

Tadalafil: the evidence for its clinical potential in the treatment of pulmonary arterial hypertension

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Abstract

Introduction: Pulmonary arterial hypertension (PAH), characterized by increased pulmonary artery pressures in the absence of elevated pulmonary venous pressures, is a progressive disease associated with reduced exercise capacity and increased mortality risk. Current treatments for PAH include nonspecific vasodilators, prostacyclin and related analogs, and endothelin receptor antagonists. Since phosphodiesterase type 5 is highly expressed in pulmonary vascular tissues, agents that selectively inhibit phosphodiesterase type 5 activity induce pulmonary arterial vasodilatation, and are being developed for the treatment of PAH.

Aims: The purpose of this review is to evaluate the existing evidence for the use of tadalafil, a selective phosphodiesterase type 5 inhibitor, in PAH.

Evidence review: Data from erectile dysfunction populations indicate that tadalafil is well tolerated with an elimination half-life of 17.5 hours. Small pilot studies in patients with PAH of mixed etiology demonstrate that tadalafil reduces pulmonary vascular resistance and is associated with improved clinical status. A multicenter, randomized, placebo-controlled clinical trial in patients with PAH is currently recruiting patients.

Clinical potential: Based on existing studies of sildenafil, a related selective phosphodiesterase type 5 inhibitor in PAH, and the findings of initial pilot studies, tadalafil appears to have excellent potential to provide therapeutic benefit in patients with pulmonary hypertension. The long elimination half-life of tadalafil makes it suitable for once-daily dosing.

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Key words: evidence, tadalafil, phosphodiesterase inhibitors, pulmonary hypertension,

Core evidence proof of concept summary for tadalafil in pulmonary arterial hypertension

Outcome measure	Emerging evidence
Patient-oriented outcomes	
Functional capacity	Tadalafil improves functional capacity
Quality of life	Tadalafil may improve quality of life
Mortality risk	No evidence
Tolerability	Tadalafil is as well tolerated as sildenafil in pulmonary arterial hypertension
Disease-oriented outcomes	
Pulmonary vascular resistance	Tadalafil selectively decreases pulmonary vascular resistance
Exercise capacity	Improvement in exercise capacity with tadalafil comparable to that with sildenafil
Economic evidence	
Cost effectiveness	No evidence

Scope, aims, and objectives

Tadalafil is a selective phosphodiesterase type 5 inhibitor approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction (Carson 2006; Doggrell 2007; Hatzimouratidis & Hatzichristou 2007). Tadalafil improves erectile function by augmentation of cyclic guanosine monophosphate (GMP) signaling in corpus cavernosum tissue. Since phosphodiesterase type 5 is highly expressed in lung vasculature, tadalafil may also offer therapeutic benefit as a pulmonary vasodilator in patients with pulmonary arterial hypertension (PAH) (Corbin et al. 2005; Hemnes & Champion 2006; Raja et al. 2006; Sastry 2006).

The objective of this article is to review the available evidence for the potential use of tadalafil in the treatment of PAH. In addition, this article will provide an overview of the pathophysiology and current treatment options for PAH. The clinical evidence in support of the use of sildenafil, another phosphodiesterase type 5 inhibitor in PAH, will be also be reviewed.

Methods

Literature searches were conducted in the databases listed below. The search terms were “tadalafil AND pulmonary AND hypertension” with no search tags unless otherwise stated. Results were limited to human studies in the English language only.

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>, 1966 to date
- EMBASE, <http://www.datastarweb.com>, 1974 to date
- BIOSIS, <http://www.datastarweb.com>. Search term “(tadalafil AND pulmonary hypertension) AND (LG=EN) AND (PT=MEETING-ABSTRACT)”
- Scopus, <http://www.scopus.com>.
- Database of Abstracts of Reviews of Effects (DARE), National Health Service (NHS) Economic Evaluation Database (NHSEED), Health Technology Assessment (HTA), <http://www.york.ac.uk/inst/crd/crddatabases.htm>. All three databases searched together. All fields searched
- National Institute for Health and Clinical Excellence (NICE), <http://www.nice.org.uk>
- Cochrane Database of Systematic Reviews (CDSR), <http://www.cochrane.org/index0.htm>. Entire site searched
- Clinical trials database, <http://www.clinicaltrials.gov>

After removal of duplicates, a total of 28 citations were identified. Records were manually reviewed and 21 citations were excluded as nonsystematic reviews (n=15), citations that did not mention clinical use of tadalafil in PAH (n=4), citations that duplicated

another report by the same authors (n=1), or citations not available for review (n=1). No systematic reviews of tadalafil in PAH have been published.

Inclusion criteria for the outcomes analysis of tadalafil in PAH used an accepted scale of hierarchy of evidence (Table 1).

Table 1 Evidence base included in the review		
Category	Number of records	
	Full papers	Abstracts
Initial search	28	0
records excluded	21	
records included	7	0
Additional studies identified	0	0
Level 1 clinical evidence (systematic review, meta analysis)	0	0
Level 2 clinical evidence (RCT)	0	0
Level ≥3 clinical evidence	3	
trials other than RCT	0	
case reports	4	
Economic evidence	0	0
For definitions of levels of evidence, see Editorial Information on inside back cover or on Core Evidence website (http://www.coremedicalpublishing.com). RCT, randomized controlled trial.		

Introduction

Phosphodiesterases are a family of 11 metallophosphydrolase enzyme isoforms that catalyze the metabolic breakdown of second messenger cyclic nucleotides in numerous cell types (Beavo 1995; Raja et al. 2006). Each phosphodiesterase isoform has a distinct pattern of tissue distribution and cyclic nucleotide substrate affinity. In vascular smooth muscle, phosphodiesterase type 5 is the predominant isoform that mediates hydrolysis of cyclic GMP. The type 5 isoform is a homodimeric enzyme with a single catalytic binding site and regulatory binding site in each component of the dimer (Blount et al. 2004).The catalytic site hydrolyzes cyclic GMP to inactive 5'-guanosine monophosphate. The regulatory domain contains an allosteric cyclic GMP binding site and a regulatory phosphorylation site. Binding of cyclic GMP to the regulatory domain enhances activity of the catalytic domain and thereby provides a negative feedback inhibition mechanism for control of cyclic GMP signaling. This same feedback mechanism serves to increase catalytic domain binding affinity of a pharmacologic antagonist as cyclic GMP levels rise during pharmacologic inhibition of enzyme activity. In vascular smooth muscle, augmented levels of cyclic GMP lead to increased vasorelaxation.

The potential clinical utility of selective pharmacologic inhibition of phosphodiesterase type 5 has been extensively evaluated in clinical trials in men with erectile dysfunction (Carson 2006; Doggrell 2007; Hatzimouratidis & Hatzichristou 2007). Normal erectile function is critically dependent on nitric oxide-induced, cyclic GMP-mediated vasorelaxation in corpus carvenosum, a specialized form of smooth muscle in the penis. In men with

erectile dysfunction related to impaired nitric oxide signaling, augmentation of cyclic GMP signaling with pharmacologic inhibition of phosphodiesterase type 5 is associated with improved erectile function. Three selective phosphodiesterase type 5 inhibitors are currently approved by the FDA for the treatment of erectile dysfunction (sildenafil, vardenafil, and tadalafil). Although there are few existing data with direct comparisons in clinical trials, these agents appear to be comparable in their overall efficacy and safety profiles in men with erectile dysfunction (Carson 2006; Doggrell 2007; Hatzimouratidis & Hatzichristou 2007). However, there are known differences in the molecular and clinical pharmacologic characteristics of these agents that may impact their clinical utility in erectile dysfunction and other disease states. All three agents are highly potent inhibitors of phosphodiesterase type 5 (IC₅₀ values for sildenafil, vardenafil, and tadalafil are 3.9, 0.7, and 5 nM, respectively), with distinct patterns of relative selectivity for other phosphodiesterase isoforms (Carson 2006; Doggrell 2007). Sildenafil and vardenafil have lower selectivity ratios with respect to the type 6 isoform (range, 6- to 35-fold), while tadalafil has a lower selectivity ratio for the type 11 isoform (range, 6- to 40-fold). Since the type 6 isoform is expressed in rods and cones in retinal tissues, partial inhibition of this isoform by sildenafil and vardenafil may account for visual change side effects reported with these agents. The type 11 isoform is known to be expressed in cardiac, pituitary, and testes tissues, but the clinical sequelae of partial inhibition of this isoform with tadalafil are unknown. When compared with sildenafil and vardenafil, tadalafil has a slightly slower onset of peak effect (peak plasma levels for tadalafil 120 min vs 60 min for sildenafil and vardenafil) and a much longer elimination half-life (tadalafil 17.5 hours vs 3.8–3.9 hours for sildenafil and vardenafil) (Carson 2006; Doggrell 2007).

Disease overview

PAH is a chronic disease of the pulmonary vasculature defined as the presence of a mean pulmonary artery pressure >25 mmHg at rest (or >30 mmHg during exercise) in the presence of mean pulmonary capillary wedge pressure <15 mmHg (Galie et al. 2004; Sastry 2006; Traiger 2007). The pathogenesis of this disorder is complex and incompletely characterized. Increased pulmonary artery blood pressures are associated with structural changes in the pulmonary circulation characterized by pulmonary arteriopathy (intimal thickening, medial hypertrophy, adventitial thickening, and plexiform lesions), *in-situ* thrombosis, and rarefaction of the microcirculation. Since the primary cause of these structural and functional changes in the pulmonary circulation is not discernible in many instances, the clinical classification of PAH is based on the presence or absence of associated clinical factors that are believed to contribute to pathogenesis of disease (Table 2).

Clinical manifestations of PAH are related to the hemodynamic effects of increased afterload on the right ventricle and systemic manifestations of the comorbid conditions associated with elevated pulmonary vascular resistance. Progressive exercise intolerance, lower extremity edema, ascites, and syncope are common clinical presentations. Although duplex

Table 2 | Clinical classification of pulmonary arterial hypertension (adapted from Galie 2004)

1. Pulmonary arterial hypertension <ul style="list-style-type: none"> a. Idiopathic b. Familial c. Associated with: <ul style="list-style-type: none"> i. Connective tissue disease ii. Congenital systemic to pulmonary shunts iii. Portal hypertension iv. HIV infection v. Drugs and toxins vi. Other systemic disorders
2. Pulmonary hypertension associated with left-sided heart diseases <ul style="list-style-type: none"> a. Left-sided atrial or ventricular heart disease b. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia <ul style="list-style-type: none"> a. Chronic obstructive lung disease b. Interstitial lung disease c. Sleep disordered breathing d. Alveolar hypoventilation disorders e. Chronic exposure to high altitude f. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease <ul style="list-style-type: none"> a. Thromboembolic obstruction of proximal pulmonary arteries b. Thromboembolic obstruction of distal pulmonary arteries c. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous <ul style="list-style-type: none"> a. Sarcoidosis, histiocytosis X, lymphangioma
HIV, human immunodeficiency virus.

echocardiography is considered an excellent screening tool in suspected cases, cardiac catheterization with direct measurement of pulmonary artery pressures is required for definitive diagnosis. PAH is associated with progressive right ventricular failure and high mortality risk. Data from a national registry demonstrated a median survival of 2.8 years after diagnosis (D'Alonzo et al. 1991).

Vascular endothelial cells release a wide array of vasoactive substances that play an important role in the normal regulation of vasomotor tone, vascular structure, and blood pressure homeostasis (Vane et al. 1990). Endothelium-derived nitric oxide is a key regulatory molecule with potent vasorelaxation effects. In lung circulation, nitric oxide is an important mediator of local vasodilatation for matching of regional blood flows to regional ventilation (Ghofrani et al. 2006). Its vasorelaxation actions are mediated by activation of guanylyl cyclase and production of the second messenger cyclic GMP in vascular smooth muscle. Phosphodiesterase type 5 is highly expressed in lung tissues and is the principal phosphodiesterase isoform responsible for hydrolysis of cyclic GMP (Corbin et al. 2005). Dysregulation of the nitric oxide system is thought to be an important factor contributing to the pathogenesis of the structural and functional

changes in lung circulation in patients with PAH (Ghofrani et al. 2006; Hemnes & Champion 2006). Accordingly, augmentation of nitric oxide signaling in vascular smooth muscle with selective type 5 phosphodiesterase inhibition may be an effective therapeutic strategy.

Current therapy options

Recent reports describe consensus clinical guidelines for the diagnosis and treatment of PAH (Galie et al. 2004; Sastry 2006; Traiger 2007). The treatment strategy for pulmonary hypertension is based on the identification and treatment of underlying conditions associated with the disease (connective tissue disease, systemic to pulmonary shunts, parenchymal lung disease, chronic thromboembolism), general supportive care to prevent further thrombosis (e.g. long-term oral anticoagulation therapy with warfarin), treating symptoms related to right ventricular failure (e.g. with digoxin and diuretics), and individualized use of several classes of vasodilating drugs to reduce pulmonary vascular resistance. Specific treatment algorithms are described in the consensus guidelines. Preliminary data from short reports suggest that different classes of vasodilating agents may be used together to provide additive benefits. In patients with symptoms refractory to medical therapy, other interventions including atrial septostomy and lung transplantation may be considered.

Calcium channel blockers are recommended for long-term use in the subset of patients who demonstrate an acute vasodilating response to these agents during cardiac catheterization. The acute hemodynamic effects may not accurately predict the long-term clinical response in all patients, so follow-up surveillance of the pulmonary vascular effects is recommended.

Prostanoids are prostacyclin analogs that mediate vasodilatation by increasing levels of cyclic adenosine monophosphate in the lung vasculature. These agents also have potent antiplatelet and antiproliferative effects. Epoprostenol has a very short half-life and can only be administered by continuous intravenous infusion. Epoprostenol has been demonstrated to reduce pulmonary vascular resistance, improve quality of life, and prolong survival in severely ill patients (Sastry 2006). Its use is limited by the necessity for chronic intravenous access and high rates of side effects. Treprostinil, iloprost, and beraprost are related compounds that can be given by other routes including subcutaneous administration (treprostinil), inhalation (iloprost), or orally (beraprost). Inhaled iloprost and subcutaneous and intravenous treprostinil are approved by the FDA for the treatment of PAH.

Bosentan is a nonselective endothelin-1 receptor antagonist that has also been approved by the FDA for the treatment of PAH. This agent blocks the potent vasoconstrictive and proliferative effects of endothelin-1 in the pulmonary vasculature and has been shown to decrease pulmonary vascular resistance and increase exercise capacity (Sastry 2006). Ambrisentan and sitaxsentan are selective endothelin-1 type A receptor antagonists that have also been shown to decrease pulmonary vascular resistance and improve

exercise tolerance (Galie et al. 2005a; Barst et al. 2006). Use of this class of agents is potentially limited by liver toxicity and the need for contraception in both men and women. Ambrisentan was recently approved by the FDA for once-daily use in patients with PAH and appears to have reduced risk of hepatotoxicity when compared with bosentan (Galie et al. 2005a).

Of particular relevance to the discussion of tadalafil in the treatment of PAH, sildenafil is a selective phosphodiesterase type 5 inhibitor that is approved by the FDA for this indication (Hemnes & Champion 2006; Raja et al. 2006). The clinical safety and efficacy of sildenafil in PAH are described in two recent review articles. A systematic review from the Cochrane Collaboration in 2004 reported on the efficacy of sildenafil in 77 subjects with pulmonary hypertension derived from four randomized clinical trials (two acute unblinded studies and two longer-term blinded crossover studies of 2–6 weeks' duration) (Kanthapillai et al. 2004). The authors concluded that the reviewed evidence demonstrated that sildenafil has an acute pulmonary vasodilatation effect and was associated with improvement in symptoms during chronic use. However, interpretation of the findings was limited by the small number of subjects and heterogeneous nature of the underlying PAH. Raja and colleagues published a more recent systematic review of the medical literature in 2006 (Raja et al. 2006). Twenty-two clinical studies of acute and chronic sildenafil therapy (alone or in combination with other agents) in PAH were identified. These authors concluded that sildenafil is an effective acute pulmonary vasodilator that is associated with evidence of clinical improvement during chronic use. Their conclusions are based primarily on a large, multicenter, double-blind, randomized clinical trial of sildenafil versus placebo in 278 patients with PAH of mixed etiology, including idiopathic PAH (n=175), PAH associated with connective tissue diseases (n=84), and surgically corrected left-to-right shunts (n=18) (Galie et al. 2005b). Subjects with 6-min walking distance <100 m or >450 m, and subjects receiving treatment with prostacyclin analogs or bosentan were excluded from the study. Eligible subjects were randomly assigned to placebo or one of three doses of sildenafil (20, 40, or 80 mg) three times daily for 12 weeks. Sildenafil significantly increased the 6-min walk distance (the prespecified primary endpoint) when compared with placebo at 12 weeks (placebo-corrected change from baseline +45 m for the 20 mg group, +46 m for the 40 mg group, and +50 m for the 80 mg group; $P<0.001$ for each sildenafil group vs placebo). The improvement in exercise capacity was consistent across prespecified subgroups. Pulmonary vascular resistance decreased significantly and functional capacity improved in patients assigned to sildenafil when compared with placebo.

There were few serious adverse events during the 12-week study and withdrawals from treatment were evenly distributed among the treatment groups. Adverse events more commonly observed during sildenafil administration when compared with placebo were headache (sildenafil 42–49% vs placebo 39%), flushing (sildenafil 9–15% vs placebo 4%), and dyspepsia (sildenafil 9–13% vs placebo 7%). Of the 265 subjects who completed the 12-week study, 259 entered an open-label, 52-week extension period and received sildenafil 80 mg three times daily. Among

222 patients in this extension phase treated with sildenafil for at least 1 year, the improvement in exercise capacity was sustained (change from baseline after 12 months +51 m). During this uncontrolled extension phase, there were 14 deaths with a calculated survival rate of 97%, substantially greater than the expected survival rate of 71% based on historical controls (Sastry 2006). Since there was no evidence of a dose–response relationship with respect to the primary endpoint of the study, sildenafil was approved by the FDA for treatment of PAH at the dose of 20 mg three times daily.

Unmet needs

It is well recognized that agents requiring greater than once-daily dosing are associated with higher rates of therapy nonadherence (Clifford-Middel 2004). Accordingly, development of an agent with less-frequent dosing requirements is desirable. The longer elimination half-life of tadalafil makes it suitable for potential development as a once-daily agent for the treatment of PAH.

Outcomes achieved with tadalafil in clinical development

Tadalafil is a selective phosphodiesterase type 5 inhibitor approved by the FDA for the treatment of erectile dysfunction (Carson 2006; Doggrell 2007; Hatzimouratidis & Hatzichristou 2007). Tadalafil is approved for use as single doses of 10–20 mg for patients with erectile dysfunction. Several small studies have investigated the effects of chronic dosing of tadalafil every 1–2 days in patients with erectile dysfunction (McMahon 2004; Mirone et al. 2005; Porst et al. 2006). In these pilot studies, tadalafil was well tolerated and associated with high rates of improvement in erectile function.

It is uncertain whether selective phosphodiesterase type 5 inhibitors approved for the treatment of erectile dysfunction (vardenafil and tadalafil) would provide benefits comparable to sildenafil in patients with PAH. All three agents bind to the same catalytic site in purified phosphodiesterase type 5 preparations and provide comparable clinical improvement in erectile function when compared with placebo in men with erectile dysfunction (Blount et al. 2004; Carson 2006; Doggrell 2007; Hatzimouratidis & Hatzichristou 2007). However, some differences in pharmacodynamic profiles of these three agents have been reported in isolated blood vessel preparations. Teixeira and colleagues evaluated the effects of sildenafil, vardenafil, and tadalafil on vasorelaxation in isolated rat aorta preparations. All agents relaxed aortic rings with intact endothelium and increased cyclic GMP levels compared with pretreatment baseline (Teixeira et al. 2006). Removal of the endothelial cell layer from the aortic ring preparation attenuated the maximum relaxation response to sildenafil and tadalafil, but not vardenafil. Vardenafil, but not sildenafil nor tadalafil, was also reported to significantly attenuate contractions induced by calcium chloride. These findings suggest that vardenafil has a distinct endothelium-independent mechanism of action related to calcium handling in the rat aorta. Tsai and colleagues studied the comparative effects of sildenafil, vardenafil, and tadalafil in isolated rat pulmonary arteries (Tsai et

al. 2006). All three agents induced vasorelaxation in pulmonary artery rings precontracted with phenylephrine, but only tadalafil significantly attenuated hypoxia-induced vasoconstriction and significantly attenuated hypoxia-induced upregulation of tumor necrosis factor alpha and interleukin-1 beta messenger RNA.

Ghofrani and colleagues studied the comparative acute hemodynamic effects of three different selective phosphodiesterase inhibitors (sildenafil 50 mg, vardenafil 10–20 mg, and tadalafil 20–60 mg) in 60 patients, mean age 51 years, with PAH of mixed etiologies including idiopathic pulmonary hypertension (n=46), Eisenmenger syndrome (n=7), CREST syndrome (limited scleroderma comprising calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) (n=4), portopulmonary hypertension (n=2), and HIV-associated pulmonary hypertension (n=1) (Ghofrani et al. 2004). Exclusion criteria were secondary forms of pulmonary hypertension and pregnancy or insufficient contraceptive measures in women of childbearing age. The first 19 patients enrolled received sildenafil 50 mg, and remaining patients were randomly assigned to receive a single dose of vardenafil 10 or 20 mg, or tadalafil 20, 40, or 60 mg. All patients also received inhaled nitric oxide before administration of their selective phosphodiesterase type 5 inhibitor. Hemodynamic measurements were made before and at periodic time intervals for 120 min after study drug. All three phosphodiesterase inhibitors reduced pulmonary vascular resistance when compared with pretreatment values, with peak effects at 40–45 min for vardenafil, 60 min for sildenafil, and 75–90 min for tadalafil. The ratio of pulmonary vascular resistance to systemic vascular resistance (a measure of the degree of selective pulmonary circulation vasodilatation) was higher after vardenafil administration when compared with sildenafil, tadalafil, and inhaled nitric oxide. Oxygen saturation improved after sildenafil administration, but not after vardenafil or tadalafil. These differences in some measures of clinical response to selective phosphodiesterase type 5 inhibitors may be attributable to known differences in potencies or other pharmacologic properties of these agents, and/or clinical differences in the patients assigned to each treatment group. Since the number of subjects in each group is small, additional studies are needed to better characterize the comparative pharmacodynamic effects of these agents in PAH.

There are further limited data on the use of tadalafil in patients with PAH. Several case reports provide anecdotal evidence of acute and chronic reductions in pulmonary vascular resistance, improved functional capacity and increased exercise capacity after administration of tadalafil 10–20 mg every 36–48 hours (Palmieri et al. 2004; Affuso et al. 2006; de Carvalho et al. 2006; Deibert et al. 2007; Kim et al. 2007). There are two additional small case series of patients with PAH treated with tadalafil.

Mukhopadhyay and colleagues studied the acute and chronic effects of tadalafil at a dose of 1 mg/kg daily (maximum 40 mg daily) in 16 patients (mean age 25 years) with symptomatic PAH associated with Eisenmenger syndrome in an open-label, uncontrolled study design (Mukhopadhyay et al. 2006). Patients with World Health Organization (WHO) class IV symptoms,

pulmonary capillary wedge pressure >15 mmHg, or pulmonary hypertension reversible with oxygen were excluded from the study. When compared with pretreatment values, tadalafil treatment significantly reduced pulmonary vascular resistance 90 min after the first dose (24.75 ± 8.49 to 19.22 ± 8.23 Wood units; $P < 0.05$) with further reductions after 12 weeks of therapy (17.02 ± 6.19 Wood units; $P < 0.05$ vs 90-min value). The vasodilatory effects of tadalafil were selective for the pulmonary circulation, as evidenced by a significant decrease in the pulmonary vascular resistance/systemic vascular resistance ratio (1.09 ± 0.34 pretreatment to 0.79 ± 0.26 90 min after the first dose, and 0.71 ± 0.26 after 12 weeks of tadalafil treatment) and reduced right-to-left shunt (1.71 ± 0.92 pretreatment to 1.27 ± 0.50 90 min after the first dose, and 1.16 ± 0.62 after 12 weeks of tadalafil treatment). WHO functional class and submaximal exercise capacity (assessed by 6-min walk distance) improved after 12 weeks of tadalafil therapy when compared with pretreatment values (WHO class 2.31 ± 0.47 pretreatment to 1.25 ± 0.44 ; 6-min walk distance 344.56 ± 119.06 m pretreatment to 387.56 ± 117.18 m; both $P < 0.001$).

Tay and colleagues reported a case series of 12 patients with PAH of mixed etiology (four patients with idiopathic pulmonary artery hypertension, four with Eisenmenger syndrome, and two with connective tissue disease; mean age 45 years) in whom chronic sildenafil therapy at a dose of 100–150 mg daily for 3–6 months was switched to tadalafil 10–20 mg daily for 3–6 months (Tay et al. 2007). All patients had a favorable response to sildenafil, defined as a $>10\%$ improvement in the 6-min walk test distance when compared with pretreatment baseline. Submaximal exercise capacity assessed by the 6-min walking test, New York Heart Association functional class, cardiac output estimated from transthoracic duplex echocardiography studies, and health function assessed by the Short-Form 36 (SF-36) score did not change after the switch from sildenafil to tadalafil therapy. Tadalafil was well tolerated with no adverse effects reported after the switch from sildenafil.

The PHIRST-1 study is a randomized, double-blind placebo-controlled study to determine the safety and efficacy of tadalafil in patients with PAH (clinicaltrials.gov identifier NCT00125918). An estimated 400 subjects with PAH will be treated with tadalafil or placebo for 16 weeks. Patients >12 years of age with idiopathic PAH or pulmonary hypertension associated with collagen vascular disease, past anorexigen use, atrial septal defect, or surgically repaired congenital shunt are eligible for the study. The primary endpoint of the study is change from baseline 6-min walk distance. Secondary endpoints include WHO functional class, Borg dyspnea scale, cardiopulmonary hemodynamics, and quality of life. After completion of the 16-week study, subjects may be eligible to enroll in a 52-week extension phase study (PHIRST-2).

Patient group/population

PAH is a heterogeneous disease of which we have limited understanding of the mechanisms that contribute to initiation and progression of the structural and functional abnormalities in the

pulmonary vasculature (Galie et al. 2004; Sastry 2006; Traiger 2007). Its relatively low prevalence also limits the ability to recruit large numbers of subjects into clinical trials. Accordingly, there are insufficient data to characterize the effects of treatment on subgroups of patients with PAH of different etiologies. Tadalafil was observed to provide clinical benefit in small populations of patients with Eisenmenger syndrome and other causes of PAH. Since the study entry criteria of the PHIRST study include several different causes of PAH, the larger study sample may provide additional information on subgroup responsiveness.

Clinical potential

Based on the preliminary findings from pilot studies with tadalafil in patients with pulmonary hypertension, the proven track record of the related agent sildenafil in PAH, the known similarities in the molecular and clinical pharmacology of tadalafil and sildenafil, and the known comparable clinical effects of these two agents in men with erectile dysfunction, it appears likely that tadalafil will provide clinical benefit in patients with PAH. Pending review of the findings of the ongoing PHIRST study, tadalafil may offer the convenience of once-daily administration for this patient population.

Tadalafil's long elimination half-life and once-daily dosage schedule make this agent a suitable candidate for development in other chronic diseases in which inhibition of phosphodiesterase type 5 may provide clinical benefit. Preliminary studies in patients with chronic heart failure indicate that phosphodiesterase type 5 inhibition is associated with improved hemodynamics, amelioration of endothelial dysfunction, and improved exercise tolerance (Katz et al. 2000; Guazzi et al. 2004; Patel & Katz 2005; Lewis et al. 2007). Chronic phosphodiesterase type 5 inhibition may also provide clinical benefit in patients with Raynaud's phenomenon (Fries et al. 2005).

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