REGULAR ARTICLE

Medical Management of Chronic Thromboembolic Pulmonary Hypertension

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Medical therapy in chronic thromboembolic pulmonary hypertension (CTEPH) has two primary goals- to prevent recurrent thromboembolic events and to reduce right ventricular afterload with targeted medications (vasodilators) for pulmonary hypertension. These medical strategies are used in conjunction with mechanical treatments for CTEPH (pulmonary thromboendarterectomy (PTE) or balloon angioplasty). In the context of this review, we discuss anticoagulation strategies, patient selection for vasodilator therapy with particular focus on hemodynamic and clinically meaningful definitions of residual pulmonary hypertension after PTE and inoperable disease and then summarize the current randomized clinical trials (RCT) which have studied effectiveness of vasodilators in patients with CTEPH.

INTRODUCTION

Medical therapies in chronic thromboembolic pulmonary hypertension (CTEPH) have 2 primary focuses: prevention of recurrent thromboembolic events with lifelong anticoagulation, and reduction in right ventricular afterload with targeted medicines (vasodilators) for pulmonary hypertension (PH). These cornerstones of medical therapy are used in conjunction with mechanical treatments for the disease: pulmonary thromboendarterectomy (PTE) and balloon pulmonary angioplasty. Vasodilators are used in the case of inoperable CTEPH as well as for patients with residual PH after PTE surgery. In this review we will address recommendations and considerations for anticoagulation, patient candidacy for vasodilator therapy, and the timing of initiating therapy after PTE, and review the randomized controlled trials (RCT) of vasodilator therapies for inoperable CTEPH and residual PH after PTE surgery.

ANTICOAGULATION

Duration and Choice of Anticoagulation

Even though a known thrombophilia is identified in a minority of CTEPH patients (32% in the international CTEPH registry[1]), this population is considered a high risk for recurrent venous thromboembolic events and thus, lifelong anticoagulation is recommended. Traditionally, vitamin K antagonists (VKAs) have been used.[2] With the increasing use of direct-acting oral anticoagulants (DOACs) as safe and effective treatments for acute venous thromboembolism (VTE), more patients have been using this class of medications for long-term anticoagulation in the setting of CTEPH. There are no direct head-to-head trials comparing these 2 anticoagulation strategies; only observational registry data are available.

VKAs have been used most frequently, given a longer period of bioavailability, and are generally reported to be safe and efficacious at preventing recurrent VTE in CTEPH patients. Jujo-Sanada et al[3] observed major bleeding in 8.1%/person-year and recurrent VTE in 1.2%/person-year in their retrospective cohort of CTEPH patients on VKAs, while Henkens et al[4] reported major bleeding events at 2.4%/person-year in CTEPH patients.

As DOAC therapy has gained traction for treatment of acute VTE with several studies demonstrating similar efficacy for prevention of recurrent VTE and fewer bleeding events,[5] more patients with CTEPH have remained on DOAC therapy as their anticoagulant of choice. Registry data have provided some perspective on using DOAC therapy in the CTEPH patient population, although several controversies regarding safety and efficacy of this class of drugs remain.[6]

Bunclark et al[7] published a large retrospective analysis specifically dedicated to evaluating VKA compared with DOAC therapy. In this cohort, 794 patients on VKAs and 204 patients on DOAC therapy had PTE surgery at the United Kingdom national PTE center from 2007 to 2018. Both groups of patients had similar hemodynamic and functional status improvement after PTE and major bleeding events were equivalent (0.67%/person-year versus 0.68%/person-year). Patients on DOAC therapy had higher rates of recurrent VTE after stabilization on oral anticoagulation therapy (4.62%/person-year) compared with those on VKAs (0.76%/person-year), although survival was similar between the 2 groups.[7] A retrospective analysis of surgical specimens presented solely in abstract form suggested a higher rate of acute or subacute thrombi in the CTEPH tissue in patients on DOAC therapy (13.3%) compared to those on VKAs (6.7%).[8] Finally, a recent

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study using the EXPERT registry (an international, multicenter prospective registry of 841 patients treated with riociguat for pulmonary arterial hypertension or CTEPH) collected data regarding hemorrhagic events and recurrent thromboembolic events in patients with CTEPH on VKA and DOAC therapy. The authors reported no difference in absolute rates of hemorrhagic events or any difference in rates of exposure-adjusted hemorrhagic events between VKA and DOAC therapy (9.5% and 12.1% respectively). However, while recurrent thromboembolic events had low absolute numbers overall, the exposure-adjusted event rate was lower in patients treated with VKAs compared those treated with DOACs (1.7% and 4.6% respectively). While data are limited and these are retrospective studies, it does call into question the efficacy of DOACs for anticoagulation in CTEPH.[9]

Conversely, Sena et al[10] examined rates of bleeding events, death, and recurrent VTE in 501 patients with CTEPH-412 patients on VKAs and 134 on DOACs. There was no difference in survival or recurrent VTE, but in patients treated with VKAs there were higher rates of major bleeding events (odds ratio: 1.94; 95% confidence interval: 1.05-3.62).[10] Overall, more studies need to be done to help settle the question of efficacy of DOAC therapy in CTEPH patient populations.

Anticoagulation in Special Patient Populations

VKAs are the preferred method of anticoagulation in patients with anti-phospholipid antibody syndrome (APS), particularly high-risk triple-positive APS. This recommendation comes from several observational cohort studies as well as a randomized open-label non-inferiority study in which patients with triple-positive APS had higher rates of recurrent thromboembolic events and shorter event-free survival on DOAC therapy compared to VKA.[11,12]

Another special situation is bariatric surgery. Absorption of any DOAC could be potentially reduced by Roux-en-Y gastric bypass, because all the drugs in this class require some degree of absorption in the proximal small bowel.[13] Regarding gastric banding or sleeve gastrectomy, given that the surface area of the stomach is dramatically reduced, medications that primarily rely on the stomach for absorption can be impacted (dabigatran, edoxaban, and rivaroxaban).[13] Low-molecular-weight heparin or VKA may be more appropriate in this patient population.

SELECTION OF PATIENTS FOR ADVANCED MEDICAL (VASODILATOR) THERAPY

PH in CTEPH is due to the combination of large-vessel thrombo-fibrotic obstruction and concomitant microscopic vasculopathy. The latter is similar to what is observed in group 1 PH[14] and provides the rationale for use of advanced medical therapy (pulmonary vasodilators) for pulmonary hypertension.

Two patient populations may be candidates for vasodilator therapy in the context of CTEPH: patients with inoperable disease or patients who have residual PH after PTE. The assessment of operability must be performed by a multidisciplinary team of PTE surgeons, radiologists, and PH specialists with experience and expertise in CTEPH.[15] More in-depth discussion regarding diagnosis and determining operability is outside the context of this review.

Inoperable Disease

For patients who are not able to be offered PTE surgery, because their vascular occlusions are inaccessible or because their degree of PH is elevated out of proportion to thrombotic burden or they have prohibitive medical comorbidities, vasodilator therapy can be considered. In the small number of clinical trials that have been conducted in this patient population, the hemodynamic thresholds at which to consider vasodilator therapy were variable—typically patients were included with a mean pulmonary artery pressure (mPAP) ≥25 mm Hg and a pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg—the hemodynamic definition of CTEPH provided in the 2015 European Respiratory Society (ERS) guidelines.[16] However, pulmonary vascular resistance (PVR) thresholds varied from trial to trial. In practice, vasodilatory therapy is typically considered with mPAP ≥25 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg and PVR ≥240 dynes/s/cm^5 (PVR of 3 Wood units [WU]). In 2019 the 6th World Symposium on PH proposed a new hemodynamic definition, lowering the threshold from mPAP ≥25 mm Hg to an mPAP of >20 mm Hg.[17] It is not yet clear if this new definition is applicable to patients with CTEPH. The ongoing MACiTEPH trial (NCT04271475; macitentan 75 mg daily versus placebo) is the first RCT to enroll CTEPH patients with this new hemodynamic definition of PH.[18]

Vasodilators Prior to PTE

There are not robust data from RCTs to currently suggest that there is a benefit from using pulmonary vasodilators prior to PTE surgery in operable patients. In spite of this, registry data reveal that a substantial proportion of operable patients are on vasodilators prior to surgery.[1] Although preoperative treatment has been reported to improve preoperative hemodynamics, it has no effects on post-PTE outcomes and may induce unnecessary delay to a potentially curative surgical intervention.[19] Data from the international CTEPH registry showed that preoperative bridging therapy was not only associated with no improvement in PTE outcomes, but also with worsened long-term survival, although in this case patients who were bridged with medical therapy to PTE likely represented a population with more severe baseline disease.[20] A prospective clinical trial was being conducted studying the safety and efficacy of riociguat as a bridging therapy to PTE surgery (NCT03273257), but unfortunately it was stopped due to slower than expected recruitment brought on by the COVID-19 pandemic.[21] At this time, it is not recommended to routinely provide bridging therapy with vasodilators if a patient is a PTE candidate, as operability assessment is a crucial early step after diagnosis that should not be delayed.

Residual PH after PTE

The exact hemodynamic definition of residual PH after PTE is not established, nor is a standard time for mea-

surement in the postoperative course. The 2015 ERS guidelines recommend performing a right heart catheterization 3 to 6 months after PTE. In the immediate postoperative period residual PH has been associated with increased operative (30-day) mortality. A PVR > 500 dynes/s/cm^5 (PVR of 6.25 WU) was associated with higher mortality (10.3% versus 0.9% respectively) in a cohort of 1500 patients who received PTE at the University of San Diego between 1999 and 2010.[22]

Regarding outcomes in patients who survive the immediate postoperative period, clinically meaningful definitions of residual PH have varied. In a retrospective national cohort study in the United Kingdom, which defined residual PH as mPAP ≥25 mm Hg and PVR > 240 dynes/s/cm^5 (PVR of 3 WU), 162 patients had hemodynamic assessment 3 months after PTE surgery. The authors reported no difference in 1- and 3-year survival when comparing those with residual PH to those without.[23] Until 2019, mPAP ≥25 mm Hg and PVR > 240 dynes/s/cm^5 (PVR of 3 WU) was the hemodynamic definition of CTEPH at the time of diagnosis, as well as the hemodynamic definition of precapillary PH.[16] It is interesting to note that these thresholds may be too sensitive to differentiate poor outcomes in postoperative patients with residual PH.

Raising the hemodynamic threshold for defining residual PH after PTE may better differentiate patients who can benefit from vasodilator therapy. A retrospective study from the United Kingdom national CTEPH registry of 881 patients who underwent PTE surgery demonstrated that an mPAP ≥38 mm Hg and PVR > 425 dynes/s/cm^5 (PVR of 5.3 WU) measured 3 to 6 months after surgery was associated with worse long-term survival. In this cohort, mPAP ≥30 mm Hg and PVR ≥318 dynes/s/cm^5 (PVR of 3.9 WU) was associated with initiation of vasodilator therapy.[24] An observational cohort study of 441 patients who underwent PTE in Sweden and Denmark between 1994 and 2020 demonstrated that using a threshold of mPAP ≥30 mm Hg measured 48 hours after PTE was associated with worse long-term survival, and this relationship strengthened after excluding patients who experienced operative mortality.[25]

Further studies will hopefully inform exact definitions of clinically meaningful residual PH after PTE and assist in standardization of the timing of initiation of vasodilator therapy or referral for post-PTE balloon angioplasty.

VASODILATOR THERAPIES

To date, there have been a number of completed randomized placebo-controlled clinical trials investigating the safety and efficacy of pulmonary vasodilators for the treatment of both inoperable CTEPH and residual PH after PTE (Table). As with the treatment of PAH, CTEPH clinical trials have evolved from monotherapy versus placebo to including patients on background therapy (possibly suggesting some benefit from sequential combination therapy in CTEPH).

Nitric Oxide Pathway

Riociguat, a soluble guanylate cyclase stimulator, is currently the only US Food and Drug Administration (FDA)-approved pulmonary vasodilator for treatment of inoperable or residual CTEPH. In CHEST-1, a RCT comprised of 261 patients with inoperable CTEPH or residual PH after PTE, riociguat significantly increased exercise capacity and reduced PVR after 16 weeks compared to placebo.[26] There was also an improvement in biomarkers of right ventricular function (N-terminal pro-brain natriuretic peptide [NT-proBNP]) as well as World Health Organization functional class and there was no significant difference in serious safety events. Importantly, in this study, operability was determined by a central adjudication committee of international CTEPH experts.

Sildenafil, a phosphodiesterase type 5 inhibitor (PDE5i) was studied in a very small population of patients with inoperable CTEPH and demonstrated an improvement in PVR compared with placebo, without an improvement in 6-minute walk distance at 12 weeks.[27]

Endothelin Receptor Antagonists

Two endothelin receptor antagonists have been studied in CTEPH: bosentan and macitentan. In the BENEFiT RCT comparing bosentan to placebo in 157 patients with inoperable CTEPH or residual PH after PTE, bosentan did not impact 6-minute walk distance, which was the primary endpoint; however, a significant reduction in PVR was seen.[28] Because the trial did not meet its primary endpoint for improvement in exercise capacity, bosentan did not gain regulatory approval.

The safety and efficacy of macitentan was studied in the MERIT-1 study, a phase 2 placebo-controlled RCT. Eighty patients with inoperable CTEPH were randomized to macitentan or placebo and the study found an improvement in PVR, exercise capacity, and NT-proBNP.[29] Patients were permitted to be on background PDE5i or oral prostacylins and there was still a treatment effect, suggesting some benefit from combination therapy in CTEPH. The FDA requested further study after an initial request for approval for macitentan for CTEPH, and there is a clinical trial currently enrolling to further define efficacy and safety of macitentan for inoperable CTEPH as well as residual PH after PTE (NCT04271475).[18]

Prostacylins

A single RCT examined long-term use of subcutaneous treprostinil (a prostacyclin analogue) in 105 patients with inoperable CTEPH.[30] High-dose (~30 ng/kg/min) subcutaneous treprostinil compared to low-dose (~3 ng/kg/min) resulted in improvement in PVR, exercise capacity, functional class, and NT-proBNP; approximately one third of these patients were on background vasodilator therapies.[30] Although not FDA approved, it is used off label in clinical practice for severe disease, and has been approved in Europe.

The oral prostacyclin agonist selexipag is approved in Japan based on an RCT that showed improvements in PVR at 20 weeks, but no effect on 6-minute walk distance.[31] An international multicenter RCT of selexipag (a prostacyclin receptor agonist) for CTEPH was recently stopped due to futility (NCT03689244)[32]; more detailed results of this study are currently awaited.

Table. Randomized Placebo-Controlled Clinical Trials for Treatment of CTEPH

Year	Drug	Study	Patient population	n	Background therapy?	Intervention	Primary endpoint	Main finding	Approval
2008	Sildenafil[27]		Inoperable	19	No	Sildenafil (40 mg 3 times a day) versus placebo	6WMD	• Did not meet primary endpoint to significantly change 6WMD • Increased WHO FC and cardiac index, reduced PVR and Nt-PRONP	No
2008	Bosentan[28]	BENEFiT	Inoperable or Residual PH after PTE	157	No	Bosentan (62.5-125 mg twice daily) versus placebo	6WMD, Change in PVR	• Met one primary endpoint: reduced PVR by 24% • Did not significantly change in 6MWD	No
2013	Riociguat[26]	CHEST-1	Inoperable or Residual PH after PTE	261	No	Riociguat (0.5-2.5mg 3 times a day) versus placebo	6WMD	• Met primary endpoint:increased 6WMD • Increased WHO FC, reduced PVR and NT-proBNP	USA, Europe, Japan
2017	Macitentan[29]	MERIT-1	Inoperable	80	Yes	Macitentan (10 mg daily) versus placebo	Change in PVR	• Met primary endpoint: reduced PVR by 26% • Increased 6WMD, reduced NT-proBNP	No
2018	Treprostinil[30]	CTREPH	Inoperable or Residual PH after PTE	105	Yes	Treprostinil 30 ng/kg/min versus treprostinil 3ng/kg/min	6WMD	• Met primary endpoint: increased 6WMD • Increased WHO FC, reduced PVR and NT-proBNP	Europe
2022	Selexipag[31]		Inoperable or Residual PH after PTE	78	Yes	Selexipag (200-1600 µg twice daily) versus placebo	Change in PVR	• Met primary endpoint: decreased PVR • Did not significantly improve 6WMD	Japan

Abbreviations: CTREPH, chronic thromboembolic pulmonary hypertension; 6MWD, 6-minute walk distance; WHO FC, World Health Organization functional class; PH, pulmonary hypertension; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; Nt-proBNP, N-terminal pro-brain natriuretic peptide.

CONCLUSIONS

The mainstays of medical therapy for CTEPH are comprised of lifelong anticoagulation for all, and in patients who have inoperable disease or residual PH after PTE, consideration for advance medical (vasodilator) therapy for PH. Future studies will hopefully improve areas of uncertainty, including a standardized hemodynamic definition of residual PH after PTE to better define which patients benefit from treatment, more rigorous examination of the efficacy of DOACs in CTEPH populations, and also the role of combination PH therapy in CTEPH.

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