Chronic Thromboembolic Pulmonary Hypertension Medical Management

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ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTEPH) is a common long-term complication of pulmonary embolism characterized by thromboembolic obstruction of the pulmonary arteries, vascular arteriopathy, vascular remodeling, and ultimately pulmonary hypertension (PH). Although pulmonary endarterectomy (PEA) surgery is the standard of care, approximately 40% of patients in the international CTEPH registry were deemed inoperable. In addition to lifelong anticoagulation, the cornerstone of PH-specific medical management is riociguat, a soluble guanylate cyclase stimulator. Medical management should be started early in CTEPH patients and may be used as a bridge to PEA surgery or balloon pulmonary angiography. Medical management is indicated for inoperable CTEPH patients and patients who have recurrence of PH after PEA surgery.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by thromboembolic obstruction of the pulmonary arteries and vascular arteriopathy leading to vascular remodeling and pulmonary hypertension (PH). If left untreated, this results in progressive right ventricular failure and death.[1,2] According to the World Health Organization's (WHO) updated clinical classification of PH, CTEPH continues to be designated as group 4 PH, with its unique pathophysiologic mechanisms.[3] Although the exact incidence of the disease is unknown, it is estimated to affect between 3 to 30 people per million based on registry data.[2,4] CTEPH causes a significant burden on society with excessive amounts of healthcare utilization, a high cost of therapy, and increased mortality.[5] Importantly, many patients with the disease can be surgically cured with pulmonary endarterectomy (PEA), which is the treatment of choice. Referral to an expert CTEPH center is recommended to complete operability assessment before patients are considered inoperable. Although the evaluation and management of CTEPH patients have been impacted by the COVID-19 pandemic, referral and evaluation at a CTEPH center is paramount in CTEPH patient management.[6] Patients who undergo PEA have an improved survival compared to patients treated with medical therapy alone.[7] This review focuses on medical management of patients with CTEPH.

MEDICAL MANAGEMENT

Medical management of patients with CTEPH can be a bridge to PEA or balloon angioplasty and a treatment option for inoperable patients; however, it is important to note that medical management should not delay surgical treatment. Although the standard of care is PEA, medical management should be considered for patients who are deemed ineligible for surgery. Approximately 40% of the patients enrolled in the international CTEPH registry were deemed inoperable due to impassable vascular obstruction, pulmonary arterial pressure

TRIAL	DRUG	RESULTS POSTED	SUBJECTS (N)	6MWD (M)	6MWD (EFFECT M)	PVR BASELINE (DYN·S/CM^5)	PVR BASELINE (DYN·S/CM^5)
CTREPH	Treprostinil	2019	105	308 ± 68[β]	+45[#,β]	845 ± 386[β]	-25
MERIT-1	Macitentan	2018	80	352 ± 81	+34[#]	957 ± 435	-16
CHEST-1	Riociguat	2014	261	347 ± 80	+46	787 ± 422	-31
BENEFIT	Bosentan	2007	157	342 ± 84	+2**	783 (95% CI 703-861)	-24

Table 1.
Key results of randomized controlled trials evaluating targeted medical therapy for chronic thromboembolic pulmonary hypertension. Adapted from Kim et al.[9-12] 6MWD: 6-minute walking distance; PVR: pulmonary vascular resistance

**: Not statistically significant; #: assessed at 24 weeks; β: high-dose treprostinil arm

disproportionate to morphological lesions, and significant medical comorbid conditions.[8] Multiple studies (Table 1) have demonstrated improvement in inoperable patients who receive targeted medical therapy,[9-12] yet there is a paucity of data for patients deemed inoperable due to medical comorbidity or for those reluctant to undergo surgery. All medical management for CTEPH includes lifelong anticoagulation and acknowledgement that antiplatelets are not a substitute for anticoagulation in these patients.[13] Data is lacking regarding preferred anticoagulation therapy in CTEPH, and it is unknown whether newer oral anticoagulants (NOACs) are superior to traditional oral vitamin K antagonists.

Currently, riociguat is the only medical therapy approved by the US Food and Drug Administration (FDA) for inoperable CTEPH and persistent PH after PEA based on randomized clinical trials (RCTs).[9,12] Presurgical medical management with PH medications and its impact on surgical outcomes has not been studied. Symptoms related to postsurgical or residual PH can be treated with off-label use of PH drugs. These patients may be candidates for BPA after PEA. There is a paucity of RCTs that are studying this patient population. In addition, the definition of clinically significant residual PH is not clearly defined.

Therapies Targeting the Nitric Oxide Pathway

Nitric oxide is an endogenous vasodilator that is decreased in patients with CTEPH.[14,15] Randomized controlled trials have studied two classes of medications to target this pathway: soluble guanylate cyclase stimulators and phosphodiesterase-5 (PDE5) inhibitors. These trials have evaluated treatment-naive patients with inoperable CTEPH and those with recurrent/persistent PH post-PEA.

Riociguat, a soluble guanylate cyclase stimulator, was approved by the FDA based on results from the CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator) study. In this randomized placebo-controlled clinical trial, patients with inoperable PH or persistent/recurrent PH after undergoing PEA experienced an improvement in 6-minute walk distance (6MWD), the primary end point, compared to placebo; they also experienced improvements in other secondary end points including pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP), and Borg dyspnea score.[9] Patients who completed this study were enrolled in a 1-year open-label extension (CHEST-2) study that demonstrated sustained improvement in 6MWD and WHO functional class, with an estimated survival rate of 97%.[12]

Sildenafil, a PDE5 inhibitor, has been studied in an RCT for patients with CTEPH, who showed no significant improvements in the primary outcome of 6MWD after 12 weeks of sildenafil versus placebo. The trial also showed significant improvements in secondary outcomes: improvement in WHO functional class and reduction in PVR.[16]

Therapies Targeting the Endothelin Pathway

Endothelin, a peptide that constricts blood vessels and dysfunction in this pathway, has been described in patients with CTEPH.[17] Two RCTs have studied endothelin receptor antagonists (ERA) in CTEPH patients. In the MERIT-1 trial (Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension), the efficacy of macitentan was studied in those with inoperable CTEPH; macitentan significantly improved the primary end point of change in PVR (P = .041) at 16 weeks from baseline compared with placebo.[11] In addition, secondary outcome data showed improvement in 6MWD at week 24 compared with baseline. Both safety and drug tolerability were similar to what was reported for macitentan in the SERAPHIN trial for patients with pulmonary arterial hypertension (PAH).[11,18] Combination therapy targeting multiple molecular pathways has been a hallmark of PAH therapy. The MERIT-1 trial was the first RCT for CTEPH to allow for PAH therapy at baseline, making the study generalizable to everyday patient populations: 61% of enrolled patients had already received PAH therapy at baseline, and 96% of them were receiving a PDE5 inhibitor.[11] At present, the MACiTEPH trial (A Study to Evaluate Efficacy and Safety of Macitentan 75 mg in Inoperable or Persistent/Recurrent Chronic Thromboembolic Pulmonary Hypertension) is investigating a higher dose of macitentan for potential CTEPH therapy.

The BENEFiT trial (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) was another RCT investigating the efficacy and safety of bosentan for patients with inoperable CTEPH, persistent PH post-pulmonary endarterectomy, or recurrent PH post-pulmonary endarterectomy. Compared with placebo, bosentan significantly improved PVR at week 16 compared to baseline, but there was no improvement in 6MWD.[10] There was also improvement in secondary end points of total pulmonary resistance and cardiac index. Reassuringly, the safety profile was similar to that of other trials for bosentan involving PAH patients.

The AMBER 1 study (Ambrisentan for treatment of inoperable chronic thromboembolic pulmonary hypertension) was designed to investigate the treatment of ambrisentan in inoperable CTEPH patients. This trial was terminated early due to a low screening rate and high screening failure, likely due to market availability of riociguat and of percutaneous BPA treatment. Hence, this study was underpowered to detect differences in efficacy outcomes,

although it did show a trend towards improvement in 6MWD, NT-proBNP, and PVR in the treated group.[19]

Therapies Targeting the Prostacyclin Pathway

Despite abundant data for drugs targeting the prostacyclin pathway in PAH, there is limited evidence for their efficacy in CTEPH. The AIR trial (Aerosolized Iloprost Randomized study), which evaluated the effect of inhaled iloprost in PH patients, contained a subgroup of inoperable CTEPH patients totaling 28% of the trial participants. Overall, the study showed significant improvements in 6MWD from baseline and improvement in WHO functional class at 12 weeks; however, there was no subgroup analysis to evaluate performance in the CTEPH group. Thus, the efficacy of iloprost in the CTEPH population is unclear.[20]

In 2019, the CTREPH study (Efficacy and Tolerability of Subcutaneously Administered Treprostinil Sodium in Patients With Severe [Non-operable] Chronic Thromboembolic Pulmonary Hypertension) evaluated the change in 6MWD from baseline to week 24 in patients with inoperable CTEPH. This study demonstrated that treatment with continuous high-dose subcutaneous treprostinil (target dose around 30 ng/kg/min at week 12) yielded improvements in 6MWD with a treatment effect of 45 meters (P = .0016) compared to low-dose subcutaneous treprostinil (target dose around 3 ng/kg/min at week 12) with a treatment effect of 4 meters. This suggests that treprostinil may provide an option to improve exercise capacity in patients with WHO functional class III or IV.[21]

Medical Therapy as a Bridge to Pulmonary Endarterectomy or BPA

Medical therapy is often used as a bridge to PEA or BPA, and it has been shown to delay the need for surgery.[22,23] Studies show that medical therapy can significantly reduce PVR in patients with severe CTEPH prior to PEA.[24,25] It has also been used to stabilize patients' hemodynamics prior to undergoing BPA, although this data is limited.[26] It is unknown if medical therapy improves postoperative outcomes, or if it potentially hinders or enhances PEA by altering the dynamic of the clot or vessel lumen. Despite the fact that it is routinely used as a bridge to PEA or BPA, further RCTs are needed to evaluate medical therapy in this role. Importantly, medical management should not delay referral to an expert center for comprehensive CTEPH management.

CONCLUSION

Pulmonary endarterectomy remains the treatment of choice for patients with operable CTEPH. For those with inoperable CTEPH, nonsurgical options such as medical therapy and BPA can be considered. In either case, treatment options should be discussed in a multidisciplinary CTEPH meeting at a CTEPH expert center such as Houston Methodist Hospital. Post-PEA patients should receive regular hemodynamic assessments. Patients with evidence of post-PEA PH should receive optimized medical therapy and be considered for BPA or repeat PEA. Current data for medical management support therapy targeting the nitric oxide pathway, and some support targeting the prostacyclin and endothelin pathways. Although data for combination therapy is lacking, it is often used in these patients. For all patients diagnosed with CTEPH, lifelong anticoagulation is a cornerstone of therapy. Referral to an expert CTEPH center is recommended to complete operability assessment by a multidisciplinary team, with periodic re-evaluation for surgical candidacy and BPA therapy.

KEY POINTS

- Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease seen in 3 to 30 per million patients, and it is associated with high mortality.
- Between 0.4% and 4.8% of patients diagnosed with acute pulmonary embolism will go on to develop CTEPH.
- Pulmonary endarterectomy (PEA) is the treatment of choice for all eligible patients with CTEPH.
- CTEPH patients should be referred early to a CTEPH expert center for operability assessment and a second opinion.
- Riociguat is the preferred medication for inoperable CTEPH and persistent PH after PEA surgery; however, medical management alone still conveys a poor prognosis for inoperable CTEPH since it is a progressive disease.

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