



INTRODUCTION

Confidence from experience: dual endothelin receptor antagonism in PAH

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Pulmonary hypertension (PH) is classified into five logical treatment-based groups [1]. Pulmonary arterial hypertension (PAH) represents the first of these five groups and is further classified as idiopathic (predisposing factors having been excluded), familial or as occurring in association with certain conditions, including connective tissue disease, congenital heart disease and HIV infection. PAH is characterised by increased pulmonary vascular resistance as a consequence of vascular remodelling, which ultimately leads to right heart failure and death. Few effective medical therapies were available for PAH 10 yrs ago, and in many cases lung transplantation was the only viable treatment option. For patients with idiopathic PAH the outlook was bleak, with relentless deterioration and a predicted 5-yr survival of 22–38% [2]. Thanks to an explosion in research over the last 10 yrs, PAH has changed from an intractable, rapidly fatal condition to a serious but treatable disease.

Although the management of patients with PAH remains a therapeutic challenge, the situation is frustrated by the continuing delays in diagnosis. The early symptoms of PAH are nonspecific and, by the time other more common conditions have been investigated and ruled out, patients have often progressed to severe disease, their quality of life already seriously compromised [3]. Increased vigilance and the adoption of international guidelines will hopefully expedite this process and lead to earlier diagnosis.

Endothelin (ET) is believed to play a pivotal role in the early stages of PAH and targeting this peptide is an important therapeutic strategy. Indeed, elevated levels of ET have been detected in all forms of PAH [4–6], as well as in idiopathic pulmonary fibrosis (IPF) [7] and chronic thromboembolic pulmonary hypertension [8]. Despite distinct aetiologies, common histopathology suggests common pathogenesis and supports targeting ET as an appropriate strategy in all these conditions. Through comprehensive blockade of the ETA and ETB receptors, the dual ET receptor antagonist, bosentan, blocks the deleterious effects of ET. As a result of a number of

clinical trials, it is widely acknowledged that bosentan not only improves exercise capacity in severely compromised patients but also results in cardiac remodelling, as measured by the Doppler right ventricular index [9], which is a prognostic factor for survival in PAH [10]. In addition, bosentan has been shown to delay time to clinical worsening [11] and to improve long-term outcome [12].

In the first paper in this issue of the *European Respiratory Review (ERR)*, DUPUIS [13] reviews the evidence supporting a pathogenic role for ET in PAH. DUPUIS [13] presents interesting pre-clinical data that highlight the potential benefits of blocking both the ETA and ETB receptor subtypes. The requirement for invasive right heart catheterisation for a definitive diagnosis of PAH requires effective collaboration and communication between respiratory physicians, rheumatologists and cardiologists. The paper by GIBBS [14] presents the cardiologist's point of view and highlights potential diagnostic pitfalls faced in pursuance of a timely diagnosis, recommending referral to specialist centres whenever possible.

Having gained an understanding of the biology behind the role of ET in PAH and the importance of accurate and timely diagnosis, the paper by HUMBERT [15] presents the mounting body of evidence in support of the efficacy of the dual ET receptor antagonist, bosentan. Several studies have shown that, in addition to providing symptomatic relief, bosentan can improve long-term outcomes in patients with PAH, and research is now focused on combining targeted therapies to further improve the outlook for patients with PAH. The management of PAH is not always straightforward and, before moving on to the potential for ET receptor antagonism in different indications, HOEPER and LAENGER [16] present details of challenging cases of PH.

In the final article of this issue of the *ERR*, DU BOIS [17] introduces the ongoing studies of bosentan in interstitial lung diseases, including IPF, a severe progressive lung disease that is fatal in the majority of patients. As well as being a well-established pathogenic mediator in PAH, ET is

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also thought to play a profibrotic role in the pathogenesis of IPF and IPF-related PH, providing a clear rationale for the investigation of bosentan in IPF. The efficacy of bosentan in IPF continues to be investigated in the BUILD (Bosentan Use in Interstitial Lung Disease) clinical trial programme.

As the papers in this issue of the *European Respiratory Review* demonstrate, clinical trials have and will continue to play an important role in developing evidence-based treatment strategies for pulmonary arterial hypertension, as well as extending the application of endothelin receptor antagonists to other endothelin-mediated diseases. The outlook is brighter for patients with these chronic conditions.

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