Pulmonary arterial hypertension and rheumatic diseases—from diagnosis to treatment

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Survival rates in pulmonary arterial hypertension (PAH) associated with rheumatic diseases, in particular connective tissue diseases such as systemic sclerosis, are even lower than in idiopathic PAH. These low survival rates highlight the need for early diagnosis and treatment in these patients. Transthoracic Doppler-echocardiography is most often used for diagnostic screening of patients at risk. Other screening tests are serum pro-brain-natriuretic peptide (pro-BNP) and diffusion capacity for carbon monoxide (DLCO), which appear to be changed early in the course of the PAH associated with connective tissue diseases. The diagnosis needs to be confirmed by right heart catheterization, which is recommended in all patients with suspected PAH. Besides the conventional background therapy, a number of specific therapies have been evaluated in randomized controlled trials in the recent years. These therapies include prostacyclins and prostacyclin analogues, endothelin-receptor antagonists and phosphodiesterase-5 inhibitors. Response to treatment can be measured by exercise capacity (e.g. 6 min walk distance) and pro-BNP, although certain aspects of validation for these outcome measures are lacking in PAH associated with connective tissue diseases.

Introduction

Pulmonary arterial hypertension (PAH) is haemodynamically defined as a resting mean pulmonary arterial pressure ≥ 25 mmHg with a normal pulmonary capillary wedge pressure of ≤ 15 mmHg on right heart catheterization. According to the clinical classification of Third World Symposium on PAH held in Venice in 2003, the diagnosis of idiopathic PAH (IPAH) is made, when no other risk factor can be identified [1]. However, PAH can occur in a variety of other conditions and circumstances including a number of rheumatic diseases. In this regard, systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematoses (SLE) and to a lesser extent rheumatoid arthritis, dermatomyositis and primary Sjögren’s syndrome are associated with PAH. The reported prevalence for PAH in connective tissue diseases shows a wide range depending on the criteria used for diagnosis, on the methods used to confirm the diagnosis and on the patient population used for the studies. In a recent study in community-based rheumatology practices in the US, the prevalence of PAH was 13.3% in patients with SSc and MCTD as analysed by echocardiography [2]. This was confirmed in a British study that used haemodynamic confirmation by right heart catheterization after a diagnostic algorithm and that found a prevalence of 12% in SSc patients [3]. PAH appears to be less common in SLE, however, well-controlled prospective trials are missing and retrospective studies reported a prevalence of up to 14% as assessed by echocardiography [4]. In rheumatoid arthritis, dermatomyositis and primary Sjögren’s syndrome, clinically significant PAH appear to be a rare manifestation. PAH is a major cause of morbidity and mortality in connective tissue diseases. While 3 yr survival rates after diagnosis in IPAH are as low as 48%, these alarming numbers are even worse in PAH associated with SSc. Median survival in untreated patients is only 12 months, and the risk of death is nearly tripled [5, 6]. This survival rate is in the range of some malignant diseases and highlights the need for early diagnosis and treatment.

The diagnostic approach

The diagnosis of PAH in connective tissue diseases requires the clinical awareness of symptoms associated with PAH, the use of screening tools and the confirmation of the diagnosis by independent diagnostic procedures. In addition, outcome measures need to be defined to assess the response to treatment in these patients.

Clinical symptoms: be aware!

As with PAH in general, clinical symptoms of PAH in connective tissue diseases are unspecific. The cardinal sign is shortness of breath on exertion, but patients often do not report this symptom until asked specifically. Additional symptoms include among others fatigue, weakness, angina, syncope and pre-syncope and abdominal distension [1]. However, these symptoms are late manifestations of the disease and haemodynamic as well as morphological changes in the pulmonary vasculature occur long before these manifestations are detectable. The same accounts for physical findings of PAH such as peripheral oedema, jugular vein distension, accentuated pulmonary component of S2, hepatomegaly and ascites.

Use of screening tools? Yes!

The lack of early clinical and physical signs is the rationale for the regular use of screening tools in patients with connective tissue diseases. This regular, e.g. yearly, use of screening tools is questioned by some authors, because approved medications are currently not available for these early stages of PAH associated with connective tissue diseases and thus an early detection would have no consequences for therapy [1]. However, based on the pathogenesis of the disease and the experience from animal models, early intervention is likely to prevent the progression of...
the disease and respective therapeutic studies are currently under way. We, therefore, recommend the use of screening tools in connective tissue disease patients unless studies show that early intervention does not improve the outcome of these patients.

Among the diagnostic procedures that can be used for screening, transthoracic Doppler-echocardiography (TTE) is the most widely used non-invasive screening test. TTE estimates the right ventricular systolic pressure (RVSP), which is equivalent to the pulmonary artery systolic pressure in the absence of pulmonary outflow obstruction, by measuring the systolic regurgitant tricuspid flow velocity [1]. Echocardiography is also important to address other causes of PAH, because it can recognize left heart valvular and myocardial diseases responsible for pulmonary venous hypertension. However, while TTE is an excellent screening tool for PAH, it has limitations: the RVSP increases with age and body mass index and is reported to be 28 ± 5 mmHg with a range of 15–57 mmHg [7]. Thus, assuming a diagnosis of PAH with a RVSP of ≥40 mmHg, a number of false positive diagnosis will be made [8]. Moreover, TTE tends to underestimate RVSP in patients with severe PAH and to overestimate RVSP in patients with normal pressures or less severe PAH [9]. Additional diagnostic screening tools might include biomarkers such as BNP and pro-BNP, which appear to be increased already in early disease stages and correlate well with haemodynamic measures and survival [10, 11]. ECG and chest radiography are less sensitive and specific for the detection of PAH. A decrease in the diffusion capacity for carbon monoxide (DLCO) without concomitant changes of restrictive parameters has been identified as one of the strongest risk factors for the later development of PAH in patients with SSC [6, 12].

Confirmation of the diagnosis

Right heart catheterization is the gold-standard to confirm the diagnosis of PAH suspected on echocardiography and is recommended in all patients with PAH [1, 9] before the initiation of specific therapies. Right heart catheterization is also used to directly measure the severity of haemodynamic changes and to test the vasoreactivity of the pulmonary circulation by using short-acting pulmonary vasodilators (see subsequently). Additional diagnostic tests have to be performed to exclude other causes of PAH that can occur in connective tissue diseases. This includes high-resolution CT for interstitial lung disease and ventilation and perfusion lung scan for chronic thromboembolic disease.

Outcome measures for treatment responses

Unfortunately, the measures of response to treatment for PAH remain limited. Endpoints most often used for clinical trials are exercise capacity measured by 6 min walk distance, pulmonary haemodynamics, clinical events and peak VO₂ [13]. However, some of these measures are not applicable for routine clinical use. For instance, right heart catheterization is an invasive diagnostic test important for the confirmation of the diagnosis, but is less adequate for repeated use to assess treatment responses. Based on the Omeract filter of truth, discrimination and feasibility for outcome measures, we currently recommend to measure 6 min walk distance and pro-BNP at baseline and regularly after treatment initiation [14]. Although these outcome measures lack certain aspects of validation in PAH associated with connective tissue diseases, they are easy to perform in daily clinical practice and are, therefore, feasible for the follow-up of such patients.

Therapeutic challenges

There is a general consensus about histopathological similarities among various forms of PAH, including IPAH and PAH associated with rheumatic diseases, leading to the assumption of shared pathogenetic mechanisms and therapeutic approaches.

Concerning the therapeutic approach, it is possible to split basic and general measures from treatments focused on the supposed main pathogenetic pathways leading to a significant imbalance between thrombogenic, mitogenic, proinflammatory and vasoconstrictive factors on the one hand and anticoagulant, antimitotic and vasodilating mechanisms on the other hand.

Basic and general therapies

Appropriate active lifestyle might be encouraged in patients affected with PAH, with particular caution for patients with advanced stages at increased risk for life-threatening syncope.

Pulse steroid therapy has been suggested as an effective treatment in PAH associated with connective tissue diseases and overlap syndromes, leading to an improvement of haemodynamic parameters and New York Heart Association (NYHA) functional class [15]. However, although intermittent pulse therapy with cyclophosphamide demonstrated efficacy on mild and moderate PAH associated with SLE [16], no controlled data are available about the efficacy on PAH associated with other autoimmune rheumatic diseases. This is in particular true for SSC, where it may be contraindicated for the enhanced risk of renal crisis in patients with the diffuse disease subset.

Considering hypoxaemia as a pulmonary vasconstrictor, supplemental oxygen should be used to maintain saturation up to 90%, obviously with a careful individual control.

Long-term anticoagulant therapy, associated with improved survival in IPAH [17], is still controversial for patients affected with PAH due to other causes, including autoimmune rheumatic diseases, because its efficacy has not been well-demonstrated by controlled trials and its relative risks and benefits should be evaluated on the individual basis.

Diuretic therapy, including aldosterone-antagonists, may produce effective clinical results by reducing the right ventricular preload.

Therapy with cardiac glycosides, although useful for refractory right ventricular failure and concomitant atrial arrhythmias, it is not considered a first therapeutic choice in PAH associated with rheumatic diseases.

Therapies targeting pathogenetic pathways

Long-term therapy with calcium-channel blockers (CCBs) has been for many years the most widely used vasodilating therapy. Nowadays, it is well-documented that this therapy is effective in IPAH in <10% of patients [18]. Patients responding to CCBs are identified by performing an acute vasodilator challenge with the use of short-acting agents, such as intravenous prostacyclin, adenosine or inhaled nitric oxide, during right heart catheterization. For this reason, all therapeutic guidelines indicate these invasive diagnostic procedures as mandatory before starting therapy with CCB agents that may also be complicated by systemic side effects. In addition, in PAH secondary to connective tissue diseases, the percentage of non-responders to CCBs is higher than in IPAH [19], thus reflecting a substantial non-efficacy of such therapy.

Agents with specific negative inotrope effects, such as verapamil, should be avoided. Angiotensin converting enzyme inhibitors demonstrated controversial results in PAH due to rheumatic diseases and their use is not included in the proposed therapeutic algorithm.
The recent advances in understanding the mechanisms leading to endothelial dysfunction in PAH allowed to identify three major pathogenetic pathways involving the following mediators: (a) prostacyclin, (b) endothelin-1, (c) nitric oxide (NO). Consequently, these mediators are modified by the new specific treatments.

Prostacyclin therapy

Prostacyclins are potent vasodilators. The introduction of continuous intravenous prostaglandin E2 (PGI2) therapy (epoprostenol) in the standardized treatment for PAH, either idiopathic or secondary to other causes, improved exercise capacity, quality of life and survival of these patients [20, 21]. Unfortunately, because of its short half-life, the continuous intravenous application is the only efficient route for drug administration and may generate several problems in terms of local and systemic side effects. For these reasons, more stable prostacyclin analogues have been developed that can be given by intravenous infusion (iloprost, treprostinil), subcutaneous injection or inhalation (treprostinil, iloprost). Many reports demonstrated their clinical and haemodynamic efficacy [22–25]. There is also an oral prostacyclin analogue available (Beraprost) that has been shown to improve functional capacity and haemodynamic parameters [26].

An interesting clinical report suggested the clinical efficacy of prostaglandin E1 (PGE1) infusion utilizing lipid microspheres as drug carriers. Lipid microspheres accumulate at sites of inflammation and vascular lesions thereby enhancing drug action and reducing side effects [27].

Endothelin-receptors antagonists

Endothelin-1 is a pleitropic molecule with vasoconstrictive effects that is increased in PAH. Bosentan was the first endothelin receptor antagonist (with affinity for both ET-A and ET-B receptors) approved in the EU and the USA for the treatment of IPAH and PAH associated with collagen vascular diseases and WHO functional class III (in the United States also WHO functional class IV). Selective oral endothelin-A receptor antagonists, such as Sitaxsentan and Ambrisentan, have been already utilized in the treatment of IPAH as well as PAH associated with connective tissue diseases. Controlled clinical trials demonstrated improvement of exercise capacity and haemodynamic parameters [28, 29], thus confirming the great therapeutic potential of orally active endothelin receptor antagonists that opened a new era in the treatment of PAH.

Nitric oxide pathway targeted therapy

Since many forms of PAH are associated with a defect of endothelium-dependent NO production, drugs interfering with the production of NO have been proposed as potential therapies. Although short-term inhalation of NO demonstrated pulmonary specific vasodilator effects in humans [30], its short half life and its potential systemic side effects allow its therapeutic use only in the short-term management of critically ill patients and not for a routinely treatment of PAH. However, its use is accepted in the context of diagnostic vasoreactivity testing. An alternative way is to increase the endogenous NO production by the inhibition of NO degradation. Specific phosphodiesterase-5 (PDE-5) inhibitors block the degradation of cyclic guanosine monophosphate (cGMP), which is the main cellular mediator of NO-induced pulmonary vasodilation. In fact, the PDE-5 inhibitor sildenafil demonstrated significant effects on exercise capacity as measured by 6 min walk test and WHO functional class as well as an improvement of haemodynamic parameters, without significant side effects related to the treatment [31]. Other specific PDE-5 inhibitors, such as vardenafil and tadalafil, differ in their kinetics of pulmonary vasorelaxation (most rapid effect by vardenafil), their selectivity for the pulmonary circulation (sildenafil and tadalafil, but not vardenafil) and their impact on arterial oxygenation (improvement with sildenafil only) [32].

Combination therapy

An attractive therapeutic approach is the combination of drugs with different mechanisms of action, with the objective to maximize their clinical benefit. Indeed, many recent report demonstrated the efficacy and good tolerability of combination therapy with prostanoids, endothelin receptor antagonists and PDE5 inhibitors in patients with severe PAH deteriorating under single-agent therapy [33–35]. This promising approach could be proposed not only for unresponsive case to single therapy but also as initial therapy.

Future directions

The growing knowledge about the pathogenetic mechanisms and the bad long-term prognosis in the majority of patients with PAH, in particular if associated with autoimmune systemic rheumatic disease, well explains the huge amount of new therapeutic approaches present in the literature, either on humans or in experimental models. Indeed, interesting reports have been published on the potential use of selective serotonin-reuptake inhibitors [36], vasoactive intestinal peptide [37], statins [38], BNP [39], selective antagonist of the platelet-derived growth factor receptor [40], anti-tumour necrosis factor (TNF)-α therapy [41], Rho-Kinase inhibitors [42], gene therapy [43, 44], sex hormones [45], selective potassium channel opener [46] and autologous haematopoietic stem cell transplantation [47]. Both basic and clinical researches are essential to improve our impact on the disease, and the possibility to achieve an early diagnosis and an effective therapy remains a big challenge for researchers and clinicians.

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