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Managing chronic thromboembolic pulmonary hypertension: pharmacological treatment options

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ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition in which organised thrombi obstruct the pulmonary vessels, causing increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. The treatment of choice is pulmonary endarterectomy, which restores pulmonary haemodynamics with acceptable periprocedural mortality rates in the majority of suitable patients. However, CTEPH may be inoperable owing to surgically inaccessible thrombi or comorbid diseases that confer an unacceptably high risk.

Pharmacotherapies, although not yet approved, may be useful in this situation or for treating residual or recurrent PH following surgery. Vasodilator drugs for PH are attracting growing interest as potential treatments for CTEPH because this disease has recently been labelled as a ''dual'' pulmonary vascular disorder: major vessel obstruction and remodelling is combined with a small vessel arteriopathy that is histologically indistinguishable from the classical pulmonary arteriopathy observed in pulmonary arterial hypertension.

Of three completed randomised controlled trials in patients with CTEPH, only one was powered to detect a treatment effect. The BENEFIT trial employed the dual endothelin-receptor antagonist bosentan. Although haemodynamics improved significantly, the second component of the primary end-point, exercise capacity, was not met.

More evidence is required to resolve whether vasodilator treatments are beneficial for inoperable chronic thromboembolic pulmonary hypertension.

KEYWORDS: Chronic thromboembolic pulmonary hypertension, drug therapy, review

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition in which organised thrombi obstruct the pulmonary vessels, causing increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. CTEPH is associated with considerable morbidity and mortality [1], and forms group IV of the current World Health Organization (WHO) classification system for PH [2]. However, there are many uncertainties surrounding CTEPH as the incidence and prevalence of this disease are not well characterised, aspects of CTEPH pathogenesis are poorly understood, diagnostic approaches have not been standardised, and this field lacks randomised, controlled trials and guidelines [1]. An international, prospective, observational registry was set up in 2007 to resolve these uncertainties, and data has now been collected from >600 patients with CTEPH. Recruitment is progressing rapidly, and the first presentation of results is expected in 2009 [3]. Currently, estimates of CTEPH incidence range from 0.1–0.5% of patients surviving an acute pulmonary embolism (PE) [4, 5], to a cumulative incidence following an acute PE of 0.8% after ~4 yrs [6], or 3.8% after 2 yrs in another study [7]. However, CTEPH may be more common than these results suggest as the majority of CTEPH cases never experience acute PE [8].

CTEPH is a potentially correctable cause of PH, and vascular disobliteration by pulmonary endarterectomy (PEA) is the treatment of choice [9]. In-hospital mortality rates for patients who have undergone PEA range from 5% to 24% [5, 10, 11], and in general, periprocedural mortality rates of 5–11% are achieved [1, 9, 12]. However, not all patients are eligible for surgery because of an inaccessible and/or distal thromboembolism, or serious comorbidities [13, 14]. Moreover, PH can persist or reappear in patients who have undergone PEA, and persistent PH is one of the most important determinants of post-PEA outcome [11, 15, 16]. Furthermore, high mean pulmonary

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arterial pressure (P_{pa}) is an independent predictor of death in patients with ''chronic PE'' (p=0.04) [17]. Taken together, these factors reveal a need for effective therapy for CTEPH.

The present article will focus on recent developments in the pharmacological treatment of CTEPH. Current thoughts regarding the epidemiology, risk factors, prognosis and vascular biology of this disease will also be considered.

PATHOGENESIS, RISK FACTORS AND VASCULAR BIOLOGY

Our understanding of CTEPH has developed in recent years such that it is now viewed as a complex ''dual'' vascular disorder. This has been demonstrated by investigations into the relationship between pulmonary vascular obstruction and haemodynamic status in patients with acute PE and those with CTEPH [18]. Whereas increases in mean P_{pa} and total pulmonary resistance correlated with the degree of pulmonary vascular obstruction in patients with PE [18], no such correlation was detectable for patients with CTEPH. This suggests that PH in CTEPH is not solely because of obstruction of proximal pulmonary arteries, but is also due to the remodelling of small distal arteries in non-occluded areas.

The majority of experts now agree that there is compelling evidence supporting the concept that PE, either overt or occult, triggers a cascade of events that eventually result in CTEPH [1, 5]. Persistent obstruction of pulmonary arteries may result in elevated P_{pa} and high shear stress in areas of the pulmonary vasculature that were spared from thromboebolic occlusion. Thus, acute PE is likely to be the initiating event, but progression of PH results from misguided pulmonary vascular remodelling (*i.e.* major and small vessel disease) [1, 19]. This theory is also supported by the histopathology of resistance vessels in the pulmonary vascular bed, which show arteriopathic changes not only in areas directly affected by the PE, but also in portions that were not involved (fig. 1) [1, 20]. Despite evidence linking CTEPH to PE, an alternative pathogenic hypothesis has been suggested in which pulmonary vascular occlusions are caused by a primary arteriopathy of pulmonary vessels and secondary *in situ* thrombosis [21]. Supporters of this theory point out that there is a lack of documented history of previous deep vein thrombosis or PE in ~50% of CTEPH cases, although it should be remembered that asymptomatic venous thromboembolism is very common [22, 23].

FIGURE 1. Material removed by pulmonary endarterectomy from the right and left pulmonary artery. The specimen is an example of type III disease (fibrosis, intimal webbing and thickening within distal segmental arteries, with no visible thrombus) [9].

The embolic and alternative hypotheses of CTEPH pathogenesis may be unified if the factors that influence the incomplete resolution of PE and organisation of thrombi in these patients are considered. These hypotheses have been elucidated in experiments by LANG *et al.* [24], which showed that no abnormalities were detected in the expression of fibrinolytic proteins or in responses to thrombin stimulation in primary endothelial cells cultured from pulmonary arteries of patients with CTEPH. However, elevated expression levels of endothelial plasminogen activator inhibitor and factor VIII have been shown in organised thromboemboli of CTEPH [25]. This suggests that *in situ* thrombosis within vascularised, fibromuscular obstructions may contribute to the persistence of pulmonary (and also peripheral) venous thrombi in CTEPH [13]. In addition to *in situ* thrombosis, other factors that might influence the incomplete resolution of PE and organisation of thrombi in patients with CTEPH include infection [19], inflammation and autoimmunity [26]. It should be noted that recent research suggests that infection with Staphylococci in patients with CTEPH enhances fibrotic vascular remodelling after thrombosis, resulting in misguided thrombus resolution, thus thrombus infection appears to be a trigger in the evolution of CTEPH [19].

Clinical risk factors have been investigated by BONDERMAN *et al.* [26]. This case–control study compared 109 patients with CTEPH to those with confirmed acute non-fatal PE (n=187). An increased risk of CTEPH was associated with prior splenectomy (odds ratio (OR) 13, 95% confidence interval (CI) 2.7–127), ventriculo-atrial shunt for the treatment of hydrocephalus (OR 13, 95% CI 2.5–129) and chronic inflammatory disorders, such as osteomyelitis and Crohn's disease (OR 67, 95% CI 7.9–8,832). A further study also identified splenectomy as a risk factor for CTEPH [27], and a recent retrospective cohort study involving 687 patients with CTEPH showed that thyroid replacement therapy (OR 6.10, 95% CI 2.73–15.05) and a history of malignancy (OR 3.76, 95% CI 1.47–10.43) were novel risk factors for CTEPH [28].

THERAPEUTIC OPTIONS FOR CTEPH

Current conventional treatments

The decision of how to treat each patient is complex and requires a multidisciplinary team of cardiologists, pulmonologists, radiologists and surgeons to estimate the degree of haemodynamic improvement that might be expected after surgery [1, 12]. These decisions are still based on the clinical experience of the multidisciplinary team, but the current therapeutic algorithm is useful in guiding this process (fig. 2) [1]. Essentially, all patients with CTEPH receive lifelong anticoagulant medication to prevent recurrent thromboembolic events, and ideally a 3-month period of watchful waiting should elapse before a full diagnostic workup and any decision regarding choice of treatment [1].

The primary treatment for suitable cases of CTEPH is PEA. PEA is performed under hypothermia and total circulatory

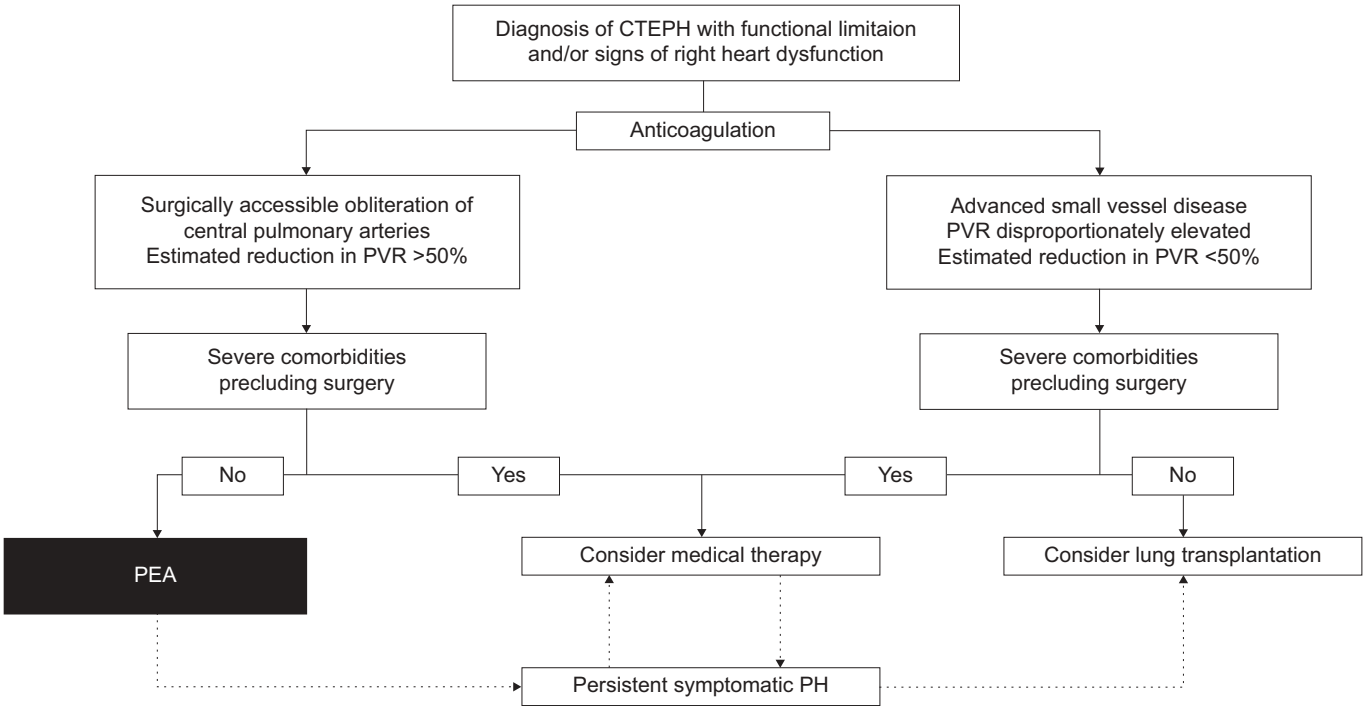

FIGURE 2. Algorithm for the therapeutic approach for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Where practical, pulmonary endarterectomy (PEA) is the preferred approach. Medical therapy refers to prostanoids, endothelin-receptor antagonists or phosphodiesterase-5 inhibitors, although there is currently a lack of firm evidence to support the use of these drugs. PVR: pulmonary vascular resistance; PH: pulmonary hypertension. Dashed arrows symbolise therapeutic considerations in case the initial approach fails. Modified from [1] with permission from the publisher.

arrest, and involves the removal of obstructive material from each pulmonary artery, and its lobar and segmental branches (20–30 branches in total; fig. 1) [12]. As has been previously mentioned, PEA is associated with excellent results: when performed in experienced centres and on carefully selected patients, PEA is associated with low periprocedural mortality rates (*e.g.* 5–11%) and generally results in near normalisation of haemodynamics and substantial improvements in clinical symptoms [1, 9, 12].

Although there is no doubt that all patients who are suitable for PEA should receive this surgical intervention [9], there is less certainty surrounding the use of other treatment options. These are usually limited to pharmacotherapies, although lung transplantation can be successful in certain cases with perioperative mortality rates of ~20% for patients with PH or CTEPH [12]. Nonspecific supportive therapies are also used in the management of post-PE patients, but these do not generally affect the underlying CTEPH disease processes [29]. In addition to the aforementioned anticoagulation, these include diuretics to treat fluid overload and oxygen to correct hypoxaemia. Calcium channel blockers have rarely been an option for treating CTEPH because true haemodynamic responders are rare and are almost exclusively observed among operable patients [29, 30].

Pharmacotherapies

CTEPH has recently become regarded as a dual pulmonary vascular disorder in which major vessel obstruction and remodelling combine with a small vessel arteriopathy, which is histologically indistinguishable from the classical pulmonary arteriopathy observed in PAH (fig. 3b). This has been demonstrated by a histopathological study of small pulmonary artery tissue from 31 patients with an established diagnosis of CTEPH, which found pulmonary hypertensive lesions (fig. 3c), including plexogenic lesions [20]. It has been proposed that such lesions most likely represent the nonspecific effect of chronic PH on exposed (non-occluded) areas of the vasculature [31]. Therefore, it is reasonable to assume that medical therapies for PH, targeting the three main pathways involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary artery in patients with PH (*i.e.* the endothelin, prostacyclin or nitric oxide pathways) [32], may be effective for patients with CTEPH. Such treatments may be particularly useful in the following situations: 1) where there is inoperable distal disease or comorbidities that make PEA a high-risk option; 2) as a therapeutic bridge to PEA or lung transplant for high-risk patients; or 3) for patients with persistent or residual PH after PEA [29].

Although a number of small pilot studies and uncontrolled trials have targeted all three clinical scenarios, the remainder of this article will focus on the few randomised, controlled trials of PH drugs for patients with CTEPH who are unable to undergo PEA.

The three randomised, controlled trials in patients with CTEPH performed to date have used a prostanoid (iloprost) [33], a phosphodiesterase-5 inhibitor (sildenafil) [34] and an endothelin-receptor antagonist (bosentan) [35]. Iloprost, 2.5 or 5.0 μg, inhaled six to nine times daily (median dose 30 $\mu g \cdot day^{-1}$) for 12 weeks, was compared with placebo for a

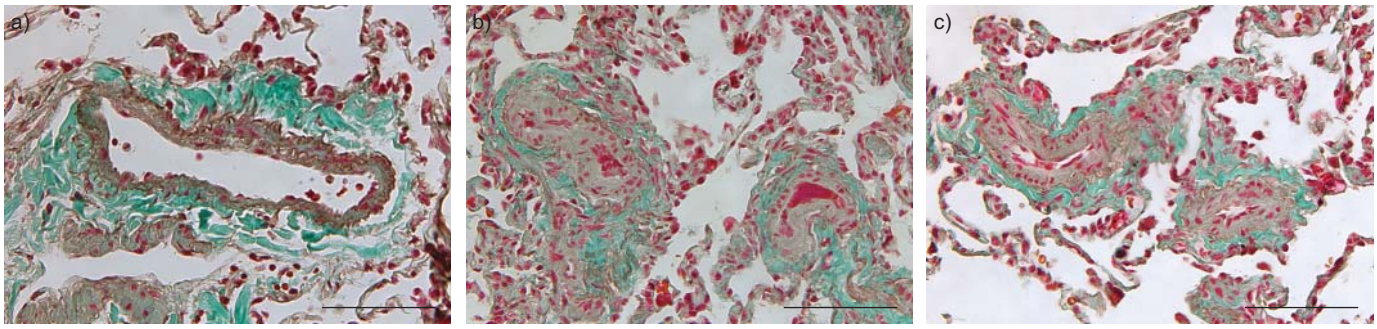

FIGURE 3. Histological sections of small pulmonary arterioles from a) normal lungs, and b) lungs of patients with pulmonary arterial hypertension and c) chronic thromboembolic pulmonary hypertension, demonstrating medial hypertrophy and intimal fibrosis with near occlusion. Scale bar=100 μm.

population of 203 patients that included 57 patients with inoperable CTEPH at baseline [33]. Because of this mixed population, it is difficult to draw any firm conclusions concerning the treatment of CTEPH. However, results were analysed according to type of PH (labelled as primary *versus* nonprimary), and these data showed that patients with nonprimary PH and primary PH experienced similar improvements in Mahler dyspnoea score and health-related quality of life in response to treatment with iloprost. A double-blind, placebo-controlled, 12-week pilot study has investigated the use of sildenafil, 40 mg three times daily, in 19 patients with inoperable CTEPH [34]. Unfortunately, this study was inadequately powered to test the primary end-point (change in 6-min walk distance). Moreover, there was no significant difference between the sildenafil and placebo groups (17.5 m improvement). Nevertheless, there were significant improvements in WHO functional class ($p=0.025$) and pulmonary vascular resistance ($p=0.044$) for the sildenafil-treated group.

A larger randomised controlled study of pharmacotherapy has been carried out in 157 patients with anatomically inoperable CTEPH who are unable to undergo PEA: the BENEFIT (bosentan effects in inoperable forms of chronic thromboembolic pulmonary hypertension) study was completed recently [36]. Studies examining the pathophysiology of CTEPH in humans and animal models have provided the following rationales for the use of endothelin-receptor antagonists in CTEPH: 1) endothelin is a potent endogenous vasoconstrictor [37]; 2) endothelin signalling pathway components are upregulated in CTEPH [38]; and 3) endothelin-mediated pulmonary vascular remodelling has been demonstrated in a canine model of CTEPH [39]. Bosentan, administered for 16 weeks, reduced pulmonary vascular resistance by 24% compared with placebo ($p<0.0001$), although there was no significant benefit in terms of 6-min walking distance [35, 36]. Larger, longer-term studies are required to evaluate a potential effect of pharmacotherapy on exercise capacity.

CONCLUSIONS

The results from clinical trials of CTEPH pharmacotherapies are far from conclusive, and there is not yet an approved drug for this indication. Nevertheless, there is clearly a need for pharmacotherapies in clinical practice. It is interesting to note that survival rates for patients given medical treatments, with or without surgery, appear to have improved in recent years. This was revealed by a study of 469 patients with CTEPH, of whom 148 (32%) had distal, nonsurgically treated disease [39]. Survival rates from time of diagnosis to 1 or 3 yrs later were 82% and 70% for the nonsurgical group and 88% and 76% in surgically treated patients, respectively. Most of the nonsurgical patients received disease-modifying pharmacotherapies; until 2004 these treatments were mainly prostanoids, but from 2004 onwards most were either an endothelin-receptor antagonist or phosphodiesterase-5 inhibitor. The same study also showed changing trends regarding the increased use of these disease-modifying pharmacotherapies before PEA. Before 2004, 29% of patients received these drugs before PEA but from 2004 onwards this rate was 65% [40].

In summary, there is an urgent need for further clinical trials of pharmacotherapies for chronic thromboembolic pulmonary hypertension to resolve the role of these treatments in a constantly growing population of off-label treated patients.

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