Review

Pulmonary hypertension: a correct diagnosis for a suitable therapy in scleroderma patients

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ABSTRACT

Systemic sclerosis (SSc) is a heterogeneous disorder characterised by dysfunction of the endothelium and dysregulation of fibroblasts, resulting in excessive production of collagen, and abnormalities of the immune system. Progressive fibrosis of the skin and internal organs is a pathologic hallmark of the disease, resulting in major organ damage and failure. Pulmonary hypertension (PH) is frequent in patients with SSc and, pulmonary arterial hypertension (PAH) represents one of the main causes of death. PH is not a specific disease, but a haemodynamic condition characterised by a mean pulmonary pressure ≥25mmHg. In SSc, because of the great variability in clinical manifestation, it is possible to identify pulmonary hypertension due to left heart disease, PH due to respiratory disease or pulmonary arterial hypertension. The knowledge of PH and the right diagnosis are crucial to assess the most appropriate therapeutic strategy. In this article, the new classification criteria of PH have been examined taking into account the SSc clinical evolution and focusing on the different underlying pathogenetic mechanisms.

Introduction

Pulmonary hypertension (PH) is not a specific disease, but a haemodynamic condition defined by a mean pulmonary arterial pressure, at right heart catheterisation ≥25 mmHg (1).

PH was previously classified into two categories: primary PH or secondary PH, according to the presence of identified causes or risk factors (2). Since the second World Symposium on PH, held in Evian in 1998 (3), a clinical classification was established in order to define different categories of PH, sharing similar pathological findings, similar haemodynamic characteristics and similar management. Five groups of disorders that cause PH were identified: pulmonary arterial hypertension (PAH-Group 1); PH due to left heart disease (Group 2); PH due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic pulmonary hypertension (CTEPH-Group 4); and PH due to unclear multifactorial mechanisms (Group 5) (4). Subsequently, further changes were carried out, reflecting some progresses in the understanding of the disease. The current clinical classification of PH is now well accepted and widely used in the daily practice of PH experts (4).

Systemic sclerosis (SSc) is a heterogeneous disorder characterised by dysfunction of the endothelium, dysregulation of fibroblasts resulting in excessive production of collagen, and abnormalities of the immune system (5). Progressive fibrosis of the skin and internal organs is a pathologic hallmark of the disease, resulting in major organ damage and failure, thus explaining the high morbidity and early death (6).

The natural evolution of SSc induces the development of different kinds of PH. Recently, a cross-sectional, international study (DETECT study), conducted in 62 experienced centers from North America, Europe and Asia on 466 adults with SSc, showed that 31% of patients were affected by PH: in particular, 19% belonged to WHO group 1 because affected by PAH, 6% belonged to WHO group 2 because of a left heart disease and 6% belonged to WHO group 3 because of a lung disease. No patients were found belonging to groups WHO 4 and 5 (7). DETECT study involved scleroderma patients with a disease duration >3 years from first non-Raynaud symptom and a predicted DLCO <60%. It means that this kind of patients had higher probability to develop pulmo-

nary hypertension. However, this study showed the distribution of the different forms of pulmonary hypertension in scleroderma population. About our country, in a recent study, Iudici *et al*. showed that prevalence of PAH (3.1%) and post-capillary PH (1.4%) was lower than Anglo-Saxon cohorts (8).

The different forms of PH show different pathological mechanisms, as follows:
PAH (Group 1). It is defined by a mean pulmonary arterial pressure at right heart catheterisation ≥25 mmHg, with a normal pulmonary capillary wedge pressure (≤15 mmHg). It is very important to highlight that values between 21 and 24 mmHg are not considered normal, even if this cohort of patients has not been widely studied. One subset is represented by SSc patients, in whom the presence of "borderline" pressure is associated with a high risk to develop PAH (9). In these patients we could find normal systolic pulmonary arterial pressure at rest, but pathologic V'O$_2$/HR slopes during exercise, which represent high risk to develop PAH (10). Increased pulmonary artery pressure is due to sustained vasoconstriction, excessive pulmonary vascular remodelling and in situ thrombosis, which leads to increased vascular resistance (11). The contributing factors likely involve accumulation of multiple events, on top of a genetic predisposition background. These factors involve vasoconstrictive and pro-remodelling processes, including inflammatory, procoagulant, antiapoptotic, and autoimmune mediators, cell–cell and cell–matrix interactions, and environmental factors over time (12). One of the most important mediator in the vascular remodelling is endothelin-1 (ET-1). ET-1 is produced by endothelial cells, and it induces vasoconstriction in contrast to prostaglandin I$_2$ (PGI$_2$) and nitric oxide (NO), in order to maintain the vascular tone. In SSc patients and in PAH patients, it is possible to observe an abnormal increase of ET-1 and a decrease of PGI$_2$ and NO (13). In physiological condition, ET-1 binds two receptors called ET$_A$, prevalently expressed on blood vessels muscle cells, and ET$_B$, mainly expressed on the endothelial cells. ET-1 binds ET$_A$ and induces vasoconstriction;

at the same time it binds ET$_B$ inducing vasodilation (14). In PAH patients and usually in SSc patients, it is possible to observe a different expression of the ET-1 receptors: ET$_A$ receptors are expressed as usual, while ET$_B$ receptor are down regulated on endothelial cells and up-regulated on muscle cells (15). It is not well established if this condition is genetically pre-defined or if it is due to a receptor's clearance impairment. In any case, the result is a vascular remodelling (13-16). ET-1, binding ET$_B$ receptors expressed in muscles cells, induces an uncontrolled cell proliferation resulting in vessel obliteration (13-16). The consequence is an increase of pulmonary vascular resistance and an increase of PAH. Although the initial damage in PAH involves the pulmonary vasculature, survival of PAH patients is closely related to right ventricular (RV) function (17). PAH induces RV pressure overload, which activates RV wall stress with consequent myocardial remodelling. At the beginning, it is an adaptive remodelling but then it becomes a maladaptive remodelling with dilatation and failure (18-20). The prevalence of PAH is well established only in scleroderma, and the rate of occurrence is estimated between 7% and 12% (21-22). The outcome for SSc patients with PAH remains poor and worse compared to other PAH subgroups. The 1-year mortality rate in patients with idiopathic PAH is approximately 15% (17) *versus* 30% in PAH-associated with scleroderma (23). Recent data suggest that in scleroderma early diagnosis and early treatment may improve long-term outcome (24).

The onset of PAH in SSc patients is on average 6.3±6.6 years after SSc diagnosis, and earlier onset is recorded in older patients (on average 58±12.5 years old). Limited systemic sclerosis (lSSc) seems to be a predisposing factor to PAH onset (25).

PH due to left heart disease (Group 2). The mechanisms responsible for the increase in pulmonary arterial pressure (PAP) are multiple and include the passive backward transmission of the pressure elevation (26). The onset could be the left ventricular systolic and diastolic dysfunctions, vascular disease, and congenital cardiomyopathies. In these con-

ditions, the transpulmonary pressure gradient and pulmonary vascular resistance (PVR) are within the normal range (27). In other circumstances, the elevation of PAP is greater than pulmonary wedge pressure; moreover an increase in PVR is also observed (post-capillary reactive or "out of proportion" PH) (28). The factors that lead to reactive (out of proportion) PH, so that the reason why some patients develop the acutely reversible vasoconstrictive or the fixed obstructive component or both are poorly understood (29, 30). A recent study showed that, in scleroderma patients, left ventricular systolic dysfunction is rare and it is more frequently observed in those with dSSc than with lSSc (31). In addition, other abnormalities are frequent: in particular, left ventricular hypertrophy was found in 22.6% patients and left ventricular diastolic dysfunction was observed in 17.7% (31). These conditions may induce PH, even if its prevalence is actually unknown (32).

PH due to lung diseases and/or hypoxaemia (Group 3). Hypoxic pulmonary vasoconstriction is a physiological phenomenon in which pulmonary arteries constrict in the presence of hypoxia, redirecting blood flow to alveoli with a higher oxygen content (6). This phenomenon might seem illogical at first, as low oxygen levels should theoretically lead to increased blood flow to the lungs, increasing gaseous exchange. This condition induces PH associated with a poor prognosis, due to a progressive right heart failure (33). However, in the majority of the patients with lung disease end/or hypoxemia, PH is mild to moderate and only a small number of patients develop severe PH (34). In SSc, the prevalence of pulmonary hypertension secondary to lung fibrosis is approximately 30% and it involves prevalently patients with diffuse disease (35). The treatment of this kind of PH is focused on management of the underlying lung disorder and hypoxia (36).

Diagnosis of pulmonary hypertension

A correct diagnosis is essential because there are specific therapeutic approaches that apply only to PAH while for the other forms of PH it is possible to treat

hypertension by addressing the etiologic condition, for example improving left heart or lungs functionality.

The evaluation process of a patient with suspected PH requires a series of investigations aiming at: confirming the diagnosis; clarifying the clinical group of PH and the specific aetiology within the PAH group; evaluating the functional and haemodynamic impairment (Fig. 1) (37). The diagnostic process starts with the identification of the most common clinical groups of PH (group 2 left heart disease and group 3 lung diseases), excluding group 4 CTEPH and the rare conditions in group 5, and recognising the different PAH types in group 1. Transthoracic echocardiography is the first step of instrumental analysis process, very useful for screening, bat not for definitive diagnosis. It provides several variables which correlate with right heart haemodynamics (including PAP), and it should always be performed in the case of suspected PH. The estimation of PAP is based on the peak velocity of the jet of tricuspid regurgitation. The simplified Bernoulli equation describes the relationship between tricuspid regurgitation velocity and the peak pressure gradient of tricuspid regurgitation: *tricuspid regurgitation pressure = 4 x (tricuspid regurgitation velocity)^2*.

This equation can estimate PA systolic pressure taking into account right atrial pressure:

PA systolic pressure = tricuspid regurgitation pressure + estimated right atrial pressure. Right atrial pressure can be evaluated based on the diameter and respiratory variation of the inferior vena cava, although a fixed value of 5 or 10 mmHg is often assumed. When tricuspid regurgitation velocity is between 2.9–3.4 m/s, PA systolic pressure will be 37–50 mmHg and, either with or without additional echocardiographic variables, PH is possible (20). If tricuspid regurgitation velocity is >3.4 m/s, PA systolic pressure will be >50 mmHg and, either with or without additional echocardiographic variables, the diagnosis is PH. The second step defines the clinical group. If transthoracic echocardiography values are suggestive of PH, using the same tool and usual electrocardiogram, the same operator can evaluate the left heart involvement in order to confirm or to exclude the PH Group 2. Pulmonary function tests and arterial blood gases will identify the contribution of underlying airway or parenchymal lung disease (Group 3). Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the

range of 40–80% predicted) and mild to moderate reduction of lung volumes (33). Peripheral airway obstruction can also be detected. Arterial oxygen tension is normal or only slightly lower than normal at rest and arterial carbon dioxide tension is decreased because of alveolar hyperventilation (37). COPD, as a cause of hypoxic PH, is diagnosed on the evidence of irreversible airflow obstruction together with increased residual volumes, reduced diffusion capacity for carbon monoxide and normal or increased carbon dioxide tension. A decrease in lung volume, together with a decrease in diffusion capacity for carbon monoxide, may indicate a diagnosis of interstitial lung disease. The severity of emphysema and of interstitial lung disease can be diagnosed using high-resolution computed tomography (CT). If clinically suspected, oximetry or polysomnography screening overnight will exclude significant obstructive sleep apnoea/hypopnea. High-resolution computed tomography (HRCT) provides detailed views of the lung parenchyma, and facilitates the diagnosis of interstitial lung disease and emphysema (33).

The exclusion of left heart disease and lung involvement leads to a suspect of thromboembolism and to ventilation/perfusion lung scan, which is still the screening method to choose for chronic thromboembolic pulmonary hypertension (CTEPH) because of its higher sensitivity than CT (38). It is important to underline that CTEPH is not common in SSc patients. If ventilation/perfusion lung scan results negative, the last possibility is a diagnosis of PAH. Right heart catheterisation (RHC) is mandatory to confirm the diagnosis of PAH and to assess the severity of the haemodynamic impairment.

Recent data suggest that in PAH SSc patients, early diagnosis and early intervention may improve long-term outcome (39). Echocardiography screening for the detection of PH has been recommended in asymptomatic patients with the scleroderma spectrum of disease (40). Compared to patients in routine clinical practice, PAH screening programs in SSc are able to identify patients with milder forms of the disease, allowing earlier management and better
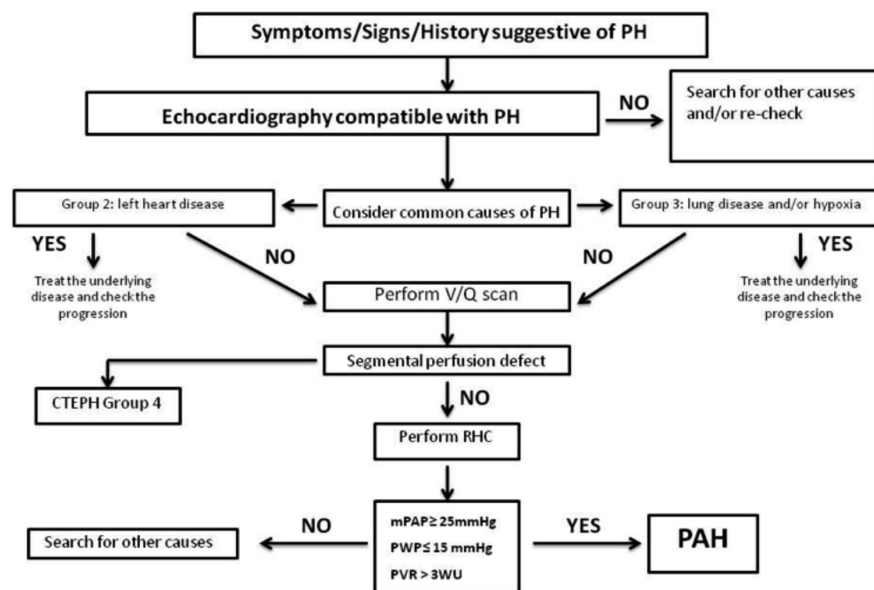
Fig. 1. Diagnostic approach to pulmonary hypertension. PH: pulmonary hypertension; V/Q: ventilation/perfusion; RHC: right heart catheter; mPAP: mean pulmonary artery pressure; PWP: pulmonary wedge pressure; PVR: pulmonary vascular resistance: WU: wood units.

results. Despite correct management, after 8 years since treatment initiation only 17% of the patients treated after symptoms onset (8 years) are alive, while patients with PAH identified by screening have 64% survival (24). Unfortunately, transthoracic echocardiography can fail. Recently, the cross-sectional, international study DETECT showed that the 7.1% of SSc-PAH patients (diagnosis through RHC) have undetectable tricuspid regurgitation, and the 35.7% of SSc-PAH patients (diagnosis through RHC) have a tricuspid regurgitation <2.8 m/sec, a value under the diagnosis threshold (7). In order to identify the missing patients, in the same study, a 2-step diagnostic approach has been added, involving SSc patients with DLCO<60% and with disease duration >3 years (7). The first step is a simple screening test, aimed at identifying the presence of telangiectasia, anticentromere antibodies, right axis deviation on electrocardiogram, low DLCO and serum biomarkers (urate and N-terminal pro–B-type natriuretic peptide [NT-proBNP]). All these features describe patients with possible PAH, without an echocardiogram approach, and the sensitivity of PAH presence is 97%. Step 2 takes into account echocardiography with tricuspid regurgitation jet and, most importantly, right atrium area evaluation (sensitivity 99%). If the nomogram indicates high probability for PAH, a RHC should be performed in order to confirm the diagnosis. With this algorithm, the number of missed PAH diagnosis is 4%, compared to 29% with the echocardiography-based approach recommended in the current European Respiratory Society/European Society of Cardiology guidelines, thus suggesting that using a broader panel of diagnostic tools provides more reliable information than echocardiography alone (41). The DETECT algorithm is not yet validated in patients with DLCO >60% (37).

Scleroderma is a systemic disease, able to involve heart, lungs, and vessels, so it is possible to have different forms of PH in the same patient (9). Despite the prevalence of this "mixed" condition is unknown, it is very important to make an appropriate diagnosis in order to use the best pharmacological approach.

The key to the problem is to understand if the pulmonary artery pressure values are proportionate or disproportionate compared to the underlying disease. In the last publication of the proceedings of the 5th World symposium on pulmonary hypertension, the concept of "out of proportion" is better identified than in the past ESC/ERS PH guidelines (3). The current haemodynamic definition of PH secondary to left heart disease combines a mean pulmonary artery pressure mPAP≥25mmHg, a pulmonary artery wedge pressure PAWP>15 mmHg, and a normal or reduced cardiac output (CO). In order to understand if the PH is completely post capillary or there is a pre-capillary component, it is possible to use the Diastolic Pressure Difference (DPD) defined as *diastolic PAP - mean PAWP*. Thanks to this data it is possible to define *Post capillary Hypertension when there is PAWP >15 mmHg and DPD<7 mmHg; combined Pre/Post capillary Hypertension when PAWP >15 mmHg and DPD>7 mmHg* (78). SSc patients occasionally develop pulmonary fibrosis and PH, but they can also develop PAH. The main issue is still to understanding if PH originates from lung disease (Group 3) or from vascular remodelling (Group 1). In this sense PFT or HRCT estimates of ILD extent are likely not enough to reliably distinguish between PAH versus PH-ILD in this patients (42). In order to overcome the term "out of proportion", the Nice proceedings 2013 indicates this new definition (Table I).

In patients with both lung disease and PAH, the use of PAH-approved drug may be considered through monitoring of gas exchange and inclusion in prospective registries. Gas exchange may be found to be deteriorated, because of interference with the hypoxic vasoconstriction, or it may be improved, because of normoxic vasodilatation and higher central venous oxygen saturation upon drug inducing cardiac index (CI) increases (3).

Recently, a group of expert, using a systematic review and applying RAND/UCLA (University of California, Los Angeles) consensus methodology, recommended that all patients with SSc should be screened for PAH. In addi-

tion, patients with mixed connective tissue disease or other CTDs with scleroderma features (scleroderma spectrum disorders) should be screened for PAH. Moreover, it was recommended that screening pulmonary function tests (PFTs) with single breath diffusing capacity for carbon monoxide, transthoracic echocardiogram, and measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) should be performed in all patients with SSc and scleroderma spectrum disorders. In patients with SSc and scleroderma spectrum disorders, transthoracic echocardiogram and PFTs should be performed annually. The full screening panel (transthoracic echocardiogram, PFTs, and measurement of NT-proBNP) should be performed as soon as any new signs or symptoms are present (43).

Treatment of pulmonary arterial hypertension

Only for pulmonary arterial hypertension (Group 1) is it possible to have a specific treatment, able to act on the vascular disease. PAH pharmacological approach starts from pathophysiological knowledge, therefore the aims of the treatment are to correct endothelial dysfunction, to antagonise the ET-1 action and to enhance PGI2 and NO activity.

The complexity of the treatment algorithm for PAH has progressively increased since the 2nd World Symposium on Pulmonary Hypertension in Evian (France) in 1998 when, apart from calcium channel blockers (CCBs) for vasoreactive patients, the only approved therapy was epoprostenol administered by continuous intravenous infusion. Five years later, at the 3rd WSPH held in Venice (Italy) in 2003, the treatment algorithm had expanded to 5 compounds belonging to 3 pharmacological classes, prostanoids, endothelin receptor antagonists (ERA), and phosphodiesterase type 5 inhibitors (PDE-5i), and included 4 different routes of administration (oral, inhaled, subcutaneous, and intravenous). In 2008, the 4th WSPH was held in Dana Point (California) and confirmed the same pharmacological approach (3). Although this progress in pharmacotherapy has been associated with a reduction of morbidity and mor-

Table I.

Underlying lung disease	mPAP ≥25 and <35 mm Hg at rest	mPAP ≥35 mm Hg at rest
COPD with FEV1 ≥60% of predicted / PF with FVC ≥70% of predicted / CT: absence of or only very modest airway or parenchymal abnormalities	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3)
COPD with FEV1 <60% of predicted / PF with FVC <70% of predicted / Combined pulmonary fibrosis and emphysema on CT	PH-COPD, PH-PF, PH-CPFE No data currently support treatment with PAH-approved drugs	Severe PH-COPD, severe PH-PF, severe PH-CPFE

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume 1s; PF: pulmonary fibrosis; CT: computed tomography; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; FVC: forced vital capacity; CPFE: combined pulmonary fibrosis and emphysema.

tality in different meta-analyses, poor outcome still characterises patients with PAH (41).

Nitric oxide pathway
Impairment of NO synthesis and signalling through the NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway is involved in the pathogenesis of pulmonary hypertension.
Soluble guanylate cyclase stimulators: while PDE-5i such as sildenafil and tadalafil, enhance the NO–cGMP pathway slowing cGMP degradation, sGC stimulators enhance cGMP production and are potentially effective also in conditions in which endogenous NO is depleted (44, 45). Pre-clinical studies with sGC stimulators have shown antiproliferative and antiremodelling properties in various animal models. Riociguat has a dual mode of action, acting in synergy with endogenous NO and also directly stimulating sGC independent of NO availability (46). An RCT [PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial)] in 443 PAH patients (44% and 6% on background therapy with ERA or prostanoids, respectively) treated with riociguat (up to 2.5 mg 3 times daily) has shown favourable results on exercise capacity, haemodynamics, WHO-FC, and time to clinical worsening. The increase in exercise capacity was also demonstrated in patients on background therapy. The most common serious adverse event in the placebo group and the 2.5 mg group was syncope (4% and 1%, respectively)

(46). The combination of riociguat and PDE-5i is contraindicated due to hypotension and other relevant side effects detected in the open-label phase of the PATENT-plus study. Riociguat is approved by the FDA and EMA for PAH and chronic thromboembolic pulmonary hypertension (CTEPH) (44).
PDE-5: inhibition of the cyclic guanosine monophosphate degrading enzyme PDE-5 results in vasodilation through the NO/cGMP pathway at sites expressing this enzyme (47, 48). Since the pulmonary vasculature contains substantial amounts of PDE-5, the potential clinical benefit of PDE-5i has been investigated in PAH (46, 47). In addition, PDE-5i exert antiproliferative effects (47, 48). PDE-5i sildenafil and tadalafil, approved for the treatment of erectile dysfunction, cause significant pulmonary vasodilation. Sildenafil is an orally active, potent, and selective PDE-5i. Five RCTs in PAH patients treated with sildenafil have confirmed favourable results on exercise capacity, symptoms, and/or haemodynamics (49).
The approved dose of sildenafil is 20 mg three times daily. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis) (50).
Sildenafil is approved for PAH patients (51). Tadalafil is a once daily dispensed, selective PDE-5i (52). An RCT (PHIRST [Pulmonary arterial Hypertension and ReSponse to Tadalafil] trial) in 406 PAH patients (53% on background bosentan therapy) treated with tadalafil (2.5, 10, 20, or 40 mg once daily) has shown favourable results on

exercise capacity, symptoms, haemodynamics, and time to clinical worsening at the highest dose (44, 51, 52). The side effect profile was similar to that of sildenafil. Tadalafil is approved for PAH patients (52).

Prostacyclin pathway
Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilation of all vascular beds (53); in addition, it is an inhibitor of platelet aggregation and also appears to have both cytoprotective and antiproliferative activities (53). Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH, as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries (54, 55).
The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues (44).
Epoprostenol (synthetic prostacyclin) has a short half-life (3 to 5 min) and it is stable at room temperature for only 8 h requiring cooling, continuous administration by means of an infusion pump and a permanent tunneled catheter (56). The efficacy of continuous intravenous (IV) administration of epoprostenol has been tested in 3 unblinded RCTs in patients with idiopathic PAH and in those with PAH associated with the scleroderma spectrum of diseases. Epoprostenol improves symptoms, exercise capacity, and haemodynamics in both clinical conditions; moreover it is the only treatment able to reduce mortality in idiopathic PAH, as reported in a randomised study (57). The meta-analysis for total mortality of the 3 epoprostenol RCTs, performed with the Mantel-Haenszel and the Peto fixed-effect methods, showed a relative risk (RR) reduction of 70% and 68% respectively (44). Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Intravenous epoprostenol is approved for PAH patients. A thermostable formulation of epoprostenol is actually approved in the United States, Canada, Japan and in most of the European countries and does not require cooling packs to maintain stability beyond 8 to 12 h (57-58).

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at room temperature. These characteristics allow administration of the compound by the IV as well as the subcutaneous and oral route (44). The subcutaneous administration of treprostinil can be accomplished by a microinfusion pump and a small subcutaneous catheter. The effects of treprostinil in PAH were studied in an RCT and showed improvements in exercise capacity, haemodynamics, and symptoms. Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8% of cases on active drug and limiting dose increase in an additional proportion of patients (59).

An RCT (TRIUMPH [inhaled TReprostInil sodium in Patients with severe Pulmonary arterial Hypertension]) with inhaled treprostinil in PAH patients on background therapy with either bosentan or sildenafil, showed improvements in 6MWD by 20 m at peak dose, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and quality-of-life measures (60).

Intravenous treprostinil is approved in the United States and European Union in patients with PAH who cannot tolerate the subcutaneous administration (based on bioequivalence) (61). Inhaled treprostinil is approved for PAH in the United States (44).

Inhaled Iloprost is a stable analogue of PGI_2 approved for PAH treatment. It is administered by inhalation, thus avoiding most of the systemic side effects associated with intravenous or subcutaneous prostanoid infusion (44). Two randomised controlled 12-weeks trials in patients with PAH have demonstrated efficacy and favourable safety profile as monotherapy (the AIR trial) and in combination with bosentan (STEP study) (62, 63). Inhaled Iloprost is approved in Europe, US, Canada and Japan (64).

Endothelin pathway

Activation of the endothelin system has been demonstrated in plasma and lung tissue of PAH patients (65). Although it is not clear if the increases in endothelin plasma levels are a cause or a consequence of PH, these data support a prominent role for the endothelin system in the pathogenesis of PAH (66). ET-1 exerts vasoconstrictor and mitogenic effects by binding two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, ET_A and ET_B receptors (67). ET_B receptors are also present in endothelial cells and their activation leads, in physiological conditions, to the release of vasodilators and antiproliferative substances, such as NO and prostacyclin that may counterbalance the deleterious effects of ET-1. In pathological condition, ET_B receptors cause vascular remodelling, leading to vessel narrowing (65, 67).

Ambrisentan is a nonsulfonamide, propanoic acid class, ERA that is selective for the ET_A receptor (68). It has been evaluated in a pilot study and in two large RCTs (ARIES [Ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled, multicentre, Efficacy Study]-1 and -2), which have demonstrated efficacy on symptoms, exercise capacity and haemodynamics of patients with idiopathic PAH, PAH associated with connective tissue disease and human immunodeficiency virus infection (69). Ambrisentan has been approved for the treatment of WHO-FC II and III patients. The incidence of abnormal liver function tests range from 0.8% to 3%. An increased incidence of peripheral edema has been reported with ambrisentan use. Ambrisentan is approved for PAH patients (44).

Bosentan is an oral active dual ET_A and ET_B receptor antagonist and the first molecule of its class to be synthesised (44). Bosentan has been evaluated in PAH (idiopathic, associated with connective tissue disease and Eisenmenger's syndrome) in five RCTs (Study-351, BREATHE [Bosentan Randomised trial of Endothelin Antagonist THErapy]-1, BREATHE-2, BREATHE-5, and EARLY [Endothelin Antagonist trial in mildly symptomatic pulmonary arterial hypertension patients]), which showed improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening (70-73). Increases in hepatic aminotransferases occurred in approximately 10% of the subjects, but were found to be dose-dependent and reversible after dose reduction or discontinuation. For these reasons, liver function testing should be performed monthly in patients receiving bosentan. Bosentan is approved for PAH patients WHO-FC II and III (44).

Disease progression occurs despite the availability of drugs that are specific for the disorder. Endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin and its analogues have been approved for the treatment of pulmonary arterial hypertension and adopted clinically on the basis of short-term trials (12 to 16 weeks) showing improvements in exercise capacity as measured by the distance walked in 6 minutes (74). However, current guidelines suggest that the primary endpoint in phase 3 trials of new treatments for pulmonary arterial hypertension should be morbidity and mortality (75). The dual endothelin-receptor antagonist macitentan was developed by modifying the structure of bosentan to increase efficacy and safety (44). Macitentan is characterised by sustained receptor binding and enhanced tissue penetration (43). In the SEPAPHIN study (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome), the first large-scale RCT, it has been investigated whether long-term treatment with macitentan reduces morbidity and mortality among patients with pulmonary arterial hypertension. 742 PAH patients were treated with 3 or 10 mg macitentan as compared with placebo for a blind median observation of 115 weeks. The primary endpoint was the time from the initiation of treatment, to the first occurrence of a composite endpoint compound by death, atrial septostomy, lung transplantation, initiation of treatment with intravenous prostanoids, or worsening of PAH. Macitentan significantly reduced this composite endpoint of morbidity and mortality among patients with PAH, and also increased exercise capacity. Benefits were shown both for patients who had not received treatment previously and for those receiving background therapy for PAH.

While no liver toxicity was shown, reduction in blood haemoglobin to 8 g/dl was observed in 4.3% of patients receiving 10 mg of macitentan (76). In conclusion, PH is a haemodynamic condition able to induce right heart failure (77). SSc patients can develop three kinds of PH: pulmonary hypertension due to left heart disease, pulmonary hypertension due to lung disease and pulmonary arterial hypertension due to vascular remodelling (7). It is important to know that there is a different prognosis for the different kinds of PH. PH due to lung disease and left heart disease shows a slowly evolution of the right heart failure, while untreated SSc-PAH patients, have an extremely poor prognosis with a median survival of 12 months following diagnosis (78). Scleroderma patients should be subjected to echocardiographic screening every year independently of the symptoms (24); patients with normal or undetectable tricuspid jet, with DLCO ≤60% and a conserved lung functionality, should be screened through the DETECT nomogram (7).

It is very important to identify as soon as possible PAH in order to immediately initiate a suitable pharmacological treatment (24), in particular early detection of less severe patients should be a priority (79). We believe that the progress in pharmacotherapy will change the clinical course of the disease.

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