Medical Therapy for Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary hypertension (PH) secondary to chronic emboli, obstructing the pulmonary arteries. This results in increased pulmonary vascular resistance and right ventricular failure. CTEPH is the only form of PH that is potentially curable, through a surgical procedure that removes the chronic emboli: pulmonary thromboendarterectomy (PTE). The first step in managing patients diagnosed with CTEPH is to determine if they are operable. The use of medical therapy should never delay referral for surgery, which should be done at a specialized center with expertise in CTEPH. Since a significant proportion of CTEPH patients are not surgical candidates, or are among the 10% to 15% of patients that have persistent or recurrent PH after surgery, there is a need for effective medical therapy.
The use of several pulmonary arterial hypertension (PAH)-targeted agents have been studied, mostly in small uncontrolled trials. A recent Phase 3 clinical trial found riociguat, a stimulator of soluble guanylate cyclase (sGC), to be effective for inoperable CTEPH.

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by chronic organized thrombi obstructing the pulmonary vasculature. Thromboembolic obstruction of the pulmonary arteries leads to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and right ventricular failure.[1] Studies following patients who present with acute pulmonary emboli suggest that about 1% to 4% of patients develop chronic thromboemboli.[2,3] In addition, about 25% of CTEPH patients never have an identifiable preceding acute pulmonary embolus.[4] Therefore, the number of patients with CTEPH is no doubt underestimated. Despite it being a mechanical problem, CTEPH can result in a secondary arteriopathy similar to that seen in PAH. Pathologic examinations of surgical biopsies or postmortem specimens have shown pulmonary hypertensive changes indistinguishable from pulmonary arterial hypertension (PAH), including intimal thickening of the small pulmonary arteries and plexiform lesions.[5] Interestingly, the small vessel changes were distal to patent pulmonary arterial segments, whereas arteries distal to embolic obstruction were normal. This is likely a result of increased blood flow to unobstructed areas.

In addition to histopathologic similarities, CTEPH and PAH can have comparable clinical presentations. It is very important to distinguish CTEPH from PAH by performing the necessary imaging studies, such as ventilation/perfusion scanning and pulmonary angiography. A correct diagnosis is of utmost importance, as PAH can be improved by PAH-targeted therapies, whereas the optimal treatment for CTEPH is surgical removal of chronic thrombi by pulmonary thromboendarterectomy (PTE). PTE often results in normal or near normal hemodynamics, and requires no therapy other than anticoagulation. Many patients return to New York Heart Association (NYHA) functional class I. This highly successful procedure is described elsewhere in this issue.

Even though PTE is the treatment of choice for CTEPH, there is a group of patients that will not be operative candidates. Patients can have obstruction of subsegmental and more distal arteries that are not surgically accessible. In addition, there is a set of patients with CTEPH who will have persistent or recurrent PH despite successful PTE. Persistent PH is due to distal disease or arteriolar remodeling of unobstructed vessels, which cannot be corrected with surgery. Recently published data from an international registry of 679 newly diagnosed patients with CTEPH found that 37% of patients were considered inoperable.[4] Nonoperability was mostly due to inaccessibility of disease (45%), followed by comorbidities and high PVR >1500 dyne·s·cm^{-5}. It cannot be overemphasized that determination of operability requires great expertise and should only be made at centers that evaluate and treat many patients with CTEPH.

RATIONALE FOR MEDICAL THERAPY

Given the clinical and pathological similarities between CTEPH and PAH, there may be a benefit to using PAH-targeted therapies in this disease, specifically in nonoperable CTEPH or persistent PH after PTE. There is evidence that endothelin-1 (ET-1), a potent vasoconstrictor upregulated in

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PAH, is also elevated in CTEPH. Animal models of CTEPH have shown elevated ET-1 levels.[6,7] In humans, ET-1 levels have been shown to be higher in patients with CTEPH when compared to healthy controls.[8] ET-1 levels in 35 patients with CTEPH correlated with the clinical severity of disease and hemodynamic outcome after PTE. Patients with higher preoperative ET-1 levels had worse postoperative outcomes and were more likely to have persistent PH after PTE. Nitric oxide and prostacyclin pathways are also known to be important in the development of PAH. However, less is known about the significance of these mechanisms in CTEPH.

Medical Therapy As a Bridge to Surgery

Recent series of CTEPH patients undergoing PTE have reported in-hospital mortality rates of 2.2% to 5%.[9,10,14] Risk of mortality seems to be related to preoperative hemodynamic severity, in particular an elevated PVR. A series of 275 patients who underwent PTE had a 4% mortality rate when PVR was less than 900 dynes·s·cm^{-5}. Mortality increased to 10% when PVR was above 900 dynes·s·cm^{-5}.[10] Another large series reported a mortality rate of 1.6% when PVR was less than 1000 dynes·s·cm^{-5}, as compared to 4.1% when PVR was greater than 1000 dynes·s·cm^{-5}.[9] Postoperative PH with a PVR greater than 500 dynes·s·cm^{-5} was associated with an even higher mortality of 10.3%. Whether surgical outcomes can be improved by refining preoperative hemodynamics with targeted PAH therapies remains unknown.

Small studies have aimed to answer the question regarding medical treatment prior to surgery. Treatment with intravenous (IV) epoprostenol in patients with CTEPH and severe PH (PVR >1000 dynes·s·cm^{-5})[11,12] was associated with preoperative improvements in PVR, mean pulmonary artery pressure (mPAP), and cardiac index. However, the impact on surgical morbidity or mortality could not be established from these small uncontrolled studies. Similar hemodynamic improvements were also seen in patients treated preoperatively with bosentan.[8,13] Twenty-five CTEPH patients, candidates for PTE, were randomized to bosentan vs no bosentan. After 16 weeks of treatment, the bosentan group had significant improvements in mPAP, total pulmonary resistance (TPR), and 6-minute walk distance (6MWD). However, outcomes after surgery were similar in both groups.

Despite the lack of good data, the use of medical treatment prior to PTE has significantly increased in the past decade. A prospective analysis found that the use of disease-modifying PAH therapies had increased from 29% in 2001 to 65% in 2006.[14] Another study reported an increase in medical treatment before PTE from 20% in 2005 to 37% in 2007.[15] This high number was confirmed in the CTEPH registry, where up to 54% of patients were on at least one PAH-targeted therapy.[4] A retrospective analysis of CTEPH patients referred for PTE compared 244 patients not on PAH therapy to 111 who were on therapy prior to surgery.[15] The patients on medical therapy had a lower mPAP at the time of surgery. However, there were no significant differences in hemodynamic parameters, mortality, or complications after PTE between the 2 groups. The only significant difference was the time to referral for surgery. The median time to referral was 9 months in those on medical therapy vs 4 months in those without therapy. Therefore, preoperative medical therapy does not seem to improve outcomes and may lead to an unwarrated delay in surgery.

Medical Therapy in Lieu of Surgery or After Surgery

In patients deemed inoperable or with persistent or recurrent PH after PTE, several PAH-targeted agents have been evaluated, mostly in uncontrolled case series. Table 1 summarizes the studies of targeted PAH therapies in CTEPH.

PROSTANOIDS

There are limited data on medical treatment for inoperable CTEPH. A small, retrospective study showed that the use of the oral prostacyclin beraprost was associated with improved hemodynamics, functional class, and mortality in patients with CTEPH compared to retrospectively matched untreated controls.[16] Treatment with IV epoprostenol in 11 inoperable CTEPH and 16 idiopathic PAH (IPAH) patients resulted in improved clinical status, exercise tolerance, and NYHA functional class after 12 months.[17] Another retrospective study found improvement in hemodynamics and 6MWD after 3 and 20 months of IV epoprosteonol in 27 patients with inoperable CTEPH.[18] Only half of the patients had improvement in NHYA functional class. By the end of the study, only 9 patients remained on epoprotenol (5 got transplants and 13 patients died).

Inhaled and subcutaneous prostanoids have also been considered for treatment of inoperable CTEPH. A multicenter retrospective study examined the effects of subcutaneous treprostinil in 99 patients with IPAH and 23 patients with distal CTEPH.[19] After 3 years, patients in both groups had significant improvement in 6MWD, dyspnea score, and NYHA functional class. Subsequently, an open-label case-control study of 25 patients with inoperable CTEPH or persistent PH after PTE found significant improvements in 6MWD, NYHA functional class, B-type brain natriuretic peptide (BNP) plasma levels, cardiac output, and PVR when treated with subcutaneous treprostinil. Survival was also better when compared to historical controls.[20] Regarding inhaled prostacyclins, the Aerosolized Iloprost Randomized (AIR) study included 47 patients with CTEPH[21] (23% total patients). A post-hoc analysis in this patient group found improvement in quality of life and dyspnea scores, without improvement in 6MWD.

PHOSPHODIESTERASE TYPE 5 INHIBITORS

A small, open-label study treated 12 patients with inoperable CTEPH and severe PH with sildenafil. Sildenafil was well tolerated and improved walk distance and PVR after 6 months.[22] A larger open-label trial of 104 inoperable CTEPH patients found similar positive results after 1 year of treatment.[23] This was followed by a single-center, double-blind, placebo-controlled pilot study that randomized 12 inoperable CTEPH patients to 12 weeks of sildenafil vs placebo.[24] This was the first randomized

Table 1.

Author, Year	Drug	Type of Study	Length of Study	Number of Patients	Outcomes
Prostacyclins					
Olschewski et al, 2002[21]	Inhaled iloprost	Multicenter randomized controlled trial (AIR)	12 weeks	• 101 iloprost (33 CTEPH) • 102 placebo (24 CTEPH)	• 16.8% iloprost patients reached combined primary endpoint (improvement in NYHA class and at least 10% improvement in 6MWD) vs 4.9% in placebo group
Ono et al, 2003[34]	Beraprost	Retrospective	2 months	• 20 beraprost • 23 matched controls	• Improved NYHA in 50% of treated patients • Decrease in mPAP • Decrease in PVR • 15% mortality on beraprost • 70% mortality in controls
Scelsi et al, 2004[17]	IV epoprostenol	Restrospective	12 Months	• 16 PAH • 11 inoperable CTEPH	• Improved exercise capacity • Improved NHYA functional class
Cabrol et al, 2007[18]	IV epoprostenol	Retrospective	3 months	• 27 NYHA III-IV	• Increase in 6MWD • Decrease in mPAP • Increased cardiac index • Decreased TPR • 50% Improved NYHA
Lang et al, 2006[19]	SQ treprostinil	Multicenter retrospective	26 months	• 99 PAH • 23 inoperable CTEPH	• Increased 6MWD • Improvement in NYHA • Survival 89% 1 year, 71% 2 years
Skoro-Sajer et al, 2007[20]	SQ treprostinil	Open-label case control	19 months	• 25 • 31 historical matched controls	• Increased 6MWD • 50% improved NHYA class • Improvement in BNP • Increase in cardiac output • Decrease in PVR
Phosphodiesterase Type 5 Inhibitors					
Ghofrani et al, 2003[22]	Sildenafil	Open label	6 months	• 12	• Decrease in PVR • Increase in cardiac index • Increase in 6MWD
Reichenberger et al, 2007[23]	Sildenafil	Open label	1 Year	• 104	• Decrease in PVR • Increase in 6MWD
Suntharalingam et al, 2007[35]	Sildenafil	RCT	12 Weeks	• 8 sildenafil • 10 placebo	• Improvement in NHYA class • Decrease in PVR • No significant change in 6MWD
Endothelin Receptor Antagonist					
Hoeper et al, 2005[25]	Bosentan	Open label	3 months	• 19	• Decrease in PVR • Increase in 6MWD • No change in NYHA class or MVO2
Hughes et al, 2006[27]	Bosentan	Open-label retrospective	1 year	• 47	• Increase in 6MWD • Decrease in PVR
Jais et al, 2008[28]	Bosentan	Multicenter RCT (BENEFIT)	16 weeks	• 77 bosentan • 80 placebo	• Decrease in PVR • No change in 6MWD
Riociguat					
Gofrhani et al, 2013[29]	Riociguat	Multicenter RCT (CHEST-1)	16 weeks	• 173 riociguat • 88 placebo	• Increased 6MWD • Decrease in PVR • Improvement in NYHA class • Inprovement in NT-proBNP

controlled trial ever done on CTEPH patients. The sildenafil group had improvements in NYHA functional class and PVR, but did not achieve the primary outcome of improvement in exercise capacity. This lack of improvement in 6MWD may be attributed to the study being underpowered. Based on these small trials, it

seems that sildenafil is well tolerated and leads to improvement in hemodynamics and functional class, without obvious improvement in exercise capacity. However, further larger studies would need to be conducted to better answer this question.

ENDOTHELIN RECEPTOR ANTAGONISTS

Several uncontrolled trials suggested that bosentan was not only safe, but may improve exercise capacity and hemodyanimcs in patients with inoperable CTEPH or persistent PH after PTE. An open-label safety study used bosentan for the treatment of 19 patients with inoperable CTEPH.[25] After 3 months of treatment, patients had improvement in PVR and 6MWD, but no improvement in peak oxygen uptake or NYHA functional class. Similar results were seen in a subsequent small case series of 16 patients with inoperable CTEPH receiving bosentan for 6 months.[26] A larger open-label retrospective study found that bosentan was well tolerated in 47 patients with inoperable CTEPH or PH after PTE. After 1 year of treatment there was improvement in 6MWD and hemodynamics, with no significant side effects.[27]

Given these positive findings, a large, multicenter, randomized, placebo-controlled trial was performed. The Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension (or BENEFIT) study, a 16-week randomized trial of bosentan therapy in 100 patients with CTEPH, was the first large randomized trial that looked exclusively at this patient population.[28] One hundred fifty-seven patients with either inoperable CTEPH due to distal disease or PVR out of proportion to obstruction, or patients with persistent or recurrent PH more than 6 months after PTE, were randomized to bosentan or placebo. After 16 weeks of treatment, there was a statistically significant improvement in PVR (-24% of baseline) in the bosentan group. Despite improvements in PVR, there was no significant difference in exercise capacity. The reasons for this "disconnect" between the hemodynamic and exercise capacity effects of bosentan in the BENEFIT trial are not clear; patient selection may have played a role, as many patients were deemed "inoperable" due to other comorbidities and not necessarily anatomically inaccessible disease.

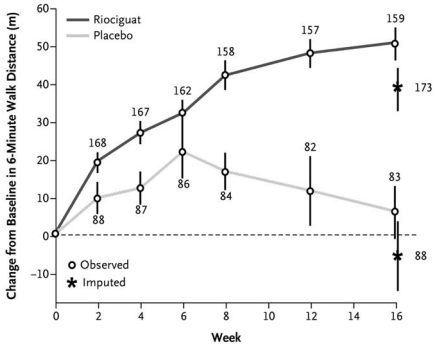

Figure 1. Mean Change From Baseline in 6-Minute Walk Distance. In CHEST-1, riociguat led to a significant placebo-corrected improvement in 6 minute walk distance. Reprinted with permission of the American Thoracic Society © 2003. Ghofrani et al. *Am J Respir Crit Care Med.* 2003; 167(8):1139-1141.

RIOCIGUAT

Riociguat is a member of a new class of drugs, soluble guanylate cyclase (sGC) stimulators. Riociguat acts both by enhancing the sensitivity of sGC to nitric oxide (NO), and as a direct sGC stimulator that will activate sGC to synthesize cyclic guanosine momophosphate (cGMP) in the absence of NO. Once sGC is activated, it converts guanosine triphosphate (GTP) to cGMP, which then leads to vasodilation.[29,30] The Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial (CHEST-1) was a large, multicenter, randomized, double-blind, placebo-contolled trial of 261 patients, randomized to riociguat vs placebo.[29] Patients included had anatomically inoperable CTEPH or persistent or recurrent PH after undergoing PTE. After 16 weeks of treatment, 6MWD increased by a mean of 39 meters in the riociguat group, compared with a mean decrease of 6 meters in the placebo group ($P<0.001$) (Figure 1). There were also significant improvements in secondary endpoints, including hemodynamics. Pulmonary vascular resistance decreased by 226 dyne·s·cm^{-5} in the riociguat group, compared with an increase of 23 dyne·s·cm^{-5} in the placebo group. There was significant improvement in other hemodynamic variables in the riociguat group, including pulmonary artery pressure and cardiac output (see Table 2). Patients treated with riociguat also had improvement in NYHA functional class and reduction in NT-proBNP, when compared to placebo. Riociguat was recently approved in the United States for the treatment on inoperable CTEPH or persistent PH following PTE.

SURGICAL VS MEDICAL THERAPY

When thinking about medical therapy in CTEPH, early referral to a center of excellence with experience in pulmonary endarterectomy needs to be emphasized. Starting medical therapy should never delay referral for surgery. PTE has the potential to normalize hemodynamic and symptomatic impairments, whereas medical therapy cannot. Patients with operable disease have been found to have a 5-year survival of 90%,[31] whereas inoperable patients have a 3-year survival of 70%.[14,32] The decision to operate is dependent on whether the disease is surgically accessible, if the anatomic lesions "fit" the hemodynamics, and the severity of comorbidities. Currently there is no consensus or accepted algorithm to guide operability. This decision is based on center and surgical expertise.[33]

The international CTEPH registry found a large variation between countries and centers regarding the number of patients deemed operable.[4] Low-volume centers reported up to 47% of patients evaluated as inoperable, whereas high-volume centers performing >50 PTEs a year reported 34% of patients inoperable. Therefore, more experienced centers may operate on cases others would deem inoperable. A recent large retrospective study from San Diego analyzed 1500 patients with symptomatic CTEPH who underwent pulmonary endarterectomy between 1999 and 2010.[9] Despite having more distal disease, the most recent 500 patients had a comparable decrease in PVR and mPAP and an in-hospital mortality of 2.2%, compared to 5.2% in the first 1000 patients. Therefore, in an experienced center, the outcomes of

Table 2. Change from Baseline to End of Week 16 in Primary and Secondary End Points and in Hemodynamic Variables.*

End Point	Placebo			Riociguat			Least-Squares Mean Difference (95% CI)	P Value†
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change		
Primary end point								
6-Min walk distance (m)‡	88	356±75	−6±84	173	342±82	39±79	46 (25 to 67)	<0.001
Secondary end points								
Pulmonary vascular resistance (dyn·sec·cm^{-5})	82	779±401	23±274	151	791±432	−226±248	−246 (−303 to −190)	<0.001
NT-proBNP (pg/ml)	73	1706±2567	76±1447	150	1508±2338	−291±1717	−444 (−843 to −45)	<0.001
WHO functional class§	87	0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV	57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class	—	0.003
Borg dyspnea score¶	88	4±2	0.2±2.4	173	4±2	−0.8±2	—	0.004‖
EQ-5D score**	87	0.66±0.25	−0.08±0.34	172	0.64±0.24	0.06±0.28	0.13 (0.06 to 0.21)	<0.001‖
LPH score††	86	46±23	−2±19	170	41±22	−7±19	−6 (−10 to −1)	0.1‖
Hemodynamic variables‡‡								
Pulmonary-artery pressure (mm Hg)	84	44±10	0.8±7.3	156	45±13	−4±7	−5 (−7 to −3)	<0.001
Mean arterial pressure (mm Hg)	78	95±11	−0.3±11.8	155	95±12	−9±12	−9 (−12 to −6)	<0.001
Right atrial pressure (mm Hg)	84	9±6	−0.6±5.2	157	9±5	−1±5	−0.6 (−1.7 to 0.6)	0.4
Cardiac output (liters/min)	83	4±1	−0.03±1.07	155	4±1	0.8±1.1	0.9 (0.6 to 1.1)	<0.001
Pulmonary-capillary wedge pressure (mm Hg)	83	9±4	0.2±4.3	151	9±3	0.6±3.7	0.6 (−0.4 to 1.5)	0.2
Arterial oxygen saturation (%)	87§§	94±2	−3±8	172¶¶	94±3	−2±4	—	—
Heart rate (beats/min)	88	76±12	2±12	173	78±12	1±12	—	—
Pao_2 (mm Hg)	87‖‖	69±11	−5±12	172¶¶	70±12	−3±15	—	—

* Plus–minus values are means ±SD. The changes from baseline to the end of week 16 are arithmetic means. The least-squares mean difference was calculated by analysis of covariance for the change from baseline to the last visit. NT-proBNP denotes N-terminal pro–brain natriuretic peptide, and Pao_2 partial pressure of arterial oxygen.
† P values were calculated with use of the stratified Wilcoxon test for the change from baseline to the last visit.
‡ The primary end point was analyzed in the modified intention-to-treat population as the change from baseline to the last observed value (not including follow-up) among patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.
§ The change in the WHO functional class was analyzed with the use of a stratified Wilcoxon test.
¶ The Borg dyspnea scale ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea. The change in the Borg dyspnea score was analyzed with the use of a stratified Wilcoxon test; an analysis of covariance was not specified for this variable owing to the nonnormal distribution of the data.
‖ These analyses were only exploratory, owing to the hierarchical testing procedure.
** Scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) range from −0.6 to 1.0, with higher scores indicating a better quality of life.
†† Scores on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire) range from 0 to 105, with higher scores indicating worse quality of life.
‡‡ All the analyses of hemodynamic variables were exploratory analyses, with the exception of heart rate, which was analyzed descriptively (and therefore has no P value associated with it).
§§ Data at week 16 were missing for 7 patients.
¶¶ Data at week 16 were missing for 20 patients.
‖‖ Data at week 16 were missing for 6 patients.

PTE are favorable even in patients with segmental level CTEPH.

CONCLUSION

CTEPH should be considered and ruled out in any patient with newly diagnosed PH. Clinically it can mimic PAH. It is important to distinguish between the two because the treatment strategies are different. The initial step in management of CTEPH should be referral to a specialized center with expertise in CTEPH, in order to assess operability. If PTE is successful, patients may return to normal or near-normal hemodanymics and exercise capacity after surgery. In those patients who are not surgical candidates or have recurrent or persistent PH after PTE, medical management with riociguat is appropriate.

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