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REVIEW

Phosphodiesterase Type 5 Inhibitors in Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare disease characterized by vascular proliferation and remodeling, resulting in a progressive increase in pulmonary arterial resistance, right heart failure, and death. The pathogenesis of PAH is multifactorial, with endothelial cell dysfunction playing an integral role. This endothelial dysfunction is characterized by an overproduction of vasoconstrictors and proliferative factors, such as endothelin-1, and a reduction of vasodilators and antiproliferative factors, such prostacyclin and nitric oxide. Phosphodiesterase type 5 (PDE-5) is implicated in this process by inactivating cyclic guanosine monophosphate, the nitric oxide pathway second messenger. PDE-5 is abundantly expressed in lung tissue, and appears to be upregulated in PAH. Three oral PDE-5 inhibitors are available (sildenafil, tadalafil, and vardenafil) and are the recommended first-line treatment for erectile dysfunction. Experimental studies have shown the beneficial effects of PDE-5 inhibitors on pulmonary vascular remodeling and vasodilatation, justifying their investigation in PAH. Randomized clinical trials in monotherapy or combination therapy have been conducted in PAH with sildenafil and tadalafil, which are therefore currently the approved PDE-5 inhibitors in PAH treatment. Sildenafil and tadalafil significantly improve clinical status, exercise capacity, and hemodynamics of PAH patients. Combination therapy of PDE-5 inhibitors with prostacyclin analogs and endothelin receptor antagonists may be helpful in the management of PAH although further studies are needed in this area. The third PDE-5 inhibitor, vardenafil, is currently being investigated in PAH. Side effects are usually mild and transient and include headache, flushing, nasal congestion, digestive disorders, and myalgia. Mild and moderate renal or hepatic failure does

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not significantly affect the metabolism of PDE-5 inhibitors, whereas coadministration of bosentan decreases sildenafil and tadalafil plasma levels. Due to their clinical effectiveness, tolerance profile, and their oral administration, sildenafil and tadalafil are two of the recommended first-line therapies for PAH patients in World Health Organization functional classes II or III.

Keywords: phosphodiesterase type 5 inhibitors; pulmonary arterial hypertension; sildenafil; tadalafil; vardenafil

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by vascular proliferation and remodeling, resulting in a progressive increase in pulmonary arterial resistance, right heart failure and, eventually, death.[1] For many years the treatment was extremely limited and the prognosis was poor, with a mean survival time of less than 3 years after diagnosis.[2] A better understanding of the pathophysiological mechanisms of PAH, in particular endothelial dysfunction, has allowed the development of several innovative therapies in the last 15 years that have modified the prognosis despite the fact that, unfortunately, there remains no cure for the disease.[3,4]

Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and have different tissue distributions. Phosphodiesterase type 5 (PDE-5) is abundantly expressed in lung tissue and appears to be upregulated in PAH.[5,6] PDE-5 is implicated in endothelial dysfunction by inactivating cGMP, the second messenger of the nitric oxide (NO) pathway in the pulmonary vasculature.[5-7] Therefore, inhibition of PDE-5 mediates the antiproliferative and vasodilating effects of endogenous NO. Furthermore, PDE-5 is abundantly expressed in the lung tissue of patients with PAH,[8-11] and this upregulation may theoretically exert a preferential effect of PDE-5 inhibitors on these vessels.[5,6,12] Given both the upregulation of lung PDE-5 production in PAH and the tissue specificity of PDE-5, the potential vasodilating and antiproliferative effects of selective PDE-5 inhibitors represent the rationale for the use of PDE-5 inhibitors to treat PAH. Three PDE-5 inhibitors initially approved for the treatment of erectile dysfunction (sildenafil, tadalafil, and vardenafil) have been now evaluated in PAH.

ENDOTHELIAL DYSFUNCTION: NITRIC OXIDE PATHWAY AND ROLE OF PDE-5

Initially, vasoconstriction was thought to be the principle mechanism in the pathogenesis of PAH; however, it is now recognized that endothelial dysfunction also plays a major role in its development. In PAH, endothelial dysfunction results in an imbalance of endothelial mediators, leading to excessive vasoconstriction, smooth muscle proliferation, and to a prothrombotic and proinflammatory state.[4] Natural endothelial production of vasodilators and antiproliferative agents, such as NO and prostacyclin, are decreased and endothelial production of vasoconstrictors and proliferative agents, such as endothelin-1, are overproduced.[13,14] As this endothelial dysfunction is recognized to have a key role in the development of PAH, affecting not only vascular tone but also promoting vascular remodeling, it represents a target for pharmacological treatments.[4] Over the years, prostacyclin analogs, endothelin receptor antagonists, and more recently PDE-5 inhibitors have become available for PAH treatment.[15]

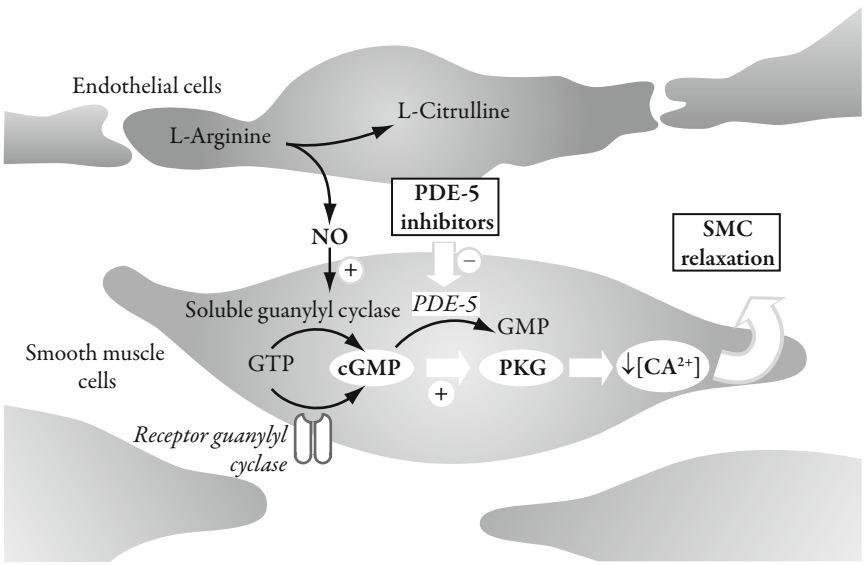
Endothelial dysfunction of PAH is associated with impaired bioavailability of NO due, at least

in part, to reduced expression of endothelial NO synthase and inhibition of its enzymatic activity, and inactivation of NO superoxide anion in the vascular endothelium of pulmonary arteries.[4,16-18] Downstream activation of soluble guanylate cyclase is thus reduced in patients with PAH with a decreased synthesis of cGMP, the second messenger of NO. Degradation of cGMP by phosphodiesterases is mainly due to PDE-5. Furthermore, in PAH, the NO pathway is impaired by the upregulation of PDE-5 in pulmonary vasculature, reducing the levels of cGMP.[5,6] Even if inhaled NO is recommended for acute vasodilator testing, its chronic administration is limited by its very short half-life and the requirement of a complex delivery system. Inhibition of PDE-5 by increasing cGMP levels may be an alternative strategy to mediate the antiproliferative and vasodilating effects of endogenous NO (Figure 1).[8,9,19]

PHARMACOLOGY OF PDE-5 INHIBITORS

PDE-5 inhibitors were initially introduced for clinical use following extensive research on agents targeting PDE-5 that were thought to be useful in the treatment of coronary heart disease.[19] Although this finding was positive, the relatively short half-life and interaction with nitrates complicated their development for cardiovascular indications.[19] The decision to undertake studies with PDE-5 inhibitors in erectile dysfunction was supported by the observation that penile erections were a common side effect in multiple-dose PDE-5 inhibitor studies. Moreover, the level of PDE-5 was found to be very high in the penile corpus cavernosum, thereby targeting PDE-5 inhibitors for penile erectile dysfunction.[20] Today, PDE-5 inhibitors are the recommended first-line treatment for

Figure 1. Endothelial dysfunction and PDE-5 inhibitors. In pulmonary arterial hypertension, endothelial dysfunction is characterized by a decreased production of endogenous NO from pulmonary artery endothelial cells. NO has vasodilatory and antiproliferative effects on smooth muscle cells, through stimulation of soluble guanylate cyclase and increased production of intracellular cGMP. Phosphodiesterase inhibitors enhance cGMP-mediated pulmonary effects through inhibition of the breakdown of cGMP by phosphodiesterase type 5. Ca=calcium; cGMP =cyclic guanosine monophosphate; GTP=guanosine triphosphate; NO=nitric oxide; PDE-5=phosphodiesterase type 5; PKG=protein kinase G; SMC=smooth muscle cells.



erectile dysfunction, and sildenafil, a potent and selective inhibitor of PDE-5, was the first PDE-5 inhibitor licensed for use in this setting. Two other commercially available PDE-5 inhibitors, vardenafil and tadalafil, are also currently approved for the treatment of erectile dysfunction. When compared with expression of PDE-5 in other tissues such as the myocardium, the expression and activity of PDE-5 is considerably higher in lung and in pulmonary vascular smooth muscle cells.[6] These inhibitors are therefore now receiving attention for their beneficial effects in PAH.

Pharmacology

Phosphodiesterase types 3, 4, and 5 are the three main types of this enzyme found in pulmonary artery contractive cells. PDE-5 specifically contributes to cGMP breakdown, thus decreasing smooth muscle cell capacity for vasodilatation whilst promoting proliferation. Experimental studies show a beneficial effect of PDE-5 inhibitors on vascular remodeling and vasodilatation.[21] The three selective PDE-5 inhibitors approved for the treatment of erectile dysfunction have been investigated for their effects on the pulmonary circulation, of which sildenafil and tadalafil are currently approved for the treatment of PAH. Sildenafil, tadalafil, and vardenafil cause significant pulmonary vasodilatation with maximum effects observed after 60, 75 to 90 minutes, and 40 to 45 minutes, respectively.[22]

Sildenafil and vardenafil have very similar molecular structures, derived from cGMP, whereas tadalafil has a different chemical structure. These structural differences are reflected in the pharmacokinetic properties and selectivity for the PDE isoenzyme (Figure 2).[23] Sildenafil and vardenafil both have a terminal half-life of approximately 4 hours, and tadalafil has a half-life of 17.5 hours. All three currently available PDE-5 inhibitors are eliminated by hepatic metabolism.[23] Sildenafil is predominantly metabolized by cytochrome P450 (CYP)3A4 into a *N*-desmethyl metabolite that also has some PDE-5 activity. This metabolite is thought to account for approximately one fifth of the drug's activity. Vardenafil also has an active metabolite that accounts for approximately 7% of total pharmacological activity. The activity of tadalafil is solely though the parent drug.[23]

Pharmacokinetic Interactions Between Bosentan and PDE-5 Inhibitors

PDE-5 inhibitors are mainly metabolized by CYP3A4. As bosentan, an oral endothelin receptor antagonist approved in treatment of PAH, induces CYP3A4 (as well as CYP2C9), this leads to a pharmacokinetic interaction whereby sildenafil plasma levels are reduced and bosentan plasma levels are increased if the two drugs are coadministered.[24] Higher doses of sildenafil might theoretically be needed in patients with bosentan background therapy, but specific trials would be required to confirm this issue. An open-label, randomized study assessed this pharmacokinetic interaction in healthy adults receiving 10 days of tadalafil 40 mg once daily and bosentan 125 mg twice. After 10 days of coadministration, bosentan decreased tadalafil exposure by 41.5% with minimal and clinically irrelevant differences (<20%) in bosentan exposure. Tadalafil plasma levels are decreased if the dose of 40 mg is coadministered with bosentan.[25] However, this pharmacokinetic interaction seems to have no impact in clinical practice on the incidence of elevated liver aminotransferase levels.[26] In the postmarketing surveillance of bosentan in PAH, 2.6% of the 4994 patients enrolled received concomitant therapy with sildenafil.[26] The rates

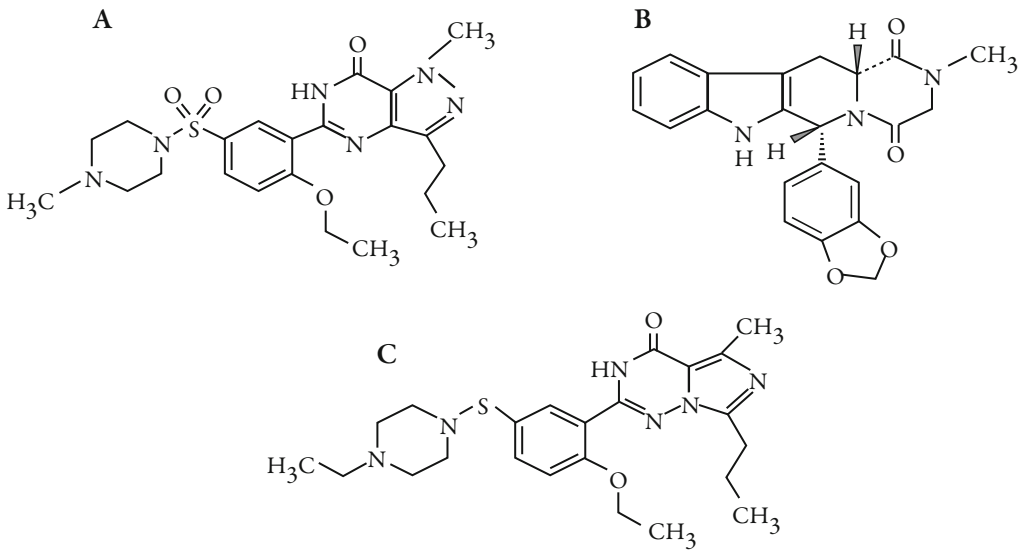
of occurrence of elevated aminotransferases in patients receiving concomitant treatment with sildenafil at baseline (*n*=119) were no higher than those observed in the overall patient population.[26] However, specific interaction studies are needed to confirm these observational data.

Side Effects

The adverse event profiles of the different PDE-5 inhibitors are generally similar. PDE-5 inhibitor class-specific side effects include headache, flushing, nasal congestion, digestive disorders (mainly dyspepsia and nausea), and myalgia, which are a reflection of their vasodilatory effects.[23,27-30] Most adverse events were transient and reported as mild or moderate and are correlated with the dose. No elevation in hepatic enzymes was noted and no dose alteration is required in mild to moderate hepatic insufficiency. Mild and moderate reductions in the creatinine clearance do not affect the metabolism of PDE-5 inhibitors. In cases of severe renal failure (creatinine clearance <30 mL/min), increases in plasma concentration may occur, intensifying and prolonging their effects. However, PDE-5 inhibitors are currently recommended in the treatment of erectile dysfunction of patients requiring chronic hemodialysis. The coadministration of PDE-5 inhibitors with nitrates is contraindicated due to a synergistic effect on the induction of hypotension. Differences in PDE selectivity may explain other differences in the side effect profiles of the PDE-5 inhibitors, and in particular visual effects (increase in light sensitivity, blue-greenish or blurred vision), which are linked to retinal PDE-6 inhibition.[31] Sildenafil inhibits the PDE analogs retinal PDE-6 and PDE-1, and vardenafil also inhibits PDE-6 but has no significant effect on other PDEs. Tadalafil inhibits PDE-11 but has little effect on PDE-6. Therefore, altered vision is mainly observed with sildenafil.[27]

Interestingly, Schermuly et al. demonstrated an upregulation of the PDE-1 in pulmonary

Figure 2. The three different phosphodiesterase type 5 inhibitors evaluated in pulmonary arterial hypertension. (**A**) Sildenafil. (**B**) Tadalfil. (**C**) Vardenafil.



artery smooth muscle cells in lungs from idiopathic PAH patients. Furthermore, inhibition of PDE-1 in animal models reverses vascular remodeling and right heart hypertrophy, suggesting that inhibition of PDE-1 may be beneficial in PAH.[32]

Pregnancy

Guidelines do not provide specific recommendations in pregnant patients with regard to drug choice, except that the endothelin receptor antagonists are contraindicated due to their teratogenic potential.[33] There are no clinical trials of patients with PAH during pregnancy, and the advice remains to strongly discourage pregnancy because of the overall maternal mortality exceeding 25%, even in the modern era of advanced therapies.[34] If the decision is made to progress a pregnancy to term, bosentan (if used) should be stopped and alternate agents should be commenced, such as calcium-channel blockers, if vasoresponsive; sildenafil and/or prostanoids (intravenous epoprostenol or inhaled iloprost) should be started early. The use of sildenafil in pregnant patients is appealing, and has now been described in several published cases in early pregnancy and beyond 28 weeks without reported untoward fetal effects.[35-37]

PDE-5 INHIBITORS IN PAH

The improved understanding of the physiopathology of PAH over the last 15 years has led to the development of several specific PAH therapies. During this period, more than 25 randomized clinical trials testing specific therapy have been conducted in PAH patients. Current approved drugs include epoprostenol and prostacyclin derivatives, oral endothelin-receptor antagonists, and oral PDE-5 inhibitors.[15] Randomized clinical trials in monotherapy or combination therapy have been conducted in PAH with two PDE-5 inhibitors: sildenafil and tadalafil; and a third PDE-5 inhibitor, vardenafil, is currently being investigated in PAH.

Differences in Acute Hemodynamic Response to PDE-5 Inhibitors

The clinical efficacy and the safety of these PDE-5 inhibitors are related to their pharmacokinetic profiles. Differences in hemodynamic and oxygen response to a single dose of these three PDE-5 inhibitors have been assessed in a randomized prospective study.[22] Hemodynamic parameters during right heart catheterization were recorded in 60 PAH patients receiving inhaled NO, and oral intake of different dosage of sildenafil, tadalafil and vardenafil. The three PDE-5 inhibitors caused significant decreases in the pulmonary vascular resistance index and the peak of vasodilatation was obtained most rapidly with vardenafil (40 to 45 minutes) as compared to sildenafil (60 minutes) or tadalafil (75 to 90 minutes). Interestingly, only sildenafil and tadalafil led to a significant decrease of the pulmonary to systemic vascular resistance ratio, suggesting a higher pulmonary selectivity as compared to vardenafil.[22] Furthermore, a significant improvement in arterial oxygenation was only observed with sildenafil and inhaled NO.

In PAH patients, the three PDE-5 inhibitors exert varying effects on pulmonary vasodilatation, differential selectivity for pulmonary circulation and impact on arterial oxygenation, suggesting that these three agents may have different effects in PAH. Even if these short-term properties of PDE-5 inhibitors in PAH may not be extrapolated to long-term response characteristics, they support the importance of evaluating the specific hemodynamic effects of each

new PDE-5 inhibitor separately, despite the fact that they are usually grouped in a common therapeutic class.

Sildenafil

Chronic sildenafil treatment has been shown to improve hemodynamics, right ventricular hypertrophy, and, in rats, survival of monocrotaline-induced pulmonary hypertension.[21,38] Furthermore, Tantini et al. demonstrated in vitro that sildenafil dose-dependently inhibited pulmonary artery smooth muscle cell proliferation induced by platelet-derived growth factor.[9]

In several uncontrolled studies, sildenafil has been reported to have favorable effects in patients with idiopathic PAH, PAH associated with connective tissue diseases, congenital heart diseases, and chronic thromboembolic pulmonary hypertension.[39-41] Two short-term randomized controlled studies assessed the effects of sildenafil in PAH.[42,43]

In a randomized, double-blind, crossover design, 22 patients with idiopathic PAH were randomized to placebo or sildenafil (dosages ranging from 25 mg to 100 mg three times a day on the basis of body weight).[42] After 6 weeks, exercise time significantly increased by 44% at the end of the sildenafil phase. With sildenafil, the cardiac index improved, whereas pulmonary artery systolic pressure decreased insignificantly. There was also a significant improvement in the dyspnea and fatigue components of the quality of life questionnaire.[42] In another randomized placebo-controlled, crossover study, including 20 patients with idiopathic PAH or congenital heart disease-associated PAH, sildenafil improved the World Health Organization (WHO) functional class, exercise capacity, and hemodynamic parameters after 6 weeks.[43]

The SUPER-1 (for Sildenafil Use in Pulmonary Arterial Hypertension) study was a pivotal 12-week, randomized, double-blind, placebo-controlled trial followed by an open extension phase (SUPER-2).[27] In the first part of the study, 278 patients with idiopathic PAH, or PAH associated with connective tissue disease or congenital heart disease, in WHO functional classes II-III, were randomly assigned to placebo or sildenafil 20 mg, 40 mg, or 80 mg three times a day.[27] In the open extension phase, all patients received sildenafil 80 mg three times a day. After 12 weeks, the 6-minute walk distance (6MWD) increased in all groups treated with sildenafil, and the mean placebo-corrected effects on 6MWD were between +45 m and +50 m for the three different dosages. However, no dose-response effect on 6MWD was observed. Furthermore, all sildenafil doses improved hemodynamic parameters and WHO functional class.[27] The analysis of the mean change in hemodynamic variables from baseline to week 12 showed a dose effect on lowering pulmonary vascular resistance. No statistical difference in the time to clinical worsening or in the incidence of clinical worsening was observed with sildenafil as compared to placebo. Among the 222 patients who continued sildenafil monotherapy as part of a long-term extension study, (all patients on 80 mg three times a day) maintained the gain in 6MWD (+51 m).[27] A post-hoc analysis of 84 patients with connective tissue disease-associated PAH receiving sildenafil in the SUPER study revealed improved exercise capacity, hemodynamics, and WHO functional class at 12 weeks when compared with placebo.[27,44]

Only one study has compared efficacy of sildenafil and bosentan as first-line therapy in PAH patients.[45] In the small controlled SERAPH study (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension),

sildenafil (50 mg twice a day for 4 weeks, then 50 mg three times a day) and bosentan were randomly assigned to 26 patients with idiopathic or connective tissue disease associated PAH in WHO functional class III. After 16 weeks, the effects of sildenafil on cardiac function and exercise capacity were comparable to those of bosentan.[45] Sildenafil reduced the right ventricular muscle mass as assessed by cardiac magnetic resonance imaging.[45]

The effects of sildenafil were also assessed in the context of combination therapy.[28,46] A small uncontrolled study has shown that the addition of sildenafil in nine PAH patients who had only a transient clinical improvement with bosentan, may improve clinical status and 6MWD without significant side effects.[46] An uncontrolled study of 12 PAH patients deteriorating despite ongoing iloprost suggested that long-term adjunct oral sildenafil may improve exercise capacity and pulmonary hemodynamics after 12 months.[47]

The double-blind, placebo-controlled PACES (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) study has investigated the effects of adding sildenafil to long-term intravenous epoprostenol in patients with idiopathic PAH, PAH associated with anorexigen use, and PAH associated with connective tissue disease and congenital heart disease.[28] In this study, 267 patients were randomly assigned to receive placebo or sildenafil (20 mg three times a day, titrated to 40 or 80 mg three times a day, as tolerated). After 16 weeks, addition of sildenafil significantly improved placebo-corrected 6MWD (+29 m) and these improvements were most prominent among PAH patients with baseline 6MWD >325 m.[28] The addition of sildenafil also improved hemodynamic measurements, time to clinical worsening, and quality of life in these patients. Seven deaths occurred during the period of this trial; all deaths were in the placebo group.[28] These data indicate that sildenafil may have a role in combination therapy; however, these results assessed an uncommon clinical situation since the availability of sildenafil, because now most of the patients receive first-line therapy before receiving epoprostenol.

Although sildenafil approval in Europe is limited to 20 mg three times daily, no data is currently available on the long-term efficacy of this lower dosage[27] and uptitration beyond this dosage (mainly 40 mg to 80 mg three times a day) may be needed in clinical practice.

Tadalafil

A small preliminary observational study assessed the acute and 12-week efficacy and safety of tadalafil in 16 patients with symptomatic Eisenmenger syndrome.[48] Hemodynamic evaluation in acute phase (90 min after single dose) and after 12 weeks showed that tadalafil significantly decreased pulmonary vascular resistance and systolic to pulmonary vascular resistance ratio and improved systemic oxygen saturation.[48] Furthermore, tadalafil allowed improvement in WHO functional class, and 6MWD (+43 m).[48]

The PHIRST (Pulmonary Arterial Hypertension and ReSponse to Tadalafil) trial is a 16-week, double-blind, placebo-controlled study followed by a long-term extension phase.[29] In this 16-week study, 405 PAH patients (idiopathic or associated PAH), either treatment-naïve or receiving bosentan,[29] were randomly assigned to receive placebo or tadalafil (2.5, 10, 20 or 40 mg once daily). Tadalafil increased the 6MWD in a dose-dependent manner but only the highest dose (40 mg) reached a level of significance (+49 m). Overall, the mean placebo-corrected effect of tadalafil on 6MWD was +33 m, with a maximum effect in the bosentan-naïve group (+44 m) as compared with 23 m in patients on background bosentan therapy.[29] The explanation for this

difference was not clear. Tadalafil plasma levels are decreased by 40% when administrated with bosentan and one can hypothesize that PAH patients treated with 40 mg of tadalafil may receive an insufficient dose to have a maximal effect.[25] Higher doses of tadalafil might theoretically be needed when used in association with bosentan, and specific trials may be required to clarify this issue. In this study, no significant change in WHO functional class was observed; however, tadalafil at the highest dose (40 mg) significantly improved the time to clinical worsening, incidence of clinical worsening and health-related quality of life.[29]

Vardenafil

Vardenafil is a once-daily dose PDE-5 inhibitor, currently approved for the treatment of erectile dysfunction. Preliminary data on the efficacy of vardenafil to treat PAH are limited to a single-dose hemodynamic evaluation that has shown a decrease of pulmonary vascular resistance without change in pulmonary to systemic vascular resistance ratio, suggesting a lower pulmonary selectivity as compared to sildenafil and tadalafil.[22] In a small uncontrolled report on five patients with PAH and chronic thromboembolic disease treated with vardenafil, maintenance dose of vardenafil (10 to 15 mg) for 3 months significantly decreased the pulmonary vascular resistance, with a 20% reduction of the pulmonary to systemic vascular resistance ratio.[49] A preliminary open-label study assessed long-term efficacy and safety of vardenafil (5 mg twice daily) and included 45 patients with idiopathic PAH, or PAH associated with connective tissue disease and congenital heart disease, in WHO functional classes II to IV.[30] After 1 year, vardenafil significantly improved 6MWD, WHO functional class and hemodynamic parameters.[30] As with other PDE-5 inhibitors, vardenafil was well tolerated and adverse events (flushing, headache, skin rash, and diarrhea) were mild and transient,[30] even though acute hemodynamic evaluation seemed to show a reduced pulmonary selectivity for vardenafil.[22] These two preliminary reports demonstrate a significant decrease of pulmonary to systemic vascular resistance ratio at 3 or 12 months.[30,49] Further randomized, placebo-controlled studies would be needed to precisely define the long-term efficacy and the place of vardenafil in the management of PAH.

Specific Cautions for PDE-5 Inhibitor Use in Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension characterized by specific pathological changes of postcapillary venous pulmonary vessels.[50,51] PVOD is usually considered to represent 5% to 10% of patients initially diagnosed as having idiopathic PAH.[50] Recent reports have illustrated the occurrence of pulmonary edema in PVOD patients treated with different PAH therapies (epoprostenol and prostacyclin derivatives, endothelin receptor antagonists, calcium-channel blockers). Clinical stabilization or mild improvement have been observed in selected cases of PVOD patients receiving PAH therapies, including epoprostenol or sildenafil.[52-54] However, Montani et al. recently reported the first case of pulmonary edema following initiation of sildenafil in a patient receiving another specific PAH therapy (bosentan).[55] In this case, the relative contribution of each therapy to pulmonary edema may be debated, but it is likely that sequential addition of treatments in a goal-oriented strategy favored the development of pulmonary edema. Moreover, this report emphasizes that all PAH therapies, including PDE-5 inhibitors, should be used with caution in PVOD.[55]

EVIDENCE-BASED TREATMENT ALGORITHM

During the 4th world symposium on pulmonary hypertension held in Dana Point, CA, USA in 2008, an updated evidence-based treatment algorithm in PAH was proposed based on the evaluation of controlled clinical trials.[15] Among PDE-5 inhibitors, only sildenafil and tadalafil have been evaluated in controlled trials and were therefore included in the algorithm.

Acute vasodilator testing with inhaled NO was used to select PAH patients who are able to respond to long-term calcium-channel blockers. In those patients, there is no indication for first line therapy with PDE-5 inhibitors (or other PAH-specific therapy). Oral high-dose calcium-channel blockers remain the treatment of choice in acute NO responders and need to be maintained if long-term response is sustained. PAH-specific therapies are indicated for PAH patients who do not respond to acute vasodilator challenge or who fail to respond long-term on calcium-channel blockers.[15]

In PAH patients in WHO functional classes II and III, a strong recommendation for sildenafil and a moderate recommendation for tadalafil were proposed. Alternative treatments for these patients were endothelin receptor antagonists (classes II and III), prostacyclin and analogs (class III) (Table 1). In patients in WHO functional class IV, the recommended treatment is continuous intravenous epoprostenol. In PAH patients with inadequate clinical response or severe patients in WHO functional class IV, combination therapy may be proposed, including prostanoids, PDE-5 inhibitors and endothelin receptor antagonists (see Table 1, B: moderate recommendation for all the different combination of two of these three treatments).[15]

Table 1. Recommendations for pulmonary arterial hypertension (PAH)-specific therapies in nonacute vasodilator responders (adapted from the evidence-based treatment algorithm proposed by the 4th World Pulmonary Arterial Hypertension Symposium, Dana Point, California, February 2008[15]).

Strength of recommendation	World Health Organization class II	World Health Organization class III	World Health Organization class IV
A : Strong recommendation	Ambrisentan, bosentan, sildenafil	Ambrisentan, bosentan, epoprostenol (intravenously), iloprost inhaled, sildenafil	Epoprostenol (intravenously)
B : Moderate recommendation	Sitaxsentan, tadalafil	Sitaxsentan, tadalafil, treprostinil (subcutaneously)	Iloprost inhaled
C: Weak recommendation			Treprostinil (subcutaneously)
E/B: Moderate recommendation on the basis of expert opinion only			Iloprost (intravenously), treprostinil (intravenously), initial combination therapy
E/C: Weak recommendation on the basis of expert opinion only			Ambrisentan, bosentan, sildenafil, sitaxsentan, tadalafil

CONCLUSIONS

In summary, PDE-5 inhibitors were initially developed for the treatment of erectile dysfunction, but their ability to increase cGMP levels in lung vasculature presented an appealing alternative strategy to mediate the antiproliferative and vasodilating effects of endogenous NO. In controlled trials, sildenafil and tadalafil in monotherapy have been shown to improve clinical status, exercise capacity and hemodynamic parameters. In combination therapy, further studies are needed but the association of PDE-5 inhibitors with prostacyclin analogs and endothelin receptor antagonists may be helpful in the management of PAH patients. Due to their profile of tolerance and their oral administration, PDE-5 inhibitors are, with endothelin receptor antagonists, a recommended first line therapy for PAH patients in WHO functional classes II or III. Randomized placebo-controlled trials are needed to clearly define the efficacy and the possible place of vardenafil in the management of PAH patients.

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