

Chronic Thromboembolic Pulmonary Hypertension:

Role of medical therapy

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease with poor prognosis if not treated. The treatment of choice is surgery with pulmonary endarterectomy. However, a significant percentage of patients are deemed non-operable due to distal distribution of the disease and arteriopathy in the non-occluded areas that is indistinguishable from pulmonary arterial hypertension (PAH). The overlap in clinical presentation, pathological features and pathogenesis between PAH and CTEPH provides a compelling rationale for exploring the efficacy of PAH-targeted therapies in CTEPH. These therapies are often considered for non-operable patients and are also used in operable patients as a bridge to surgery or as post-PEA therapy for persistent pulmonary hypertension, despite the fact they are not licensed for CTEPH.

Two randomised clinical trials (RCTs) have been performed in non-operable CTEPH patients. The BENEFiT study, with the endothelin receptor antagonist bosentan, did not show improvement in walking distance. Recently, the CHEST-1 trial, with the soluble guanylate cyclase stimulator riociguat, met study endpoint and demonstrated significant improvement in walking distance in patients with non-operable CTEPH.

There is an urgent need for more RCTs designed to clarify whether administration of PAH-targeted therapies improves clinically meaningful endpoints in various CTEPH populations.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) are dyspnoea-fatigue syndromes caused by an increase in pulmonary vascular resistance (PVR) leading to right ventricular failure [1]. CTEPH and PAH have historically been associated with a poor prognosis, but in the majority of cases, CTEPH can now be cured surgically with pulmonary endarterectomy (PEA) [2].

CTEPH is a rare disease with an estimated incidence of 2,500 new cases per year in the United States [3]. Recent follow-up studies in patients presenting with acute pulmonary embolism (PE) suggest that CTEPH develops in 0.6% to 9% of patients having experienced an acute PE [4-8]. However, a significant number of CTEPH patients (25% to 75%) have no history of acute PE [9-12]. Therefore, the true incidence of CTEPH is likely to be underestimated by studies that only follow patients after an acute PE [13]. A prospective cohort study by Condliffe *et al.* [14] involving all UK PH centres reported an incidence of 1.75 cases/year/million in 2006. Recent UK data show that CTEPH is diagnosed in 14% of incident cases referred to designated National PH Centres in 2010-2011. The prevalence standardised for age and sex (per million and per year) is 16.6 in England, 14.3 in Scotland and 12.3 in Wales [15]. These data suggest that CTEPH may be more common than previously thought.

CTEPH results from the obstruction of the pulmonary vascular bed by non-resolving thromboemboli, which may completely occlude the lumen or form different grades of stenosis, webs and bands. CTEPH is often described as a two-compartment disease including mechanical intraluminal obstructions and a variable degree of arteriopathy in non-occluded areas that is indistinguishable

from PAH [16]. CTEPH patients often display severe pulmonary hypertension (PH) that cannot be fully explained by the degree of pulmonary vascular obstruction visible on imaging. In these cases, the increased PVR may be due to distal obstructive thrombotic lesions situated beyond the subsegmental level, but also to vasculopathy present at the pre-capillary level. These distal lesions, which are difficult to treat by surgical disobliteration with PEA, may be responsible for out of proportion elevated PVR prior to surgery and for persisting/residual PH following PEA. Patients presenting with a distal disease that is not suitable for surgery are often considered for management with PAH-targeted therapies [17-19] despite the fact these medications are not approved for the treatment of CTEPH.

The present article will focus on recent developments in the pharmacological treatment of CTEPH and review the evidence supporting the use of PAH-targeted therapies in CTEPH.

Overlap in clinical and pathological presentation between PAH and CTEPH

The diagnosis of PAH and CTEPH requires a common methodical step-by-step workup to elucidate the cause of PH [20]. However, physical findings, chest roentgenograms, electrocardiograms, echocardiograms and pulmonary function tests may not differentiate the two conditions [21]. The differential diagnosis between CTEPH and PAH is made from imaging investigations: ventilation/perfusion scanning, angiography-computed tomography (CT) and pulmonary angiography. A correct diagnosis of CTEPH or PAH is of crucial therapeutic relevance as PAH can be improved by PAH-targeted therapies, whereas CTEPH is potentially cured by PEA.

The management of CTEPH can be complicated by the presence of small vessel disease, mimicking the histopathological changes observed in PAH. There appear to be three categories of small-vessel disease that may contribute to CTEPH: 1. obstruction of small subsegmental and more distal arteries that are out of reach for the PEA surgeon; 2. pulmonary arteriopathy of small muscular arteries and arterioles distal to unobstructed elastic arteries; and 3. pulmonary arteriopathy of small muscular arteries and arterioles distal to obstructed elastic arteries. Histopathology of the lung tissue taken from patients with CTEPH reveals plexiform lesions and intimal thickening of the small pulmonary arteries and arterioles appearing very similar to those seen in other forms of severe non-thromboembolic PAH [22].

PEA is the treatment of choice for CTEPH [23], however, only about 60% of the presenting patients will be operated and 10-15% of the operated patients will be left with clinically significant PH [2, 21, 23, 24]. In these patients, peripheral arteriolar remodelling is a cause of severe morbidity or even mortality after an otherwise successful surgery.

The similarities in clinical and pathological presentation between CTEPH and PAH suggest that PAH-targeted therapies may be of benefit in selected patients with CTEPH, especially those with substantial small-vessel arteriopathy.

Evidence for the presence of similar therapeutic pathways in CTEPH and PAH

Alterations of several signalling pathways contribute to the development of PH. Three of these pathways, the endothelin, nitric oxide and prostacyclin pathways, represent the targets of the current therapeutic management of PAH. Studies examining the pathophysiology of CTEPH in animal and human models have

provided a rationale for the use of endothelin receptor antagonists. It is known that endothelin-1 (ET-1) is a potent endogenous vasoconstrictor and that endothelial signalling pathway components are up-regulated in CTEPH [25]. Elevated ET-1 levels have been reported in animal models of CTEPH and treatment with bosentan, a dual endothelin receptor antagonist, prevented pulmonary artery remodelling in a canine model of CTEPH [26, 27].

Reesink *et al.* [28] have investigated the correlation between ET-1 levels and haemodynamics after PEA. ET-1 levels were increased in 35 CTEPH patients (1.62 ± 0.21 pg/mL) compared with healthy controls (0.75 ± 0.06 pg/mL, $p < 0.02$). ET-1 levels correlated with mean pulmonary arterial hypertension (mPAP; $r = 0.70$), cardiac index (CI; $r = -0.76$), total pulmonary resistance (TPR; $r = 0.72$), mixed venous oxygen saturation ($r = -0.87$), and 6-minute walking distance (6MWD; $r = -0.59$; $p < 0.005$; $n = 23$). Three months after PEA, ET-1 levels had decreased ($p < 0.002$). Pre-operative ET-1 levels were higher in patients with poor post-operative outcome and were correlated with haemodynamic outcome after PEA (mPAP: $r = 0.67$, $p < 0.0001$). These results suggest that CTEPH and PAH share a common pathophysiological mechanism involving endothelin.

The contribution of the nitric oxide and prostacyclin pathways to the development of PAH is well documented but less is known on the involvement of these mechanisms in CTEPH.

Current medical therapy and clinical evidence for the management of CTEPH with PAH-targeted therapies

Before discussing the rationale and data supporting medical therapy in CTEPH, the importance of early referral to a PEA centre has to be emphasised. In the

absence of a consensus definition for operability [29], the decision to operate hinges on the correlation between the anatomic location of the disease and the increase in PVR, but it is also dependent on centre expertise. An experienced surgeon may operate on cases some would deem non-operable and hemodynamics may be improved far beyond what can be expected with PAH-targeted therapies. With operable CTEPH patients, surgery can improve PVR by 80% [24] with a 5-year survival of 90% [30]. In contrast, medical therapy will improve PVR by 25% [19] with a 3-year survival of 70% [14]. Thus, all patients with CTEPH should be referred to an expert PEA centre to be assessed for operability.

In the following paragraphs, we review current medical treatment and discuss the evidence supporting the management of CTEPH patients with PAH-targeted therapies.

Anticoagulation

All patients with CTEPH should receive lifelong anticoagulation adjusted to a normalised target ratio between 2.0 and 3.0. The rationale is to prevent *in situ* pulmonary artery thrombosis and recurrent venous thromboembolism. When the disease is fully established, significant regression of pulmonary hypertension from anticoagulation is not expected.

Medical therapy in non-operable CTEPH and post-operative persistent pulmonary hypertension

The effects of PAH-targeted therapies have been investigated in CTEPH patients with a distal lesion distribution caused by surgically inaccessible obstructions or by arteriopathy of distal small muscular arteries. In the international registry on

CTEPH [12] including 679 patients from 27 centres, 247 (36.4%) patients were deemed non-operable and 16.7% of the operated patients had residual PH at the end of intensive care stay [2]. Persistent PH after PEA may be caused by surgically inaccessible obstruction and/or small vessel arteriopathy. Increasing evidence suggest that the PAH-targeted therapies empirically used in patients with severe non-operable CTEPH may benefit these patients with suboptimal responses to surgery.

Several open-label studies have been performed with prostanoids, endothelin receptor antagonists, PDE-5 inhibitors and soluble guanylate cyclase (sGC) stimulator in patients with non-operable CTEPH and/or with persistent PH after PEA.

Prostanoids

Epoprostenol

In a retrospective study including patients with non-operable CTEPH (n = 16) and IPAH (n = 16) treated with IV epoprostenol and followed-up for 1 year, Scelsi *et al.* [31] reported in both groups a significant improvement in NYHA functional class and exercise capacity. There was no difference in outcomes or adverse events between IPAH and CTEPH patients.

In a French retrospective cohort of non-operable CTEPH patients (n = 27) treated with IV epoprostenol and followed for a mean duration of 20 months, there was a significant increase in exercise capacity and CI and a decrease in NYHA functional class, PVR and mPAP [32]. At the end of the study, only 9 patients were still on epoprostenol, 5 had been transplanted and 13 had died. The 2-year survival rate was 59 %. Prospective and larger studies are needed to ascertain the effects of epoprostenol in non-operable CTEPH.

Iloprost

A post-hoc subgroup analysis from a double blind, placebo-controlled PH study (the AIR trial [33]), compared 33 CTEPH patients treated with inhaled iloprost, with 24 receiving placebo. Patients on iloprost had improved quality of life and dyspnea scores but did not increase their 6MWD when compared with patients who had received placebo.

Beraprost

In a trial reported by Ono *et al.* [34], the effects of conventional treatment with (n = 20) and without (n = 23) beraprost were compared in patients with non-operable CTEPH. There was a significant decrease in TPR and an improvement in NYHA functional class in the beraprost group. After a mean follow-up period of 58 months there were fewer deaths in this group compared with conventional treatment.

Treprostinil

A retrospective study compared the effect of subcutaneous treprostinil in patients with PAH (n = 99) and non-operable CTEPH (n = 23). After a mean follow-up of 26 months, significant improvements in NYHA functional class, exercise capacity and survival compared with historical cohorts were seen in both groups [35]. In a subsequent case-control study, patients with non-operable CTEPH (n = 19) or persistent PH after PEA (n = 6), treated with subcutaneous treprostinil, were compared with 31 matched conventionally treated patients. Treprostinil induced significant improvements in exercise capacity, NYHA functional class, plasma N-terminal-pro brain natriuretic peptide (NT-proBNP) levels, PVR, CI and survival [36].

Endothelin receptor antagonists

Bosentan

Hoeper and colleagues [37] performed a prospective open label multicentre study including 19 non-operable CTEPH patients treated with bosentan. After 3 months, there was a significant decrease in PVR ($-303 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; $p < 0.001$) and NTproBNP (-716 pg/mL ; $p = 0.027$), and an improvement in 6MWD ($+73 \text{ m}$; $p = 0.009$). There was no significant change in NYHA functional class or peak oxygen uptake. At the same time, Bonderman *et al.* [38] reported on a series of 16 non-operable CTEPH patients treated for 6 months with bosentan: NYHA functional class improved by one class in 11 patients, 6MWD increased from $299 \pm 131 \text{ m}$ at baseline to $391 \pm 110 \text{ m}$ at 6 months ($p = 0.01$). Hughes *et al.* [39] investigated the efficacy and safety of bosentan in a European multicentre, open label retrospective study including patients with non-operable CTEPH ($n = 39$) or persistent PH after PEA ($n = 8$). After 4 months of treatment, 6MWD had increased ($+49 \text{ m}$; $p < 0.001$) and 17% patients had an improvement in NYHA functional class. By 1 year, 2 patients had died and 2 had deteriorated requiring prostanoid treatment. The improvement in exercise capacity was maintained ($+52 \text{ m}$ vs baseline; $p < 0.001$). During follow-up, 28 patients had a repeat right heart catheterisation. In these patients, there was a significant increase in CI ($+0.2 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$; $p = 0.004$) and decrease in TPR ($-138 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; $p = 0.003$).

One large RCT has been performed in patients with non-operable CTEPH: the BENEFiT (Bosentan Effects in iNoperable Forms of chronic Thromboembolic pulmonary hypertension) study ($n = 157$) [19]. One hundred and fifty-seven patients were enrolled and randomised: 80 to placebo, 77 to bosentan. Although

there was a significant 24% reduction in PVR after 16 weeks of treatment ($-146 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; $p < 0.0001$) in one of the co-primary endpoints, there was no change in the 6MWD ($+2.2 \text{ m}$; $p = 0.5449$). Significant changes were also reported in secondary endpoints: CI ($+0.3 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$; $p = 0.0007$) and NT-proBNP (-622 pg/mL ; $p = 0.0034$).

This study demonstrated a positive treatment effect of bosentan on haemodynamics in this patient population but no improvement was observed in exercise capacity.

Phosphodiesterase type-5 inhibitors

In 2 open label studies, patients with non-operable CTEPH were treated with sildenafil for 6 months ($n = 12$) [40] and 12 months ($n = 104$) [18]. In both studies, sildenafil was well tolerated and there were significant improvements in both exercise capacity and haemodynamics. A small randomised, placebo-controlled pilot trial with sildenafil reported by Suntharalingam *et al* [41] enrolled 19 patients with non-operable CTEPH or persistent PH after PEA. The primary endpoint (change in 6MWD at 12 weeks) was not met ($+17.5 \text{ m}$ vs placebo) possibly because the trial was small and underpowered but significant improvements in NYHA functional class and PVR ($-197 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; $p < 0.05$) were reported in the sildenafil group. At the end of the trial, patients could transfer to open label sildenafil. After one year of sildenafil treatment, patients had improved exercise capacity, haemodynamics and NT-proBNP levels compared with baseline values.

Together these studies suggest that sildenafil might be beneficial in CTEPH but larger, multicentre, placebo-controlled trials are needed to confirm these findings.

Combination therapy

Further studies are required to determine whether the benefits of combination therapy seen in PAH extend to CTEPH.

New compounds

Riociguat, a new oral sGC stimulator, has shown promising results in the treatment of PAH [42]. In a 12-week, multicentre, open-label, uncontrolled phase II study, a median 6MWD increase of 55 m from baseline ($p < 0.0001$) was observed in CTEPH patients treated with riociguat [43].

Ghofrani *et al.* recently presented results from the Phase III, multicenter, RCT : the Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial-1 (CHEST-1) at the American College of Chest Physicians (ACCP) in October 2012 in Atlanta [44]. The CHEST-1 trial investigated the efficacy and safety of riociguat in patients with non-operable CTEPH ($n = 263$). Enrolled patients were assessed by an independent adjudication committee as non-operable, or had persisting or recurrent PH after PEA. The trial met its primary endpoint, demonstrating a statistically significant improvement in 6MWD (+46 m; $p < 0.0001$) in patients treated for 16 weeks with riociguat compared with placebo. Riociguat also showed statistically significant improvements in secondary endpoints including PVR, NT-proBNP and NYHA functional class. The long term safety and efficacy of riociguat need to be evaluated, but early results are promising.

Medical therapy in operable CTEPH: bridging to PEA

There is a significant number of operable CTEPH patients who are haemodynamically unstable in the pre-operative period, making PEA a high-risk procedure. These patients include those in New York Heart Association

(NYHA) functional class IV, those with mPAP greater than 50 mmHg, CI less than $2 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and/or PVR greater than $1200 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$. The operative mortality has been reported previously to be less than 5% when PVR is below $900 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ but greater than 20% when PVR is above $1200 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ [24]. Whether improving haemodynamics with pre-operative PAH treatment improves surgical outcome is unknown and remains largely speculative.

The concept of introducing medical therapy as a ‘therapeutic bridge’ between diagnosis and PEA was introduced by Nagaya *et al.* [45]. These authors followed 12 patients with severe CTEPH treated with continuous IV epoprostenol for 7 weeks prior to PEA. Epoprostenol significantly decreased pre-operative PVR by 28% and increased CI by 35%. Bresser *et al.* [46] retrospectively analysed 9 PEA candidates treated with continuous IV epoprostenol before surgery. Substantial improvements in CI, mPAP and TPR were seen in all patients after PEA but the impact on post-PEA morbidity and mortality could not be established. Reesink *et al.* [47] analysed pulmonary haemodynamics and functional capacity in 25 PEA candidates treated with (n = 13) or without bosentan (n = 12). After 16 weeks of treatment, significant improvements were observed in TPR, mPAP, and 6MWD, in the bosentan group compared with the control group, although post-PEA outcomes were similar in both groups.

The outcomes of these studies should be interpreted with caution. Nagaya, and Bresser’s experiences [45, 46] are based on small patient populations participating in retrospective and uncontrolled studies. The study presented by Reesink [47] was prospective and randomised but included a limited number of patients. More recently, Jensen *et al.* [48] retrospectively analysed the medical

treatment of the CTEPH patients referred to their institution for PEA between 2005 and 2007. They observed that the use of PAH-targeted therapies before surgery had significantly increased from 19.9 % in 2005 to 37 % in 2007, but was not associated with significant improvement in pre-operative pulmonary haemodynamics and post-operative outcome. In the recent international CTEPH registry [12], 28.3% of the operable CTEPH patients were prescribed at least one PAH-targeted therapy at diagnosis. It is possible that this increased use of medications in operable patients could delay patients' referral for PEA. The optimal duration of a therapeutic bridge to PEA is still not clearly defined. Selection of suitable candidates for bridging therapy should be carefully carried out in expert centres.

In summary, a substantial number of patients (operable and non-operable) are currently being treated with off-label treatments. The results from the international CTEPH registry have shown that nearly 38% of the CTEPH patients (54% non-operable and 28% operable) are treated with at least one PAH-targeted therapy at diagnosis [12].

Most of the studies investigating the use of PAH-targeted therapies in the management of patients with distal CTEPH show beneficial effects. However, these results come from predominantly observational uncontrolled studies and should be interpreted with caution. A post-hoc analysis from the AIR study demonstrated no improvement in 6MWD with inhaled iloprost [33]. In both RCTs performed in CTEPH patients, the BENEFiT study with bosentan [19] and the CHEST-1 study with riociguat [44], significant improvements in haemodynamics (PVR) were reported after 16 weeks of treatment but improvement in exercise capacity was only observed with riociguat.

The lack of effect of bosentan on 6MWD in the BENEFiT trial was surprising, as significant improvements in haemodynamics and NT-proBNP levels were observed and several open label studies with bosentan had previously reported improved exercise capacity [37-39].

However recently presented CHEST-1 trial results [44] could provide further evidence to support medical treatment in selected non-operable CTEPH patient. Also, there is no experts' agreement on the criteria defining operability; therefore it is difficult to characterise the CTEPH patients who might benefit from medical therapies. The results from the CHEST-1 trial [44] with riociguat highlight the need for a careful description of the patients who may benefit from PAH-targeted therapies and for meaningful endpoints, which are specific for CTEPH e.g., time to clinical worsening, number of patients being successfully bridged to PEA due to substantial improvement in PVR and lower operative concerns.

Safety aspects

Disease co-morbidities (e.g., COPD, cardiac disease) are important factors in the choice of an appropriate medical therapy for patients with CTEPH. These patients are generally older than patients with PAH, and tend to have more frequent and more severe co-morbidities. There are currently no studies specifically reporting on the safety/tolerability of PAH-specific therapies in CTEPH, although published trials and observational studies suggest no unexpected adverse events or safety issues for up to 1 year of treatment.

Survival and long-term outcome

It is generally accepted that most patients with CTEPH have a progressive disease [21]. Survival from CTEPH before the advent of modern treatments including PEA was poor. Lewczuk *et al.* reported a 3-year survival rate of 12% when mPAP was greater than 30 mmHg at diagnosis [49] and Riedel a 5-year survival rate of 10% when the mPAP was greater than 50 mmHg [50].

In a study of 35 patients with distal CTEPH managed in the modern era, Suntharalingam *et al.* [51] reported the 1- and 3-year survival rates to be 77% and 53% respectively. Recently, Condliffe *et al* [14] described the follow-up of CTEPH patients in the UK national cohort; 148 (32%) patients had a distal non-operable disease and despite the mPAP being 49 mmHg, the 1-year and 3-year survival rates were 83% and 76%, respectively (90% of the patients of this cohort were treated with PAH-specific treatments). The 5-year survival rate of patients with persistent PH after PEA has been reported to be 90% (25% of the patients were treated with PAH-specific treatments) [30]. Prospective data on the effects of PAH-specific therapies on the long-term outcome of CTEPH patients are currently being collected in the international CTEPH registry [52] and are expected to contribute to the assessment of the usefulness of PAH-specific therapies in the management of CTEPH patients.

Conclusions

PEA is considered as the first choice of treatment for selected CTEPH patients but there is no experts' agreement on the criteria defining operability, therefore it is difficult to characterise the CTEPH patients who might benefit from

medical therapies. The surgery can be a cure for some patients but may also lead to persistent PH in others. In patients deemed non-operable and in those with persistent PH following PEA, the similarities in pathobiology between CTEPH and PAH suggest that PAH-targeted therapies may play the role. There is yet no scientific evidence to make such a recommendation and it is possible that the small vessel component of CTEPH may not mimic PAH when it comes to medical therapy with the current agents. There is no PAH targeted therapies approved for CTEPH currently and the status of riociguat is pending. However recently presented CHEST-1 trial results could provide further evidence to support medical treatment in selected non-operable CTEPH patient. Although the results of this trial are encouraging, there remain numerous unanswered questions and unmet needs regarding the role of medical therapy in CTEPH. Long term data are needed to better define and understand benefits from PAH targeted therapies in CTEPH. Accordingly, we need to continue exploring and better defining the role of PAH targeted therapies, operability definition, and clinically meaningful endpoints in CTEPH.

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