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Trends in pulmonary arterial hypertension

R. Souza and C. Jardim

Past decades have witnessed an increasing interest in the field of pulmonary arterial hypertension (PAH). The large number of publications related to PAH reflects this interest. As a result, in contrast to 15 yrs ago, there are now at least seven different drugs as specific therapy targeting the pulmonary circulation that are approved for use in the USA and European Union, with some of them also approved for use in Canada, Japan, Australia and in some countries in Latin America. These medications have proved to increase exercise capacity [1–5], haemodynamics [2, 3, 6], quality of life [7–9] and even survival [5]. Nevertheless, there is still room for further improvements, since the mortality rate remains significantly high [10, 11].

Haemodynamically, PAH is characterised by progressive increase in pulmonary vascular resistance, as a consequence of vascular remodelling within the pre-capillary territory, leading to right ventricular failure and, eventually, death [12]; numerically, this is translated to the presence of a mean pulmonary artery pressure >25 mmHg, with normal pulmonary artery occlusion pressure (<15 mmHg) [13]. This definition, although extremely important for the proper characterisation of a pre-capillary impairment, might be misleading when focusing on specific patients or, more properly, specific forms of PAH. The most recent published nomenclature for pulmonary hypertension date from 2003 [13], and despite the fact that it has been recently revised (at the International Symposium of Pulmonary Hypertension, held in Dana Point, CA, USA, in the first quarter of 2008) it still includes in group 1 (PAH) several diseases that share the haemodynamic profile of pre-capillary pulmonary hypertension but present a completely distinct clinical course, such as idiopathic PAH, scleroderma-associated PAH and portopulmonary hypertension [10, 14, 15]. This recognised and accepted limitation of the classification may be impossible to transpose at this moment; however, it raises the importance of clinical registries in enabling the recognition of different prognostic factors, clinical courses and even different responses to available therapies. Particularly, in what is presently considered to be a rare disease, putting this amount of data together in a registry is of major value.

Recently, many studies have concentrated their attention on the epidemiology of PAH, providing substantial data for the better knowledge of PAH, in the same manner that the National Institutes of Health registry did in the 1980s [16]. These studies vary in terms of quality of data (some are single centred, others lack routine use of right heart catheterisation for the appropriate diagnosis of PAH), but we now have data available from France [17], Scotland (UK) [18], Switzerland [19], China [20], USA [21] and Brazil [22].

It is noteworthy that, independent of the study, the majority of the patients are still diagnosed with more advanced disease (functional class III or IV); even considering that the initial symptoms of PAH patients are not specific, this is quite alarming and should reinforce the importance of programmes that aim to improve disease awareness by the medical population [23]. Most of the studies also reported that ~50% of PAH patients had idiopathic PAH.

Some of these studies also allowed the estimation of the PAH prevalence. The French registry [17] evidenced a prevalence of 15–25 cases per million adult inhabitants; similar data were also demonstrated in the Swiss registry (about 15.5 cases per million adult inhabitants) [19]. In Scotland [18], however, a much wider variation was seen: from 26 cases per million (when limiting the analysis to the data from expert centres only) to 52 cases per million (when considering national hospitalisation reports, which may have biased the quality of PAH diagnosis). Independent of the estimates, these data reinforce that, at least in Europe, PAH should still be considered a rare disease.

Although none of the studies was designed to properly evaluate first-line treatment, the USA-based registry from a single reference centre [21] and the Chinese registry [20] reported a high proportion of patients using calcium channel blockers, despite the relatively rare response to the acute vasodilator challenge. To what extent this directly reflects drug availability (especially in China), and the consequences of such conduct, are so far only matter of speculation.

It is also noteworthy to evaluate some of the differences between the registries. The most

AFFILIATIONS
Pulmonary Dept, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil.

CORRESPONDENCE
R. Souza
Pulmonary Dept
University of São Paulo Medical School
R. Afonso de Freitas 451 ap 112
São Paulo 04006-052
Brazil
Fax: 55 1130697202
E-mail: rogerio.souza@incor.usp.br

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interesting one is the proportion of HIV-associated PAH patients in the French and USA-based registry. In the French registry, ~6.2% of PAH cases were associated with HIV (of note is the 5.4% prevalence within the prevalent cases and 9.9% within the incident cases), while in the USA-based registry the proportion was ~1% (in both prevalent and in incident cases). This might be related to underestimation of the importance of HIV-associated PAH in terms of referral to this particular centre in the USA. Recent data from France have confirmed that the prevalence of PAH was 0.46% in HIV-infected subjects [24].

The data derived from two reference centres in Brazil [22], although lacking gold-standard diagnostic procedures, have raised the importance of national registries to identify regional characteristics that may prevent the direct extrapolation of international guidelines for diagnosis and treatment [25, 26]. About 30% of the PAH patients of those reference centres presented schistosomiasis-associated PAH, a clinical condition mainly restricted to developing countries. Schistosomiasis, together with sickle cell disease, may represent the most prevalent causes of PAH worldwide, also changing the idea of a rare condition to the concept of an unrecognised burden of PAH. A recent screening study has demonstrated a 4.6% prevalence of PAH in patients with hepatosplenic schistosomiasis [27]. Considering the estimate of 200 million people infected [28], from which 4–8% may develop hepatosplenic schisosomiasis [29], the number of patients expected to develop PAH is remarkable.

Recently, similar screening studies, based on initial echocardiogram followed by right heart catheterisation if any sign of pulmonary hypertension was identified, were performed in patients with sickle cell disease [30], systemic sclerosis [31, 32] or HIV [24]. Besides allowing the recognition of patients with better haemodynamic profile, as compared with previously described populations of established symptomatic disease, these screening programmes also allowed the identification of a significant proportion of patients with left heart disease, reinforcing the role of invasive haemodynamics for the appropriate diagnosis of PAH. In the French study of systemic sclerosis, ~8% of the 599 included patients presented with PAH; notably, echocardiographic evidence of left ventricular dysfunction was found in 18% of the cases [31]. Similarly, in sickle cell disease, ~46% of patients with pulmonary hypertension at right heart catheterisation presented with post-capillary disease [30]. These data strengthen the importance of adequate diagnostic algorithms and respecting regional characteristics, as well as the idea that different diseases within group 1 should be evaluated separately in terms of prognosis and treatment response, since they share the haemodynamic profile of pre-capillary impairment but certainly not the same pathophysiology, as a whole.

Along with screening programmes, the role of exercise testing performed during invasive haemodynamic monitoring has also been addressed as an attempt to unmask right ventricular dysfunction in patients with normal rest haemodynamics, and also to evaluate specific PAH treatment response. PROVENCHER *et al.* [33] have demonstrated that specific therapy in idiopathic PAH led to a better cardiac index at the peak pulmonary artery pressure during exercise, suggesting that exercise haemodynamic tests are more accurate for the prediction of improvements in exercise capacity in this subgroup of patients. TOLLE *et al.* [34], through invasive maximum cardiopulmonary exercise testing, have studied patients referred for exercise testing mostly due to dyspnoea of unknown aetiology. Their results support the concept that a subgroup of patients with exercise-induced pulmonary hypertension (and normal rest haemodynamics) does exist and may correspond to a intermediate step within the progressive process through which an individual develops PAH, passing from normal rest haemodynamics to established rest PAH. The same concept has been recently brought up [35], based on magnetic resonance imaging studies performed by LANKHAAR *et al.* [36], demonstrating that arterial compliance and resistance remains inversely related during the course of PAH, thus suggesting that increased arterial stiffness and, therefore, reduced compliance, may be the most important mechanical phenomenon at early phases in PAH development. TOLLE *et al.* [34], however, believe that dynamic pulmonary vasoconstriction and not decreased compliance is the main mechanism related to exercise-induced PAH. It may be that both mechanical behaviours are present to differing degrees. These studies have opened the possibility of finely evaluating mildly symptomatic patients and also determining the main haemodynamic mechanisms related to functional limitation in PAH patients, potentially allowing the use of more specific therapeutic approaches at early phases of the disease.

The benefit of earlier interventions in patients with mild PAH was not known until the recent trial published by GALIÈ *et al.* [37]. In this trial, a total of 185 PAH patients in New York Heart Association functional class II were followed for 6 months while receiving endothelin receptor antagonist (bosentan) or placebo. The results evidenced improvements in pulmonary vascular resistance and longer time to clinical worsening in the treated group. Nevertheless, the study did not show statistically significant improvements in 6-min walk distance, reinforcing the discussion about the validity of this submaximal test for the evaluation of patients with better preserved functional capacity. Equally important is the demonstration that these mildly symptomatic patients tend to deteriorate over time, clinically and haemodynamically [37]; although logical, this progressive deterioration had never been demonstrated in a controlled manner before and strengthens the rationale for treating even mildly to moderately symptomatic patients.

As mentioned earlier, specific treatment represented a significant improvement in the management of PAH. Patients have improved in terms of functional capacity, haemodynamics, quality of life and, at least in one controlled trial, better survival has also been demonstrated [1–9] (several other studies have also advocated improved survival but against historical and/or predicted survival [38–41]). Nevertheless, in overall terms, survival remains poor, even for the treated population [10]; none of the available treatments have demonstrated any perspective of cure for PAH, or even significant long-term reversibility and control of the disease. Combining drugs from the three different classes currently available for PAH management [11] seemed a natural approach in this regard. Combination therapy also goes toward the multiple-hits hypothesis, which reflects the several different pathways involved in the genesis of PAH, as recently suggested by a number of studies [42, 43], and that should be contemplated in any attempt of disease cure.

However, it is not necessarily the case that more is better. There is a clear risk of increasing drug toxicity, notwithstanding the increased costs that might derive from the use of multiple drugs. Furthermore, a class effect might also exist, meaning that patients may respond to one class of treatment better than to another, so that, instead of combination, changing therapy would be enough to reach some degree of improvement. This assumption may seem pessimistic but is not; it only emphasises the need for controlled studies in order to evaluate the safety and efficacy of combining available treatments. Fortunately, despite the widespread use of combination therapy in daily practice, investigators have been trying to demonstrate which combinations lead to better results while having an acceptable safety profile.

Until now, three double-blind randomised controlled trials regarding combination therapy have been published. The first randomised controlled trial was published in 2004 [44]; 33 patients were enrolled in the study, in which patients started treatment with epoprostenol associated to bosentan or placebo. The study was underpowered to reach the primary end-point, which was change in total pulmonary resistance. Moreover, two patients died in the epoprostenol/bosentan group during the study; if the limited sample size of the study did not allow any further interpretation about those deaths, at least a word of caution remained.

The second randomised controlled trial was published in 2006 [45] and evaluated the addition of iloprost in patients under treatment with bosentan monotherapy; therefore, a different design was adopted, compared with the first randomised controlled trial (the epoprostenol/bosentan trial [44]) that had combined therapy as first line treatment. In this trial, a total of 67 patients treated with bosentan were randomised to receive inhaled iloprost or placebo. The addition of iloprost improved haemodynamic measurements, exercise capacity, functional class and delayed clinical worsening [45], without significant changes in the safety profile, suggesting a potential benefit of the chosen add-on strategy.

Recently, the largest trial of combination therapy in PAH was published, evaluating the addition of sildenafil for clinically stable patients already receiving epoprostenol at steady doses [46]. A total of 267 patients were enrolled in the study, in which the results favoured the add-on strategy in terms of exercise capacity (+28.6 m compared with the placebo group), health-related quality of life, haemodynamics and time to clinical worsening. The authors suggested that the benefit of addition of sildenafil was independent of the baseline level of epoprostenol. Of note is the dose of sildenafil (80 mg *t.i.d.*) used in the study, which differs from the currently approved dose (20 mg *t.i.d.*).

Taken together, these trials reinforce the importance of well-designed and adequately powered studies for the evaluation of combination therapy. Patient recruitment is increasingly difficult, although there will not be a safer way to properly conclude about the risk benefit (and why not also cost benefit) ratio of combination therapy than trials addressing significant surrogate markers in a controlled manner. Ideal, but utopian, would be the head-to-head comparison of all available treatments, as well as of all possible combinations, evaluating survival as end-point. The current impossibility of such a kind of trial, due to costs, the number of patients needed and the long duration, does not preclude performing trials with feasible and proper designs that, even if they do not answer all the questions, add a significant amount of information to the arsenal of PAH treatment. In the same direction are studies exploring new compounds and different pathophysiological pathways.

The results of the use of ambrisentan, an A-selective endothelin receptor antagonist, have been recently published [47]. The 12- and 48-week results suggest that ambrisentan improves and sustains exercise capacity, as measured by 6-min walk distance, decreases natriuretic peptide levels and delays clinical worsening. In terms of safety profile, no increase in liver enzymes or interaction with warfarin use was reported, in contrast to other endothelin receptor antagonists. Current therapy, considering all endothelin receptor antagonists, prostanoids and phosphodiesterase (PDE) inhibitors, may be defined as a counterpoint for the imbalance between vasoconstrictors/pro-proliferative and vasodilators/anti-proliferative substances. New efforts now exist towards the control of vascular remodelling as a whole, from its promotion through modulation and reversion.

The remodelling process of the pulmonary circulation characteristic of PAH is a complex scenario of many factors, starting with genetic predisposition and culminating with disproportional smooth muscle and endothelial cell proliferation, resulting in vascular obliteration and consequent increase in right ventricle afterload [48]. From all genetic factors that might be involved with PAH to the different ways through which the right heart might respond, in terms of ventricular fibrosis, remodelling and contractility, the number of pathways and their consequences now under the attention of worldwide experts has remarkably increased in recent years.

It is now well known that mutations within the type-II bone morphogenic protein receptor gene (BMPRII) pre-dispose to the development of PAH [49]. Moreover, patients carrying the mutation develop the disease at an earlier age and present a more severe phenotype compared with idiopathic PAH patients [50]. More recent studies also suggest that the BMPRII pathway also has a role as a therapeutic target, by means of gene transference [51] or through restoration of mechanisms with antiproliferative properties, such as the peroxisome proliferator-associated receptor-γ (PPAR-γ)/apolipoprotein E axis, that are depleted in PAH [52]. Rosiglitazone (a PPAR-γ agonist) was demonstrated to inhibit growth-factor-modulated pulmonary artery smooth muscle cell proliferation. The potential cardiac toxicity associated with this class of drugs, however, raises attention to its use in terms of its safety profile [53–55].

Inflammation also has an increasingly recognised role in PAH, at least as a modulator of disease progression in specific forms of PAH [56, 57]. Several forms of PAH, including idiopathic PAH, reveal inflammatory infiltrates in the perivascular territory along with expression of chemokines [58]. High serum levels of cytokines have also been described in PAH [59]. Moreover, patients with systemic inflammatory conditions, such as lupus and mixed connective tissue disease, may

present dramatic improvements in pulmonary haemodynamics with immunosuppressive therapy as first-line treatment for PAH [60, 61]. The clear role of interfering with possible inflammatory processes in other forms of PAH is still to be determined.

The interest in growth factors, particularly in the ability of platelet-derived growth factor (PDGF) to induce vascular remodelling through proliferation and migration of smooth muscle cells and fibroblasts [62, 63], has also been growing, also because drugs that inhibit several tyrosine kinases, such as PDGF receptor α and β, are already available due to their other clinical indications, such as for treatment of leukaemia. Several case reports, with all the caution that evidence based on case reports deserves, reported improvement in haemodynamics and exercise capacity with the short- and long-term use of imatinib mesylate [64–66]. The development of left heart dysfunction as a side-effect of the chronic use of tyrosine kinase inhibitors [67] raisies concerns about their safety in the chronic management of PAH. This particular aspect is under evaluation in an ongoing multicentre trial.

Different classes of drugs also under current evaluation are the soluble guanylate cyclase stimulators and activators. These drugs modulate the activation of cyclic guanosine monophosphate in a nitric oxide-independent manner. In experimental models, these drugs have demonstrated a greater and more sustained vasodilator effect, compared with PDE5 inhibitors [68]. Preliminary data suggest that this class of drugs might be safe for acute administration in PAH patients, resulting in favourable haemodynamic effects [69]. More studies, however, are needed before any conclusion is made.

The potential of these different pathways, among others not discussed in the present summary, is incredibly promising for the future of pulmonary arterial hypertension. Certainly, within the next decade, a completely different reality will become true, but most of it will depend on the proper interpretation of what we have achieved so far. The main objective of the present update was to stimulate scrutiny of the whole course of events during recent years, with regard to all the resulting progress achieved in pulmonary arterial hypertension management and the perspectives that are now opening. The difficulties associated with the study of the pathophysiology and treatment of a rare condition, such as pulmonary arterial hypertension, tend to increase. Patients will already be undergoing specific therapy, there will be more competition between new trials, the validity of currently used end-points will be increasingly questioned, and also the differences among the different forms of pulmonary arterial hypertension will be more prominent. The only way to diminish the impact of such difficulties is by an international effort aiming to gather more information through enlargement of DNA, tissue and data banks and, also, aiming to standardise trial design, resulting in faster, safer and consequently better translation from experimental studies to clinical practice.

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