EXPERT OPINION

Current therapies for the treatment of systemic sclerosis-related pulmonary arterial hypertension: efficacy and safety

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Introduction: Systemic sclerosis (SSc) is a rare connective tissue disease characterized by chronic inflammation and fibrosis of the skin, vascular abnormalities and variable involvement of organs. Patients with limited SSc typically develop pulmonary arterial hypertension (PAH). TNF-α, VEGF, platelet-derived growth factor and endothelin-1 play a key role in the development of PAH.
Areas covered: This paper addresses the efficacy and safety of current drugs used for the treatment of PAH.
Expert opinion: Bosentan, ambrisentan, sildenafil, tadalafil, iloprost, epoprostenol and treprostinil were associated with hemodynamic improvements in PAH patients. Ambrisentan has a better safety profile compared with bosentan, regarding the risk of increase in hepatic transaminases. Flushing, dyspepsia and diarrhea were the most frequent adverse events in patients treated with sildenafil, while headache, myalgia and flushing were the adverse events in those receiving tadalafil. Inhaled iloprost is also effective, but it requires multiple daily nebulizations up to 15 min each and may induce cough, flushing, jaw pain and headache. Epoprostenol is considered the most effective approved therapy for severe PAH in WHO functional class III and class IV. TNF-α inhibitors reduce the systemic inflammation in patients with chronic immune-mediated diseases and improve the endothelial function, decreasing the risk of PAH progression.

Keywords: anti-endothelin-1, phosphodiesterase type 5 inhibitors, prostanoids, systemic sclerosis-related pulmonary arterial hypertension, TNF-α inhibitors

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1. Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by chronic inflammation and fibrosis of the skin, vascular abnormalities and variable involvement of organs, including kidneys, gastrointestinal tract, heart and lungs [1,2]. Depending upon the extent of skin involvement, SSc is classified into two main subtypes: limited SSc (lSSc) and diffuse SSc (dSSc). It is estimated that pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) account for 30% of the deaths in SSc patients [3]. PAH is defined by a mean pulmonary arterial pressure > 25 mmHg with a capillary wedge pressure ≤ 15 mmHg. Patients with dSSc are at increased risk of ILD and might develop PAH as a result of hypoxemia and primary pulmonary parenchymal disease. On the contrary, patients with lSSc typically develop PAH, rather than ILD, in a range between 10 to 15 years after the onset [4-6]. The prevalence of PAH in SSc patients varies depending on the population studied and diagnostic method used between 7% (right heart catheter)

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Article highlights.

- PAH is defined by a mean pulmonary arterial pressure > 25 mmHg with a capillary wedge pressure ≤ 15 mmHg.
- Bosentan, ambrisentan, sildenafil, tadalafil, iloprost, epoprostenol and treprostinil were associated with sustained clinical and hemodynamic improvements in patients with PAH.
- Ambrisentan seems to have a better safety profile compared with bosentan regarding the risk of increase in hepatic transaminases.
- Ambrisentan shows a higher frequency of other adverse events such as nasal congestion, peripheral edema and headache.
- Both sildenafil and tadalafil improve 6-min walking distance test and WHO functional class.
- Flushing, dyspepsia and diarrhea were the most frequent adverse events in patients treated with sildenafil, while headache, myalgia and flushing were the most frequent adverse events in those receiving tadalafil.
- Epoprostenol is considered the most effective approved therapy for severe PAH in WHO functional class III and class IV.
- TNF-α inhibitors reduce the systemic inflammation in patients with chronic immune-mediated diseases and improves the endothelial function, decreasing the risk of PAH progression.

This box summarizes key points contained in the article.

and 27% (echocardiography) [7,8]. In PAH registries, PAH in association with connective tissue disease is the second most common type of PAH after idiopathic PAH. PAH is a vascular remodeling disease characterized by enhanced proliferation and suppressed apoptosis of pulmonary artery smooth muscle cells. Although the exact pathogenesis of PAH is still unknown, potassium channel function and endothelial dysfunction are involved [9-11]. The endothelium represents the main regulator of vascular wall homeostasis and favors a relaxed vascular tone and low levels of oxidative stress by releasing mediators such as nitric oxide (NO), prostacyclin-2 (PGI2) and endothelin (ET)-1, as well as by controlling local angiotensin II activity [10,12]. ET-1 has opposing actions depending on the location of the ET_A or ET_B receptor at which it binds [13]. At ET_B receptors on vascular endothelial cells, ET-1 induces vasodilation, while at ET_A and ET_B receptors on smooth muscle cells ET-1 favors persistent vasoconstriction and cellular proliferation [13]. PAH patients have increased pulmonary production and decreased clearance of ET-1, which result in increased levels of circulating ET-1 and ET-1 converting enzymes. These elevated levels of ET-1 together with the increased production of thromboxane, the cellular proliferation and the decreased synthesis of the vasodilators NO and PGI2 favor and maintain excessive vasoconstriction [13]. Furthermore, VEGF is a critical mediator of inflammation both in chronic immune-mediated and allergic diseases [10,14,15]. It is known that VEGF is a proangiogenic factor that alters the microvascular network, and thus, correlates and may contribute to the development and progression of endothelial dysfunction and hypertension [10,11]. Indeed, Cool *et al.* [16] confirmed a central role of VEGF in PAH, demonstrating exuberant expression of the VEGF receptor KDR in the endothelial cells of plexiform lesions in severe PAH. Other several growth factors, including platelet-derived growth factor (PDGF), basic fibroblast growth factor, epidermal growth factor (EGF), have been implicated in the pathogenesis of PAH [17]. Recent studies suggest that cytokines are key players in the pathogenesis of PAH. IL-6, a pleiotropic cytokine, is significantly elevated in the serum and lungs of patients with PAH [18]. Booth *et al.* [19] confirmed that the serum levels of TNF-α may promote the progression of the endothelial dysfunction. Furthermore, TNF-α seems to favor the expression of IL-6. Inflammatory cells are present within and around the remodeled arteries and patients with PAH have elevated levels of inflammatory cytokines, including TNF-α. Elevated serum TNF-α level was observed in patients with PAH secondary to chronic thromboembolic disease and connective tissue disease [20]. TNF-α can inhibit pulmonary artery smooth muscle cell pyruvate dehydrogenase activity and favor the development of PAH [21]. Finally, Truchetet *et al.* [22] demonstrated that the frequency of $IL\text{-}17A^+$ cells was higher in the skin of SSc patients with greater severity of skin fibrosis, confirming the important role of this cytokine in the development of chronic inflammatory autoimmune diseases [23]. Nevertheless, the role of IL-17 in the pathogenesis of PAH is still unknown. However, chronic inflammatory autoimmune diseases appear as an independent risk factor for the development of endothelial dysfunction [24,25]. Despite major therapeutic advances, PAH indicates a worse prognosis in SSc patients with an unadjusted risk of death of 2.9 when compared to idiopathic PAH, while predictors outcome are similar in both groups [26]. However, even in the modern management era, 1-year mortality is estimated to be 8 – 15% in patients with idiopathic, familial/heritable or anorexigen-associated PAH [27,28] and is about 30% in SSc-related PAH (SSc-PAH) [29]. Current guidance suggests that an early diagnosis of PAH and early therapeutic intervention may result in an improvement in long-term outcomes [27,30-32]. Based on our experience, in this review, we discuss the efficacy and safety of the current drugs used and of the potential therapeutic perspectives for the treatment of SSc-PAH.

2. Bosentan

Bosentan is an oral competitive specific dual ET_A and ET_B receptor antagonist and is approved for the treatment of World Health Organization (WHO) functional classes III and IV PAH and for active SSc digital ulcers. Bosentan therapy is started with 62.5 mg twice daily (b.i.d.) for 4 weeks with a target dose of 125 mg b.i.d. thereafter. Bosentan is

metabolized by the cytochrome (CYP) P450 isoenzymes CYP2C9 and CYP3A4 and it is also an inducer of these two enzymes and, thus, it can modify the exposure of coadministered agents metabolized through these pathways such as sildenafil [33]. The European League against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research group have generated 14 evidence-based and consensus-derived treatment recommendations, including the SSc-PAH [34]. Bosentan is metabolized by the hepatic CYP450 isoenzymes CYP2C9 and CYP3A4 to form the two primary metabolites Ro 48-5033 and Ro 47-8634, which are further metabolized to form Ro 64-1056. Notably, Ro 48-5033 is the only pharmacologically active metabolite and may produce ≤ 20% of the pharmacological effects of bosentan. Dose-dependent autoinduction of CYP2C9 and CYP3A4 occurs with repeat bosentan administration, reaching maximum after 4 – 5 days. About 95% of bosentan and its metabolites are excreted fecally. The therapeutic efficacy of oral bosentan in the treatment of idiopathic PAH or PAH associated with connective tissue diseases such as SSc has been evaluated in randomized, double-blind trials [35,36]. Rubin *et al.* [35] enrolled 213 patients with PAH: 150 patients with primary PAH, 47 with SSc-PAH and 16 systemic lupus erythematosus (SLE)-PAH. One hundred ninety were in WHO functional class III and 18 in WHO functional class IV. Sixty-nine subjects received placebo, while 144 were treated with 62.5 mg b.i.d. of bosentan for 4 weeks followed by either of two doses of bosentan (125 or 250 mg b.i.d.) for a minimum of 12 weeks. After 16 weeks of therapy, patients receiving bosentan presented a statistical improvement of the 6-min walking distance test of the Borg dyspnea index (a measure of perceived breathlessness on a scale of 0 – 10, with higher values indicating more severe dyspnea) [36] and of the WHO functional class. In particular, 38% of patients receiving 125 mg of bosentan and 34% of those receiving 250 mg of bosentan improved to WHO functional class II and 3 and 1% to class I, respectively. However, there was no dose-dependent effect at any time of treatment and the difference from placebo was significant for both doses of bosentan. The adverse events reported were headache, dizziness and worsening of symptoms of PAH, abnormal hepatic function, flushing, syncope, cough and dyspnea. With the exception of abnormal hepatic function, which was more frequent in the group receiving 250 mg of bosentan, the number of the other adverse events resulted similar in both groups of treatment and in the placebo group. Furthermore, nine patients treated with bosentan and five patients receiving placebo interrupted the therapy as a result of adverse events. The most frequent adverse events leading to the discontinuation of treatment were abnormal hepatic function in the two bosentan groups and worsening of symptoms of PAH and syncope in the placebo group. Notably, increasing the dose of bosentan to 250 mg b.i.d. led to a greater increase in the aminotransferase levels, confirming that the well-tolerated dose of bosentan is 125 mg b.i.d. Therefore, this study confirmed the efficacy and safety of bosentan treatment in patients with PAH either primary or associated to SSc and SLE. Humbert *et al.* [37] evaluated the efficacy and safety of the combination of bosentan with the prostaglandin epoprostenol in the treatment of PAH. Among the 33 patients enrolled, 27 had primary PAH, 5 had SSc-PAH and 1 had SLE-PAH. Twenty-five patients were in WHO functional class III and 8 patients were in class IV. Twenty-two patients received bosentan plus epoprostenol and 11 patients received placebo plus epoprostenol. Both groups of therapy decreased the total pulmonary resistance (TPR) determined by right heart catheterization after 16 weeks of treatment. However, the combination bosentan plus epoprostenol showed greater effectiveness, although not statistically significant in improving TPR. Both groups of therapy also improved the 6-min walking distance test and the WHO functional class. Indeed, 13 patients in the bosentan plus epoprostenol group and 5 subjects in the placebo plus epoprostenol reached WHO functional class I or class II. The only adverse events associated with the treatment of bosentan that occurred in the patients receiving the combination bosentan plus epoprostenol was leg edema. Only two patients, one in each treatment group, were withdrawn from the study because of the increases in hepatic transaminases. Two patients receiving bosentan plus epoprostenol died as a result of cardiopulmonary failure (one with SSc-PAH) and a third patient died after being withdrawn from the study for PAH worsening. This study, confirmed that the combination bosentan plus epoprostenol was effective and well tolerated in the treatment of PAH. Sasayama *et al.* [38] treated 18 Japanese patients (2 males, 16 females) with bosentan. Thirteen patients had primary PAH, 4 had SLE-PAH and 1 had PAH secondary to mixed connective tissue disease. At baseline, patients' symptoms were evaluated by the Borg dyspnea index and the WHO functional class for pulmonary hypertension, and hemodynamic measurements were performed with a Swan-Ganz catheter. Efficacy of the bosentan therapy was also assessed by the 6-min walking distance test. The patients were treated with bosentan starting with a dose of 62.5 mg/day for the first week, then 62.5 mg b.i.d. for the next 3 weeks and, finally, 125 mg b.i.d. for the subsequent 8 weeks. The authors confirmed the efficacy and safety of bosentan. In particular, after 12 weeks of therapy, the pulmonary vascular resistance, the mean pulmonary arterial pressure, both systolic and diastolic blood pressure and Borg dyspnea index decreased. On the contrary, cardiac index and 6-min walking distance test increased. At the beginning of the study, 17 patients were in WHO functional class III and 1 patient was in class IV. After 12 weeks of therapy, 10 patients improved to WHO class I or class II, while the remaining 8 patients were in class III. The only adverse events that occurred in the patients receiving bosentan were headache, dizziness and myalgia. Finally, aminotransferase concentrations resulted in elevation in some cases but mostly returned to normal values without discontinuation of treatment. Dimitroulas *et al.* [39] analyzed the effect

of bosentan therapy on N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels in 10 patients with SSc-PAH. Six patients had lSSc, four patients presented dSSc and 6 patients had pulmonary fibrosis. All patients were treated with 62.5 mg b.i.d. of bosentan for 4 weeks followed by 125 mg b.i.d. After 20 weeks of treatment, NT-proBNP plasma concentrations decreased and 6-min walking distance test increased from baseline values. Nine patients were in WHO functional class III and 1 patient was in class IV before treatment. After 20 weeks of treatment, three patients improved to WHO class II and no patients deteriorated to class IV. The authors demonstrated that NT-proBNP plasma concentrations increased in proportion to the degree of the right ventricular dysfunction. Therefore, NT-proBNP may be used in combination with other surrogate markers, such as the 6-min walking distance test, to evaluate the efficacy of bosentan. The authors also confirmed the safety of bosentan, reporting only dyspeptic symptoms and worsening of arthritis of the hands in two patients. Finally, bosentan was also proven to improve the hemodynamics for the patients with Eisenmenger's syndrome [40].

3. Ambrisentan

Ambrisentan is an oral selective ET_A receptor antagonist with a lower rate of hepatic injury [41]. Ambrisentan is approved for the treatment of patients with PAH with WHO functional class II or class III. Galiè *et al.* [42] evaluated the efficacy of ambrisentan for the treatment of PAH in two Phase III randomized, double-blind, placebo-controlled studies (ARIES-1 and ARIES-2) that were identical in design except for the investigative sites and the doses of ambrisentan studied. Indeed, ambrisentan was administered at a dose of 5 or 10 mg in ARIES-1 and 2.5 or 5 mg in ARIES-2. The 6-min walking distance test was increased in each ambrisentan dose group at week 4 and this effect was maintained at weeks 8 and 12. A statistically significant improvement in time to clinical worsening and in the distribution of WHO functional class in patients receiving ambrisentan compared with placebo were observed in ARIES-1 and in ARIES-2, respectively. Borg dyspnea score improved and NT-proBNP plasma concentrations decreased after 12 weeks of ambrisentan therapy in both ARIES-1 and ARIES-2. Ambrisentan was well tolerated and peripheral edema, headache and nasal congestion resulted more frequent in patients receiving ambrisentan. Notably, only nasal congestion seemed to increase with ambrisentan dose in both ARIES-1 and ARIES-2. However, no patients treated with ambrisentan developed severe aminotransferase concentrations > 3 times upper limit of normal. A total of 383 patients completing either the ARIES-1 or ARIES-2 study were eligible to continue on ambrisentan for the ARIES-E extension study [43], which confirmed the long-term efficacy and safety of ambrisentan. ARIES-3 [44], a long-term, open-label, multicenter, single-arm study reconfirmed the efficacy and safety of ambrisentan in 224 patients with PAH due to idiopathic or familial PAH, connective tissue disease, chronic hypoxemia, chronic thromboembolic disease or other etiologies. As compared to bosentan, ambrisentan has several favorable qualities that potentially make it more acceptable to patients. Ambrisentan is administered once daily and, thus, this may result in improved adherence. There is a low risk of liver enzyme increase associated with the treatment of ambrisentan which can be used safely in high risk subjects who have previously failed bosentan therapy because of liver enzyme abnormalities. Finally, ambrisentan is metabolized by CYPP450 CYP3A4 and CYP2C1 and it does not inhibit or induce CYP enzymes. Therefore, ambrisentan has a more favorable metabolism and drug interaction profile than bosentan, and it can be used with cyclosporine, being the only established drug–drug interaction [45]. Furthermore, ambrisentan has no clinically relevant effect upon the pharmacokinetics or pharmacodynamics of sildenafil and warfarin [46]. Maron *et al.* [47] retrospectively analyzed the patients enrolled in ARIES-1 (201 individuals) and ARIES-2 (192 individuals) to determine if the treatment with spironolactone influenced the efficacy of ambrisentan. The association of ambrisentan plus spironolactone improved change in 6-min walking distance test by 94% at week 12, improved plasma NT-proBNP and resulted in a 90% relative increase in the number of patients improving ≥ 1 WHO functional class.

4. Macitentan

Macitentan is a new oral dual (ET_A and ET_B) receptor antagonist with increased *in vivo* preclinical efficacy resulting from sustained receptor binding and tissue penetration properties [48,49]. Pulido *et al.* [50] enrolled 742 patients with symptomatic PAH: 250 patients were treated with placebo, 250 patients received macitentan 3 mg and 242 patients received macitentan 10 mg. Two hundred and twenty-four patients presented connective tissue disease-associated PAH. Almost all patients were in WHO functional class II and class III. The 6-min walking distance test and WHO functional class significantly improved in both macitentan groups after 6 months of treatment. Further, patients in both macitentan groups presented significant decreases in pulmonary vascular resistance and increases in the cardiac index. Macitentan was well tolerated and the most commonly reported adverse events were headache, nasopharyngitis and anemia. Finally, there is also a low risk of liver enzyme increase associated with the treatment with macitentan.

5. Sitaxentan

Sitaxentan, a selective ET_A receptor antagonist with moderate clinical efficacy [51], was withdrawn from the market worldwide in 2010, due to an increasing number of deaths attributed to acute liver failure [52].

6. Sildenafil

Phosphodiesterase type 5 inhibitors (PDE-5Is) act by blocking PDE-5-dependent metabolism of cyclic guanosine monophosphate, thereby increasing downstream effects of NO [53]. Sildenafil was the first PDE-5I approved for the treatment of PAH in 2005. Because the terminal half-life of sildenafil ranges from ~ 3 to 4 h in healthy individuals, the drug is administered three times daily. The currently approved dosage is 20 mg of sildenafil three times daily. Galiè *et al.* [54] enrolled 278 patients with symptomatic PAH (either idiopathic or associated with connective tissue disease or with repaired congenital systemic-to-pulmonary shunts). Seventy patients were treated with placebo, 69 patients received 20 mg of sildenafil, 67 patients received 40 mg of sildenafil and 71 patients received 80 mg of sildenafil orally three times daily for 12 weeks. The 6-min walking distance test increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13%), 46 m (+13.3%) and 50 m (+14.7%) for 20, 40 and 80 mg of sildenafil, respectively. All sildenafil doses reduced the mean pulmonary artery pressure and improved the WHO functional class. Flushing, dyspepsia and diarrhea were the most frequent adverse events. Rubin *et al.* [55] confirmed the efficacy and safety of sildenafil by showing sustained improvements in 6-min walking distance test and WHO functional class with an estimated 3-year survival rate of 79%.

7. Tadalafil

Tadalafil is another PDE-5I used in PAH patients. Galiè *et al.* [56] evaluated the efficacy of tadalafil for the treatment of PAH in a 16-week, double-blind, placebo-controlled study (PHIRST). Among the 405 patients with PAH enrolled, 95 presented connective tissue disease-associated PAH. Among the PAH patients, either treatment-naïve or on background treatment with bosentan, were randomized to receive placebo or tadalafil 2.5, 10, 20 or 40 mg/day orally. In particular, 82 patients received placebo, 82 patients were treated with tadalafil 2.5 mg, 80 patients were treated with tadalafil 10 mg, 82 patients received tadalafil 20 mg and, finally, 79 patients received tadalafil 40 mg. Tadalafil improved the 6-min walking distance test in a dose-dependent manner. However, tadalafil 40 mg was the only dose that consistently demonstrated improvements in 6-min walking distance test compared with placebo and achieved the pre-specified value of statistical significance ($p < 0.01$). Furthermore, the time to clinical worsening and the health-related quality of life significantly improved in the tadalafil 40 mg group compared with placebo. All doses of tadalafil were generally well tolerated and the most commonly reported adverse events were headache, myalgia and flushing. The primary objective of PHIRST-2 study was to evaluate the long-term safety and durability of efficacy of both the tadalafil 20 and 40 mg [57]. A total of 357 eligible patients from PHIRST were enrolled in PHIRST-2 and assigned to continue tadalafil 20 mg/day (absent clinical worsening; n = 63) or to receive tadalafil 40 mg/day (all other patients; n = 294) for 52 weeks. Long-term treatment with tadalafil was well tolerated in patients with PAH. In patients receiving either tadalafil 20 or 40 mg, the improvements in 6-min walking distance test demonstrated in the 16-week PHIRST study appeared sustained for up to 52 additional weeks of treatment in PHIRST-2. The most common adverse reported event was headache. Shapiro *et al.* [58] evaluated the risks and benefits of switching patients from sildenafil to tadalafil in 98 patients with PAH of different etiology, including connective tissue disease-associated PAH. Ninety subjects were on sildenafil for > 1 year and 76 patients received sildenafil 80 – 100 mg three times daily. Ninety-five patients were successfully transitioned and maintained on tadalafil 40 mg. The switching was well tolerated and headache was the most commonly reported adverse event. However, tadalafil appears to have beneficial effects on PAH, irrespective of the underlying etiology [59]. Takatsuki *et al.* [60] demonstrated that tadalafil monotherapy favored the improvements in hemodynamics in 33 PAH pediatric patients, confirming that tadalafil was also a safe treatment option for pediatric patients. The American College of Cardiology, the American Heart Association and the European Society of Cardiology recommended starting intravenously epoprostenol as first-line treatment for patients with severe PAH (WHO functional class III and class IV) and sildenafil or ambrisentan or bosentan as first-line treatment for patients with WHO functional class III [61]. However, combination therapy including tadalafil is recommended as second-line treatment for those patients who do not respond to the initial treatment. Nowadays, the most widely used combinations are ET receptors blockers (bosentan) with PDE-5I (tadalafil, sildenafil) [62,63].

8. Iloprost

Iloprost is a chemically stable derivative of prostacyclin with a longer half-life. Olschewski *et al.* [64] enrolled 203 patients with selected forms of severe PAH and WHO functional class III and class IV and treated then with inhalations of 2.5 or 5 µg of iloprost (6 or 9 times/day; median inhaled dose: 30 µg/day) or with inhalation of placebo. The absolute change in the distance walked in 6-min was significantly larger (by 36.4 m) in the iloprost group than in the placebo group ($p = 0.004$) at 12 weeks of therapy: in particular, 58.8 m among those with primary PAH and 12 m among those with non-primary PAH. More patients in the iloprost group than in the placebo group presented an improvement in the severity of WHO functional class. Hemodynamic values, clinical symptoms (dyspnea) and quality of life were significantly improved at 12 weeks in patients treated with iloprost. However, Opitz *et al.* [65] showed that only a minority of subjects could be stabilized with inhaled iloprost monotherapy during

a follow-up period of 5 years. Lopez-meseguer *et al.* [66] treated eight patients with PAH in WHO functional class IV with inhaled iloprost plus oral sildenafil. However, the iloprost plus oral sildenafil combination treatment improved both the 6-min walking distance test and the WHO functional class at 3 months of therapy. Survival at 1 and 5 years was 100 and 75%, respectively. Finally, among the four potential lung transplantation candidates, only one underwent transplantation after 6.8 years and one died after 1.2 years. Therefore, the combination iloprost plus oral sildenafil represents an effective therapeutic regimen in patients with severe PAH. Nevertheless, iloprost requires multiple daily nebulizations up to 15 min each and may induce cough, flushing, jaw pain and headache.

9. Beraprost

Beraprost was another orally active prostanoid, licensed in Japan and South Korea, that did not prove to be effective in inducing and maintaining improvement after 12 months of therapy [67].

10. Epoprostenol

Epoprostenol is a synthetic prostacyclin with a < 5 min of half-life and, thus, is administered continuously via an indwelling central venous catheter. It is considered the most effective approved therapy for severe PAH in WHO functional class III and class IV. Three studies [68-70] demonstrated the efficacy of epoprostenol therapy to favor the improvement in hemodynamics, exercise capacity and survival. The most common adverse events were headache, flushing, jaw pain and diarrhea.

11. Treprostinil

Treprostinil is a chemically stable prostacyclin analog with demonstrated safety and efficacy when administered by intravenous, subcutaneous or inhaled routes of administration [71-73]. Jing *et al.* [74] enrolled 349 patients with PAH and treated 233 patients with oral treprostinil and 116 with placebo. Oral treprostinil treatment improved both the 6-min walking distance test and the combined 6-min walking distance test/Borg dyspnea score after 12 weeks of therapy. The most commonly reported adverse events were the worsening disease including right ventricular failure and worsening PAH. However, oral treprostinil may be considered a valid alternative therapeutic regimen for PAH patients not requiring more intensive treatment.

12. Potential therapeutic perspectives

As we have previously reported, several proinflammatory molecules, such as TNF-α, VEGF, PDGF and EGF [10,11,14,15,22-24], may favor and promote the progression of endothelial dysfunction which is implicated in the pathogenesis of PAH [17,19]. PDGF also acts as a smooth muscle mitogen, responsible for pulmonary arterial remodeling. Imatinib is a tyrosine kinase inhibitor agent used for the treatment of chronic myelogenous leukemia which is also a PDGF inhibitor. IMPRES, a Phase III randomized clinical trial [75], tested the efficacy and safety of imatinib in PAH patients. However, although imatinib improved the 6-min walking distance test and hemodynamic parameters, the drug was withdrawn from the market worldwide in early 2013, due to serious adverse events such as subdural hematomas. TNF-α inhibitors have demonstrated efficacy in large, randomized controlled clinical trials either as monotherapy or in combination with other anti-inflammatory or disease-modifying antirheumatic drugs in the treatment of chronic immune-mediated or inflammatory diseases [76-85]. There are several TNF-α inhibitors available for clinical use, including anti-TNF-α monoclonal antibodies (mAbs) (infliximab, adalimumab, golimumab and certolizumab pegol) and a fusion protein that acts as a 'decoy receptor' for TNF-α (etanercept) [76-84]. Arenas *et al.* [86] evaluated the effects of etanercept administration in ovariectomized rats which presented high levels of TNF-α. Etanercept decreased the serum TNF-α levels and increased the tissue expression of endothelial NO synthase and vasodilatory response to bradykinin. Dulai *et al.* [87] confirmed that TNF-α inhibitors (etanercept, infliximab, adalimumab) may have a beneficial effect on arterial stiffness in patients with rheumatoid arthritis improving, thus, accelerated atherosclerosis and consequently reducing the cardiovascular risk. Szekanecz *et al.* [88] suggested that etanercept and adalimumab may exert beneficial effects on the lipid profile improving the endothelial dysfunction. Further, TNF-α inhibitors are able to reduce the expression and production of VEGF, NO and inducible NO synthase [89]. The administration of TNF-α inhibitors reduces the systemic inflammation in patients with chronic immune-mediated diseases and improves the endothelial function decreasing the risk of PAH progression. Moreover, Bargagli *et al.* [90] demonstrated that infliximab reduced pulmonary pressure and improved the quality of life in a patient with severe PAH secondary to advanced scleroderma. Wang *et al.* [91] confirmed the effectiveness of TNF-α inhibitors in reducing PAH. Although TNF-α inhibitors are generally well tolerated, their use may increase the overall risk of opportunistic infections, in particular the reactivation of latent tuberculosis, whereas no overall increased risk of lymphoma and solid cancer development has been proven [92,93]. The appearance of neutralizing antibodies has been described in patients treated with infliximab, which is a chimeric human/mouse mAb, as well as in those treated with adalimumab, in spite of its fully human sequence [94]. Therefore the administration of an immunosuppressive drug like methotrexate is warranted to prevent their development. While infliximab may induce infusion reactions, etanercept, adalimumab, golimumab and certolizumab pegol may induce injection-site reactions [76,79,83]. Finally, relying on these findings, TNF-α inhibitors may represent a potential valid alternative

therapeutic regimen for connective tissue disease-associated PAH.

13. Conclusion

Although PAH still remains an incurable disease with a severe prognosis, the past 20 years have represented a huge progress in terms of treatment for PAH. In addition to specific PAH therapies, oral anticoagulants (i.e., warfarin, acenocumarol) are used to decrease the risk of pulmonary *in situ* microthrombosis in patients with PAH. It is essential to make an early diagnosis and to treat PAH patients with specific and effective drugs.

14. Expert opinion

Long-term studies demonstrated that bosentan, ambrisentan, sildenafil, tadalafil, iloprost, epoprostenol and treprostinil were associated with sustained clinical and hemodynamic improvements in patients with PAH. Although both bosentan and ambrisentan improve the 6-min walking distance test and the WHO functional class, ambrisentan seems to have a better safety profile compared with bosentan regarding the risk of increase in hepatic transaminases. However, ambrisentan shows a higher frequency of other adverse events compared with bosentan such as nasal congestion, peripheral edema and headache. Once-daily dosing of ambrisentan compared with twice-daily dosing of bosentan may favor the patient's compliance. Macitentan does not seem to have an efficacy profile superior to sildenafil and ambrisentan. However, there is also a low risk of liver enzyme increase associated with the treatment with macitentan, and headache, nasopharyngitis and anemia are the most commonly reported adverse events. Clinical trials demonstrated the efficacy of sildenafil and tadalafil in improving 6-min walking distance test and WHO functional class. Flushing, dyspepsia and diarrhea were the most frequent adverse events in patients treated with sildenafil, while headache, myalgia and flushing were the most frequent adverse events in those receiving tadalafil. Furthermore, once-daily dosing of tadalafil compared with three times daily of sildenafil may favor the patient's compliance. The use of inhaled iloprost plus sildenafil in patients with severe PAH and WHO functional class III and class IV is also effective. Nevertheless, iloprost requires multiple daily nebulizations up to 15 min each and may induce cough, flushing, jaw pain and headache. Epoprostenol is considered the most effective approved therapy for severe PAH in WHO functional class III and class IV. Treprostinil may be considered a valid alternative therapeutic regimen for PAH patients not requiring more intensive treatment. Combination regimens (i.e., bosentan plus epoprostenol, bosentan plus tadalafil, bosentan plus sildenafil, ambrisentan plus spironolactone) may be clinically beneficial in PAH. Imatinib, a tyrosine kinase inhibitor agent used for the treatment of chronic myelogenous leukemia, inhibits PDGF which acts as a smooth muscle mitogen, responsible for pulmonary arterial remodeling. Nevertheless, although imatinib appeared to be effective in treating PAH, the drug was withdrawn from the market worldwide in early 2013, due to serious adverse events such as subdural hematomas. Elevated serum TNF-α level was observed in patients with PAH secondary to chronic thromboembolic disease and connective tissue disease; it promotes the progression of the endothelial dysfunction and favors the development of PAH inhibiting pulmonary artery smooth muscle cell-pyruvate dehydrogenase activity. The administration of TNF-α inhibitors reduces the systemic inflammation in patients with chronic immune-mediated diseases and improves the endothelial function, decreasing the risk of PAH progression. Therefore, TNF-α inhibitors may be considered potential therapeutic agents for the therapy of PAH. Prospective clinical trials are required to further characterize these findings. Although TNF-α inhibitors are generally well tolerated, the physicians should take into account the risk of adverse events, such as opportunistic infections, infusion and injection-site reactions. Appropriately designed clinical trials are needed to evaluate the efficacy of new drugs acting on different therapeutic targets (i.e., growth factors, cytokines) to improve the pharmacological baggage and the therapeutic response.

Declaration of interest

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