. In a randomized, placebo-controlled study, Surie et al. [87] evaluated the effects of preoperative bosentan therapy on RV remodeling and function. After 16 weeks of treatment, the bosentan group showed greater improvements in the 6MWD and functional and remodeling CMR parameters than the controls, indicating that preoperative bosentan therapy improved heart function and attenuated RV hypertrophy.

However, not all research results support the use of bridging therapy. An open-label trial was designed to assess the effects of inhaled iloprost before and after PEA [88]. The results showed that preoperative iloprost inhalation had no significant effects on the mPAP or PVR but decreased the systemic vascular resistance and mean arterial pressure in all patients. Jensen et al. [89] retrospectively analyzed the efficacy of bridging therapy in 355 patients. Sildenafil and bosentan were the most commonly used medications. Compared with the controls, the PAH-targeted therapy group had a higher mPAP at diagnosis and at the referral visit (50 vs. 46 mmHg, $p = 0.02$; 48 vs. 46 mmHg, $p = 0.04$), while the preoperative mPAP in the same group slightly decreased after PAH-targeted therapy (48 vs. 50 mmHg, $p = 0.03$). The rest of the hemodynamic parameters at diagnosis, at the referral visit, and after PEA were comparable between the two groups. More importantly, a subgroup analysis showed that the hemodynamic parameters at the three time points and the post-PEA outcomes did not differ between the combination therapy group and the control group. However, the PAH-targeted therapy group showed a longer median time to referral visit for the assessment of PEA (8.9 vs. 4.4 months, $p < 0.01$). In a retrospective study including 172 operated CTEPH patients, Tromeur et al. [84] reported that the duration of PAH-targeted therapy seemed to be associated with 1-month mortality (OR = 1.47, 95% CI = 1.00–2.17). The registry study mentioned above included 679 patients from 27 centers [35]. The authors reported that patients receiving PAH-targeted therapy had a less favorable WHO FC and hemodynamics than those who did not receive targeted therapy, while no significant difference was observed in either the postoperative PVR or postoperative complications between the two groups, similar to the results reported by Nagaya et al. [85]. However, PAH-targeted therapy is an independent predictor of mortality (HR = 2.62, 95% CI = 1.3–5.28). Charalampopoulos et al. [90] compared the effects of PAH-targeted therapy on exercise performance, measured by CPET, between inoperable and operable CTEPH patients. After medical treatment, the CPET parameters significantly improved in inoperable patients, including peak oxygen consumption, work load, and oxygen pulse. In operable candidates, improvements of these parameters were not caused by medical therapy but the sequential PEA procedure.

Prior to BPA

Reperfusion pulmonary edema (RPE) is a major complication of BPA. The pulmonary edema predictive scoring index (PEPSI) is an effective tool for predicting the occurrence of RPE [91, 92]. PEPSI is the product of the sum total change in pulmonary flow grade scores multiplied by the baseline PVR [91]. Feinstein et al. [93] found that a pre-BPA mPAP greater than 35 mmHg also correlated with the development of RPE (OR = 4.8, $p = 0.04$). Hence, PAH-targeted therapy prior to BPA may improve the effectiveness/outcomes of BPA by optimizing pre-BPA hemodynamics. Although this strategy has been applied in several studies, there have been no clinical trials specifically designed to investigate its efficacy in BPA, especially for patients who have not previously received PAH-targeted therapy [94, 95].

Ongoing clinical trials

The ongoing PEA bridging study (clinicaltrials.gov identifier NCT03273257) is a phase II RCT, of which the objective is to investigate the efficacy of riociguat as bridging therapy in operable candidates with high preoperative PVR. The treatment duration is 3 months. The primary end point is the change of PVR from baseline to immediately before PEA. Data from this study may help us have a better understanding of the role that bridging therapy plays in operable patients. The RACE study (clinicaltrials.gov

identifier NCT02634203) is an open-label, randomized study designed to compare the efficacy of riociguat versus BPA. The primary end point is the change of PVR from baseline to 26 weeks. The MR BPA trial (UMIN Clinical Trials Registry ID: UMIN000019549) is another open-label, randomized study that shares the same objective with the RACE study. The primary end point is the change of mPAP from baseline to 12 months. The results of the RACE and MR BPA trials may help us establish the optimal treatment option for the management of inoperable patients. The JPMS-CTEPH study (clinicaltrials.gov identifier NCT02117791) is a prospective cohort study that aims to evaluate the long-term safety and effectiveness of riociguat for the treatment of CTEPH. In the first year, the evaluation will be carried out after 4 and 12 months riociguat treatment. Then, the evaluation will be carried out yearly for the next 7 years.

There is an ongoing prospective cohort study (clinicaltrials.gov identifier NCT02970851) investigating the effects of bosentan on myocardial perfusion and metabolism. Its method is very similar to the one we have introduced above [38]. The primary outcome measures are myocardial ventricular right maximum standardized uptake value (measured by ^{18}F-FDG PET/CT) and myocardial blood flow (measured by ^{82}Rb PET/CT) at different stages.

The MERIT-2 study (clinicaltrials.gov identifier NCT02060721), the long-term extension of the MERIT-1 study [61], is an ongoing trial designed to evaluate the safety, tolerability, and efficacy of long-term macitentan treatment in CTEPH patients. Although Asian populations (Chinese, Koreans, Thais, and Vietnamese) were enrolled in the MERIT-1 study [61], Japanese patients were not involved. Thus, an open-label study (clinicaltrials.gov identifier NCT03809650) aims to evaluate the efficacy and safety of macitentan in Japanese patients with inoperable or persistent/recurrent CTEPH.

The SELECT (clinicaltrials.gov identifier NCT03689244) is a phase III RCT, of which the objective is to examine the efficacy and safety of selexipag in inoperable or persistent/

Table 5 Ongoing clinical trials related to PAH-targeted therapy for the treatment of CTEPH

Study	Clinicaltrials.gov identifier	Design	Objective	Primary outcome measures
PEA bridging study	NCT03273257	RCT	To investigate the efficacy of riociguat as bridging therapy in operable CTEPH patients	The change of PVR from baseline to immediately before PEA
RACE	NCT02634203	Open-label	To compare the efficacy of riociguat versus BPA	The change of PVR from baseline to 26 weeks
MR BPA	UMIN000019549[a]	Open-label	To compare the efficacy of riociguat versus BPA	The change of mPAP from baseline to 12 months
JPMS-CTEPH	NCT02117791	Cohort	To evaluate the long-term safety and effectiveness of riociguat	The number of patients with drug emergent adverse events and reactions
Prior et al.	NCT02970851	Cohort	To investigate the effects of bosentan on myocardial perfusion and metabolism	Myocardial ventricular right maximum standardized uptake value (measured by ^{18}F-FDG PET/CT) and myocardial blood flow (measured by ^{82}Rb PET/CT) at different stages
MERIT-2	NCT02060721	Open-label	To evaluate the safety, tolerability, and efficacy of long-term macitentan treatment in CTEPH patients	The safety and tolerability profiles of long-term macitentan treatment
Yokoyama et al.	NCT03809650	Open-label	To evaluate the efficacy and safety of macitentan in Japanese patients with CTEPH	The percent of baseline PVR at week 16
SELECT	NCT03689244	RCT	To examine the efficacy and safety of selexipag in CTEPH patients	The percent of baseline PVR at week 20
ATMOS	NCT03754660	Open-label	To investigate the safety and tolerability of the inhaled drug BAY1237592 as well as it impacts on PVR in PAH and CTEPH patients	Peak percent reduction in PVR from baseline
AMBER-1	NCT01884675	RCT	To investigate the safety and efficacy of ambrisentan in CTEPH patients	The change of 6MWD from baseline to week 16
AMBER-2	NCT01894022	Open-label	To investigate the long-term safety of ambrisentan in CTEPH patients.	The safety profiles of long-term macitentan treatment

PAH, pulmonary arterial hypertension; *CTEPH*, chronic thromboembolic pulmonary hypertension; *PEA*, pulmonary endarterectomy; *RCT*, randomized controlled trial; *PVR*, pulmonary vascular resistance; *BPA*, balloon pulmonary angioplasty; *mPAP*, mean pulmonary arterial pressure; *6MWD*, 6-min walking distance

[a] The MR BPA trial is registered in the UMIN Clinical Trials Registry (ID: UMIN000019549)

recurrent CTEPH patients. The primary end point is the percent of baseline PVR at 20 weeks. All participants who complete the 52 weeks of the double-blind treatment period will enter the open-label extension stage.

The ATMOS study (clinicaltrials.gov identifier NCT03754660) is an open-label trial which aims to investigate the safety and tolerability of the inhaled drug BAY1237592 as well as it impacts on PVR in PAH and CTEPH patients. This study has two parts. In part A, the drug will be tested in treatment-naïve patients. In part B, the highest safe, well tolerated and effective dose chosen from part A will be tested in patients who are receiving PAH-targeted therapy.

Ambrisentan is an ET_A-selective receptor antagonist [96]. The AMBER-1 and AMBER-2 studies were designed to assess the efficacy, safety, and tolerability of ambrisentan in inoperable CTEPH; both studies were terminated in 2017 (clinicaltrials.gov identifier NCT01884675 and NCT01894022, respectively). However, no publications relevant to the AMBER-1 or AMBER-2 studies are yet available. Ongoing clinical trials mentioned above are summarized in Table 5.

Conclusion

Although many achievements have been made in medical therapies over the last decade, PEA remains the only potentially curative treatment for CTEPH. For patients who are considered inoperable for various reasons, BPA is an attractive alternative and it may be another curative treatment in the future, particularly in combination with prior PEA. Thus, the assessment of operability should be cautiously made by a multidisciplinary team in a specialized CTEPH center.

The efficacy of PAH-targeted therapy in CTEPH has been supported by high-quality evidence [14]. Surprisingly, an international prospective registry study revealed comparable survival rates between those who received and did not receive PAH-targeted therapy, despite better hemodynamics in those who were medically treated [35]. It should be stressed that riociguat and macitentan were not available during the data collection phase of this study. Further work is needed to uncover the effects of these two drugs on long-term survival. Combination therapy has been successfully used in PAH. Whether CTEPH patients could also benefit from this strategy is of great interest. The role of bridging therapy remains unclear. Although high-risk patients may benefit from this treatment, the results from the latest studies are quite discouraging [35, 84]. Ongoing PEA bridging study (clinicaltrials.gov identifier NCT03273257) may provide useful data on this topic. Both riociguat and BPA have been demonstrated to be effective for the treatment of CTEPH. The results of the RACE and MR BPA trials may tell us which one is the optimal option for the management of inoperable patients. Universal and standardized end points of clinical trials will be helpful for comparing the efficacy of different interventions. A deterioration in the 6MWD and WHO FC and a delay in the time to clinical worsening are clinically meaningful end points for future clinical trials [97]. Last but not least, current medical treatments are far from curative. A better understanding of the pathogenesis of CTEPH is critical for preventing the transformation from pulmonary embolism to CTEPH and helping inoperable CTEPH patients; thus, research related to this field is encouraged.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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