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SERIES "PULMONARY HYPERTENSION: BASIC CONCEPTS FOR PRACTICAL MANAGEMENT"
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Endothelin receptor antagonists in pulmonary arterial hypertension

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ABSTRACT: The endothelin (ET) system, especially ET-1 and the ET_A and ET_B receptors, has been implicated in the pathogenesis of pulmonary arterial hypertension (PAH). Together with prostanoids and phosphodiesterase 5 inhibitors, ET receptor antagonists have become mainstays in the current treatment of PAH.

Three substances are currently available for the treatment of PAH. One of these substances, bosentan, blocks both ET_A and ET_B receptors, whereas the two other compounds, sitaxsentan and ambrisentan, are more selective blockers of the ET_A receptor.

There is ongoing debate as to whether selective or nonselective ET receptor blockade is advantageous in the setting of PAH, although there is no clear evidence that receptor selectivity is relevant with regard to the clinical effects of these drugs.

For the time being, other features, such as safety profiles and the potential for pharmacokinetic interactions with other drugs used in the treatment of PAH, may be more important than selectivity or nonselectivity when selecting treatments for individual patients.

KEYWORDS: Endothelin, endothelin receptor antagonists, hypertension, pulmonary

The purpose of the present article is to summarise the biological basis and clinical data underlying the practical use of endothelin (ET) receptor (ETR) antagonists in the field of pulmonary hypertension (PH). Other treatments, such as prostanoids and phosphodiesterase 5 inhibitors, as well as future developments, are covered in separate articles in the present series [1].

BIOLOGY OF THE ENDOTHELIN SYSTEM

Production of endothelin

ET is a 21-amino-acid peptide that was discovered in 1988 [2]. It is ubiquitously and predominantly produced by the vascular endothelium and, to a lesser extent, by other cell types, including pulmonary artery smooth muscle cells [3] and lung fibroblasts [4]. Various promoters can stimulate the biosynthesis of ET, including hypoxia, growth factors, cytokines, shear stress, thrombin and angiotensin II. Interestingly, ET biosynthesis is inhibited by nitric oxide [5] and prostacyclin, two factors whose downregulation contributes to the pathophysiology of pulmonary arterial hypertension (PAH). For editorial comments see page 236. The inactive 39-amino-acid precursor pro-ET, more commonly referred to as big ET, is hydrolysed to mature ET through the action of numerous ET-converting enzymes, also abundantly expressed in the lungs [6]. ET is considered a paracrine mediator since the majority of its production is released toward the underlying interstitial space, with a smaller measurable amount released into the circulation. In this regard, elevated circulating ET levels are generally accepted as representative of the activation of the tissue ET system. Pre-clinical studies suggest that the lungs are the principal production site of ET, since rat lungs display the highest immunoreactive ET levels [7], with mRNA expression levels five times higher than in any other organ studied [8]. The lungs not only produce but also clear plasma ET from the circulation, with a ~47% single-pass extraction of plasma ET by human lungs [9, 10]. In normal subjects, there is, however, no significant arteriovenous ET gradient across the pulmonary

For editorial comments see page 236.

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circulation since clearance and secretion into the plasma are balanced [10].

There are three ET isoforms, termed ET-1, ET-2 and ET-3 [8], which are encoded by three distinct genes. ET-1 is considered the predominant and more important pathophysiological isoform.

Endothelin receptors

There are two distinct ETRs, the ET_AR and ET_BR. Both are also ubiquitously distributed on various cell types and were first described in the lungs [11]. They are part of the G-protein-coupled receptor (GPCR) family possessing seven transmembrane domains. The ET_AR and ET_BR are both simultaneously expressed in all cell types studied, with one notable exception; only the ET_BR is expressed on endothelial cells [12]. As discussed in more detail below, this particular and unique distribution of the endothelial ET_BR is associated with distinct pre-clinical effects and has generated some debate as to the optimal pharmacological approach to blockade of the ET system. Although the ET_AR displays equal affinity for all ET isoforms, the ET_BR is more sensitive to the effects of ET-3 [13].

The biology and pharmacology of ETRs are quite complex and remain incompletely understood. A wide variety of actions can be elicited through ETR-stimulation by activation of numerous intracellular pathways. Moreover, some functional studies support the existence of cross-regulation or cross-talk between ETRs in various cells types [14–16]. As is the case for many other GPCRs, there is also evidence that the ET_AR and ET_BR can form functional heterodimers and that this may be of some pharmacological importance [15, 17–19]. Finally, numerous post-translational modifications of the ET_AR and ET_BR have been demonstrated after stimulation with ET-1, and this may also modulate receptor activity [20].

Substantial pre-clinical research is, therefore, still required in order to clarify these issues, their relevance to human disease and their impact upon the optimal approach to pharmacological blockade of the ET system. Since they have differing pharmacological profiles, with various selectivities for the ET_AR and ET_BR, it is clear that prudence must be exercised in the clinical evaluation of this new class of drugs, and that, eventually, direct comparative trials of ETR antagonists could be justified in order to clinically evaluate pharmacologically distinct agents.

In the peripheral human lung, the ET_AR:ET_BR ratio is ~30:70 [21]. This ratio is quite variable between species, and the receptors are mostly found on smooth muscle cells and in the alveolar walls [22]. In human pulmonary arteries, the ET_AR is largely predominant in larger vessels, with an increasing proportion of ET_BR in more distal pulmonary arteries, reaching a proportion of ~40% [23].

Effects of endothelin in the lungs

ET is a potent pulmonary vasoconstrictor. The vasoconstrictive effect of ET is mediated by both the ET_AR and the ET_BR [16]. In isolated human small pulmonary arteries and rat lungs and rat resistance pulmonary arteries, combined blockade of both the ET_AR and the ET_BR is necessary in order to achieve optimal inhibition of vasoconstriction [15, 16, 24–27]. Furthermore, there is evidence of cooperation or cross-talk between the receptors since combined blockade of both receptors results in greater inhibition of pulmonary vasoconstriction than blockade of either receptor alone [15, 16].

ET is a mild pulmonary vasodilator. Stimulation of the endothelial ET_BR can release vasodilators such as nitric oxide (NO) and prostacyclin (prostaglandin I_2) [28, 29]. Under normal conditions, the endothelial ET_BR does not seem to contribute significantly to pulmonary vascular tone [16, 30], and removal of the endothelium does not affect ET-1-induced pulmonary arterial vasoreactivity [16]. Under conditions of PH, however, when baseline pulmonary vascular tone is increased, the vasodilatory role of the ET_BR can be unmasked by selective ET_BR stimulation using a low concentration of ET-1 or by selective ET_BR blockade [16, 30, 31]. With higher agonist concentration, the mild vasodilatory role of the ET_BR is lost and overcome by potent sustained vasoconstriction [16].

ET promotes lung vascular and interstitial remodelling (fig. 1). ET stimulates the proliferation of human pulmonary artery smooth muscle cells through both the ET_AR and the ET_BR [23]. ET stimulates human endothelial cell proliferation through activation of the ET_BR [32]. ET also causes lung fibroblast activation and proliferation [4, 14], with extracellular matrix deposition and contraction. Interestingly, transgenic mice overexpressing ET-1 in the lungs did not develop PH, but demonstrated evidence of lung inflammation with some degree of fibrosis [33].

Endothelin receptor antagonists

Numerous ETR antagonists have been developed [34]. They are distinguished pharmacologically on the basis of their various affinities for the ET-$_AR$ and ET_BR, as determined by binding studies in cell culture. There are currently three ETR antagonists that have been approved for the therapy of PAH in various countries. Bosentan (Tracleer™; Actelion Pharmaceuticals, Allschwil, Switzerland), the first ETR antagonist, approved in 2001, shows an almost equal affinity for both receptors, with an ET_A:ET_B affinity ratio of ~40:1. Bosentan is thus commonly referred to as a combined or dual ETR blocker. Sitaxsentan (Thelin™; Encysive Pharmaceuticals, Houston, TX, USA), approved in 2006 in European countries, displays an ET_A:ET-$_B$ affinity ratio of 6,000:1 and is thus considered and presented as an ET_AR-selective antagonist. Another agent recently approved in the USA (June 2007) is ambrisentan (Letairis™: Gilead Sciences, Foster City, CA, USA, in the USA; Volibris™: GlaxoSmithKline, London, UK, in other parts of the world). This drug is also presented as a selective ET_AR blocker, although many of its published ET_A:ET_B affinity ratios display an ET_A:ET_B selectivity of about one log, slightly higher than that of bosentan [35]. Based on pre-clinical data and because of the apparently complex pharmacology of ETRs, there could be clinically significant differences in the efficacy/safety profile of these agents, which would ultimately require careful clinical evaluation in randomised trials.

Evidence that endothelin-1 contributes to PH and pre-clinical studies

There is clear evidence of activation of the ET system in virtually all pre-clinical models of PH, as well as in all categories of human PH [36]. Plasma and lung ET-1 expression are increased in PH, and correlate with disease severity, including the degree of pulmonary remodelling, as measured using intravascular ultrasound [37–39]. Although it has

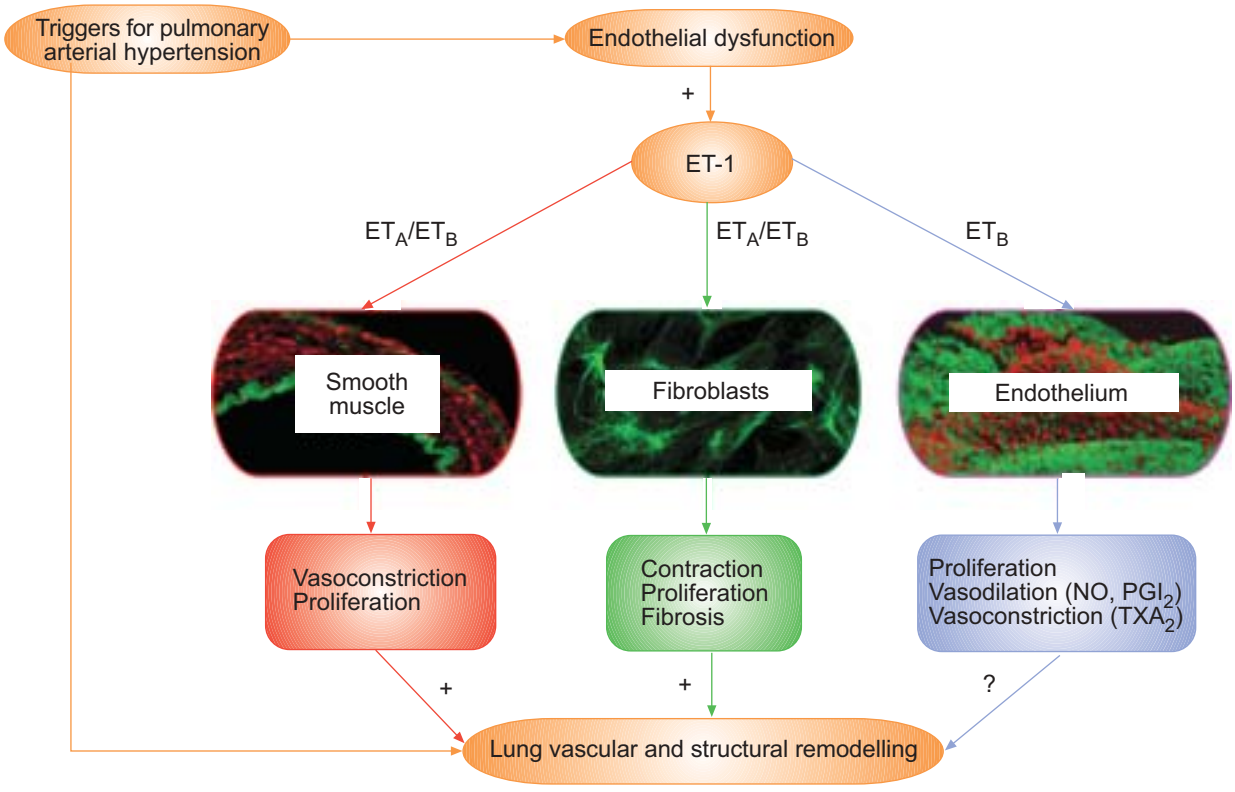

FIGURE 1. Endothelin (ET)-1 in pulmonary arterial hypertension. NO: nitric oxide; PGI_2: prostacyclin; TXA_2: thromboxane A_2; +: stimulation; ?: unknown effect.

become evident and proven by clinical trials that ET-1 contributes to the adverse endotheliopathy associated with PH, ET-1 is probably secondarily activated and not a primary cause of PH. Chronic ET-1 infusion causes a reduction in pulmonary vascular reactivity to NO in rats, but does not result in PH [12]. Furthermore, overexpression of ET-1 alone does not result in PH in transgenic animals [33], suggesting that other mechanisms must be operating concomitantly.

Lung tissue and pulmonary arteries from human subjects with PH display increased ET-1-binding capacity [23]. The *in vivo* capacity of animals models and human lung to clear ET-1 from the circulation is, however, reduced in various types of PAH, suggesting that a reduction in endothelial ET_BR activity occurs in PAH [30, 40–42]. How the proportion of ET_AR and ET_BR are affected by the various pathological conditions and how the cooperation between receptors is modified remain to be clearly established. Despite these outstanding issues, ETR antagonists have clearly demonstrated their effectiveness in all pre-clinical models of PH [36, 43–45]. ETR antagonists can improve haemodynamics, right ventricular hypertrophy and survival. They have demonstrated their capacity to cause beneficial remodelling of pulmonary arteries, reduce pulmonary fibrosis and improve the endothelial function of pulmonary vessels. These effects have been obtained with both highly selective ET_AR antagonist and agents displaying little differential selectivity and considered dual ET_AR/ET_BR blockers. There have been too few direct pre-clinical comparisons of agents of differing ETR selectivity to permit any firm claim of superiority among them.

CLINICAL DATA

Three different ETR antagonists are currently available for PAH, bosentan, sitaxsentan and ambrisentan. These three compounds differ in several aspects, including pharmacokinetics, receptor affinity and chemical structure. Whereas bosentan and sitaxsentan are sulphonamide analogues, ambrisentan is a propanoic acid derivative.

Bosentan

Following its approval by the US Food and Drug administration (FDA) in 2001, bosentan is now available in many parts of the world. For the time being, the authorities have approved the drug only for patients with PAH of functional class III (Europe) or III/IV (USA and Canada).

Early acute haemodynamic interventional studies with bosentan showed that the drug acts as a nonselective pulmonary vasodilator [46]. A randomised placebo-controlled phase II trial (AC-351) conducted in 32 patients with PAH showed significant haemodynamic improvement in the bosentan group, with a decrease in pulmonary vascular resistance (PVR) of 223 $dyn \cdot s \cdot cm^{-5}$ following 12 weeks of treatment, and a corresponding increase in PVR of 191 $dyn \cdot s \cdot cm^{-5}$ in the placebo group. The placebo-corrected increase in 6-min walking distance was 76 m in the bosentan group [47]. In the subsequent phase III trial (Bosentan Randomized trial of Endothelin Antagonist THErapy (BREATHE)-1; the design of this and other studies are detailed in table 1), bosentan improved the 6-min walking distance by 44 m after 16 weeks of treatment compared with the placebo group; in addition, there were significant improvements

TABLE 1 Selection of clinical studies of endothelin receptor antagonists in the field of pulmonary hypertension

Acronym	Title	Drug	Description	[Ref.]
ARIES	Ambrisentan in PAH – a phase III, randomized, double-blind, placebo-controlled, multicenter, efficacy study of ambrisentan in subjects with pulmonary arterial hypertension	Ambrisentan		
ARIES-1			RPCT of 5 and 10 mg ambrisentan *q.d.* compared to placebo in PAH patients	[48]
ARIES-2			RPCT of 2.5 and 5 mg ambrisentan *q.d.* compared to placebo in PAH patients	[49]
BREATHE	Bosentan Randomized Trial of Endothelin Antagonist THErapy	Bosentan		
BREATHE-1			RCT of bosentan *versus* placebo in PAH patients	[50]
BREATHE-2			RPCT of co-treatment with bosentan or placebo in PAH patients receiving epoprostenol	[51]
BREATHE-3			Uncontrolled trial of bosentan in children with PAH	[52]
BREATHE-4			Uncontrolled trial of bosentan in HIV-infected patients	[53]
BREATHE-5			RPCT of bosentan *versus* placebo in patients with Eisenmenger physiology	[54]
EARLY	Endothelin Antagonist tRial in miLdlY symptomatic PAH patients		RPCT of bosentan *versus* placebo in PAH patients presenting in functional class II	NYP
BENEFiT	Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension		RPCT of bosentan *versus* placebo in CTEPH patients	NYP
COMPASS-2	Effects of Combination Of bosentan and sildenafil *versus* sildenafil Monotherapy on morbidity and mortality in symptomatic PAtientS with PAH-2		RPCT of bosentan *versus* placebo as add-on therapy in PAH patients already receiving sildenafil	Ongoing
STRIDE	Sitaxsentan To Relieve ImpaireD Exercise	Sitaxsentan		
STRIDE-1			RPCT of 100 and 300 mg sitaxsentan *q.d. versus* placebo in PAH patients	[55]
STRIDE-2			RPCT of 50 and 100 mg sitaxsentan *q.d. versus* placebo in PAH patients	[56]

RPCT: randomised placebo-controlled trial; PAH: pulmonary arterial hypertension; RCT: randomised controlled trial; CTEPH: chronic thromboembolic pulmonary hypertension; NYP: not yet published.

in Borg dyspnoea index, World Health Organization functional class and time to clinical worsening.

The BREATHE-1 study explored two dosages of bosentan, 125 and 250 mg *b.i.d.* Both doses proved to be equally effective as regards improving 6-min walking distances, but elevation of aminotransferase levels to more than three times the upper limit of normal occurred more often at a dose of 250 mg *b.i.d.* (14%) than of 125 mg *b.i.d.* (4%). For these reasons, the approved target dose of bosentan is 125 mg *b.i.d.* Owing to the observed hepatotoxic side-effects, European authorities required the introduction of a post-marketing surveillance system in order to obtain further safety data. Within 30 months, this system assembled data from 4,994 patients, representing 79% of those exposed to bosentan in Europe during that time period [57]. The reported annual rate of aminotransferase level elevation was 10.1%, and 3.2% of patients had to discontinue the drug for this reason. Aminotransferase level elevation was reversible in all cases, and there was no permanent liver injury.

An extended observation of 169 patients enrolled in the first two randomised trials of bosentan in PAH (AC-351 and BREATHE-1) found that 96 and 89% of these patients remained alive after 1 and 2 yrs of treatment, respectively, and that 85 and 70% remained alive and on bosentan monotherapy at that time at the end of 12 and 24 months, respectively [58]. Another, retrospective, analysis of 103 idiopathic PAH (IPAH) patients given first-line treatment with bosentan revealed overall survival rates of 90 and 87%, and event-free survival rates of 61 and 44%, after 1 and 2 yrs, respectively, suggesting a substantial rate of monotherapy failure with long-term treatment [59]. It is of note that long-term survival was similar in class III IPAH patients given first-line treatment with bosentan and a matched population of patients initially treated with epoprostenol [60].

BREATHE-1 only enrolled patients in functional classes III and IV. Therefore, the effects of the drug in patients with earlier stages of PAH were unknown. The Endothelin Antagonist tRial in miLdlY symptomatic PAH patients (EARLY) was another randomised placebo-controlled trial that was designed specifically to assess the effects of bosentan in PAH patients presenting in functional class II. The trial enrolled a total number of 185 PAH patients. As the results have not yet been fully published, they cannot by displayed in detail here.

However, preliminary communications show that the main results of EARLY were a significant fall in PVR, a nonsignificant increase in 6-min walking distance and a significant decrease in the number of predefined events of clinical worsening by 77% compared to the placebo group. Importantly, this study was the first to support the hypothesis that early medical intervention is capable of prolonging the time to clinical worsening. Based on these results, it is expected that the authorities will extend the approval of bosentan to PAH patients in functional class II.

The initial clinical trials performed with bosentan included mainly adult patients with IPAH and PAH associated with connective tissue disease, predominantly scleroderma. A more-recent randomised placebo-controlled trial performed in patients with Eisenmenger syndrome (BREATHE-5) showed significant improvements in haemodynamics and 6-min walking distance, comparable to what has been found in patients with IPAH [52]. Additional uncontrolled studies revealed similar safety/efficacy profiles in children with PAH (BREATHE-3) and in patients with HIV-associated PAH (BREATHE-4), as well as in patients with mild (Child A) liver disease and portopulmonary hypertension [52, 53, 61, 62].

Bosentan has also been studied in combination with other PAH medications. A small randomised placebo-controlled trial of co-administration of bosentan with intravenous epoprostenol *versus* epoprostenol alone (BREATHE-2) failed to show significant beneficial effects, but this trial was underpowered and therefore inconclusive [51, 63]. Uncontrolled case series have provided preliminary evidence that the addition of bosentan to various prostanoids is safe and results in improved exercise capacity [64, 65]. The opposite approach, *i.e.* addition of inhaled iloprost to bosentan, was evaluated in two randomised controlled trials, the Safety and pilot efficacy Trial in combination with bosentan for Evaluation in Pulmonary arterial hypertension (STEP)-1 and the Combination Therapy of Bosentan and Aerosolised Iloprost in Idiopathic Pulmonary Arterial Hypertension (COMBI) trial, although with mixed results [66, 67]. Both trials found that the combination was safe, but only STEP-1 showed clinical improvement, whereas the COMBI study was negative in that regard. Preliminary studies also suggest that bosentan can be safely combined with sildenafil, a phosphodiesterase 5 inhibitor also approved in PAH [68, 69]. Two uncontrolled trials found significant improvements in exercise capacity when sildenafil was added to bosentan in patients with IPAH. In contrast, there was no clear benefit of this approach in patients with scleroderma-associated PAH, suggesting that not all forms of PAH respond similarly to medical therapy [69, 70]. A potential concern regarding the combination of bosentan and sildenafil is a pharmacokinetic interaction between the two substances, resulting in increased plasma concentrations of bosentan but decreased plasma concentrations of sildenafil [71]. Although there have been no safety signals that would suggest increased hepatotoxicity with this combination to date [57], whether the efficacy of sildenafil could be diminished by co-administration of bosentan remains a matter of debate. The Effects of Combination Of bosentan and sildenafil *versus* sildenafil Monotherapy on morbidity and mortality in symptomatic PAtientS with PAH (COMPASS)-1 study showed that the acute haemodynamic response to sildenafil was similar in patients pre-treated with bosentan and treatment-naive patients (unpublished data), but these data are not sufficient to exclude the hypothesis of bosentan diminishing the efficacy of sildenafil. The COMPASS-2 study is currently underway, examining the long-term effects of adding bosentan to sildenafil, and another randomised controlled trial is studying the opposite approach, *i.e.* the addition of sildenafil to bosentan.

In addition to PAH, bosentan has also been studied in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Several uncontrolled case series have suggested that bosentan improves haemodynamics and exercise capacity in this patient population, in a similar manner to what has been observed in patients with PAH [72, 73]. The Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension (BENEFiT) study was a randomised placebo-controlled study addressing the safety and efficacy of bosentan treatment in patients with inoperable CTEPH. The study enrolled 157 patients and the two co-primary end-points were changes in PVR and 6-min walking distance after 16 weeks. The complete results of this study are not yet openly available, but preliminary communications reveal that there was a significant decrease in PVR in the bosentan group, whereas the 6-min walking distance remained unchanged. The reasons for this discrepancy are unclear, but one hypothesis suggests that patients with CTEPH tend to be older and more deconditioned than those with IPAH and that it may take >16 weeks before haemodynamic improvement translates into better exercise capacity. However, further studies are clearly needed in order to elaborate the effects of bosentan (and other drugs) in patients with CTEPH.

No randomised controlled trials have been performed in patients with lung disease, *i.e.* chronic obstructive pulmonary disease or interstitial lung disease, and PH. A small safety trial published recently suggested that bosentan did not worsen gas exchange in patients with pulmonary fibrosis and PH [74], but many more data are required before the use of bosentan or other ETR antagonists can be endorsed in this setting.

Sitaxsentan

Sitaxsentan was approved in Europe in 2006 for patients in functional class III, and in Canada and Australia in 2007, for patients in functional classes II and III. The US FDA has so far denied approval of sitxsentan due to a perceived lack of sufficient data to demonstrate clinical efficacy.

In a pilot study, the drug was evaluated in 20 patients with PAH at doses ranging 100–500 mg sitxsentan *b.i.d.* There were significant improvements in haemodynamics and exercise capacity, but there were also two cases of serious liver injury, one of them fatal (the daily dose of sitaxsentan was 600 mg in this patient) [75].

The subsequent Sitaxsentan To Relieve ImpaireD Exercise (STRIDE)-1 trial evaluated lower dosages of sitxsentan, *i.e.* 100 or 300 mg *q.d.*, in patients with IPAH and PAH associated with connective tissue disease or congenital heart disease [55]. The primary end-point of this trial was peak oxygen uptake, determined by cardiopulmonary exercise testing. This end-point was met only in the 300-mg subgroup. In contrast, the 6-min walking distance increased significantly in the 100-mg

group (35 m) and in the 300-mg group (33 m), respectively, and haemodynamic parameters such as cardiac index and PVR also improved significantly in both groups. Clinical worsening occurred in three (5%) out of 60 patients in the placebo group, zero (0%) out of 55 in the 100-mg group and one (2%) out of 63 in the 300-mg group, a difference that did not reach significance. During the 12-week observation period, the incidence of liver abnormalities, as defined by aminotransferase level increases to more than three times the upper limit of normal, was 3% in the placebo group, 0% in the 100-mg group and 10% in the 300-mg group.

The STRIDE-2 trial then assessed the safety and efficacy of sitaxsentan at doses of 50 and 100 mg *q.d.*, again in a randomised double-blind placebo-controlled fashion [56]. After 18 weeks, patients treated with 100 mg *q.d.* showed significantly improved functional class and 6-min walking distance (31.4 m) compared to the placebo group, whereas the changes were nonsignificant for the 50-mg group. The time to clinical worsening was not significantly improved by sitaxsentan. Increases in aminotransferase levels to more than three times the upper limit of normal occurred in 6% of the placebo patients compared to 5% in the 50-mg group and 3% in the 100-mg group. Based on these data, the dosage with the best benefit:risk ratio appeared to be 100-mg *q.d.*, and only this dose has been approved for PAH to date.

STRIDE-2 included an open-label arm of 60 patients treated with bosentan. At the end of the 18-week study period, the 6-min walking distance had improved by 29.5 m in this patient group, a nonsignificant difference from the sitaxsentan groups. Aminotransferase level elevations occurred in 11% of the bosentan-treated patients, again not significantly different from the sitaxsentan group. Given the fact that the bosentan arm of this study received open-label treatment, any data comparing the effects of sitaxsentan and bosentan must be interpreted with great caution.

Long-term data for sitaxsentan are available, mainly from the open-label extension of STRIDE-2 (STRIDE-2X). In this study, patients previously treated with bosentan at a dose of 125 mg *b.i.d.* continued treatment, as did those on 100 mg sitaxsentan *q.d.* Patients who had received placebo or 50 mg sitaxsentan *q.d.* were randomised to receive either 100 mg sitaxsentan *q.d.* or bosentan. After 1 yr of treatment, the risk of treatment discontinuation because of aminotransferase level elevation was significantly lower with sitaxsentan (1%) than with bosentan (9%). Changes in 6-min walking distance after 3, 6, 9 and 12 months of treatment did not differ between sitaxsentan and bosentan, but clinical worsening over the first year of the study was observed significantly more often in patients treated with bosentan (30 *versus* 20%; p=0.03).

Sitaxsentan inhibits the hepatic enzyme cytochrome P_{450} 2C5, a fact that is especially important when patients are receiving warfarin anticoagulation therapy; in these patients, reduction of the warfarin dose by 80% from baseline when sitaxsentan is started, followed by careful adjustment, is recommended. With this strategy, bleeding events were no more common in the sitaxsentan groups than in the placebo or bosentan groups in the two pivotal trials. In contrast, there appear to be no significant interactions between sitaxsentan and sildenafil, but data regarding combination treatment with other PAH remedies are not yet available for sitaxsentan.

Ambrisentan

Ambrisentan was approved in the USA in June 2007 for PAH patients in functional classes II and III, and is expected to be available in Europe and other parts of the world in 2008.

The first clinical study of ambrisentan in PAH included 64 patients, who were treated in a double-blind fashion with 1, 2.5, 5 and 10 mg ambrisentan *q.d.* [76]. The primary end-point, change in 6-min walking distance at 12 weeks of treatment, improved with all doses by a mean of 36 m (range 34–38 m), and was accompanied by significant improvements from baseline in functional class and haemodynamics. This study was not powered to detect efficacy differences between different dosages. Aminotransferase level elevation was reported in two (3%) out of 64 patients, both treated with 5 mg *q.d.*

The ensuing Ambrisentan in PAH – a phase III, randomized, double-blind, placebo-controlled, multicenter, efficacy study of ambrisentan in subjects with pulmonary arterial hypertension (ARIES)-1 enrolled 202 patients with PAH who were randomised to placebo or ambrisentan at doses of 5 and 10 mg *q.d.*, respectively. The results from this trial have not been fully reported, but preliminary communications [48] reveal significant improvements in 6-min walking distance (30.6 m in the 5-mg group and 51.4 m in the 10-mg group), functional class and quality of life scores after 12 weeks of ambrisentan treatment. ARIES-2 compared placebo treatment with ambrisentan at doses of 2.5 and 5 mg *q.d.* Again, only preliminary results are available, showing significant improvements in 6-min walking distance (32.3 m in the 2.5-mg group and 59.4 m in the 5-mg group) and time to clinical worsening (significant in both groups)[49]. It is of note that none of the patients exposed to ambrisentan in the ARIES-1/2 trials developed transaminase level elevation.

Preliminary communications reveal that ambrisentan has also been studied in patients who had had to discontinue receipt of bosentan (n=31) or sitaxsentan (n=5) due to liver toxicity. After a mean exposure time to ambrisentan of 1.1 yrs, none of these patients had to discontinue the drug because of aminotransferase level elevation.

Like ARIES-1/2, the results of ARIES-E, the ongoing long-term extension of ARIES-1 and -2, have not been fully published. Preliminary data presented at the May 2007 meeting of the American Thoracic Society [77] after analysis of 383 patients, showed a 1-yr survival rate of 95%, with >90% of these patients remaining on monotherapy after this time. Aminotransferase level elevation was observed in eight (2.1%) out of 383 of the patients, and only one of these had to discontinue use of the drug for that reason. The most common adverse events were headache and peripheral oedema, which were rated as mild or moderate in all cases and did not result in drug withdrawal.

There seem to be no pharmacokinetic interactions between ambrisentan and other drugs commonly used in PAH patients, such as warfarin and sildenafil. However, combination data

from use of ambrisentan and other PAH remedies are not yet available.

CONCLUSION

The introduction of ETR antagonists has reshaped the treatment of PAH, and current treatment guidelines recommend these substances, especially for PAH patients in functional class III [78, 79]. However, as with other PAH treatments, there remains an unmet need for robust data on the impact of these drugs on long-term outcome and survival [80].

Now that three different substances are available, questions naturally arise surrounding superiority. Selectivity or non-selectivity for ETRs is currently a topic of hot debate, but the currently available clinical data do not permit any conclusions to be drawn concerning whether selectivity matters in regard of short- or long-term efficacy. For the time being, the clinically important differences between the three ETR antagonists surround safety and side-effects.

Liver aminotransferase level elevation appears to be more common with bosentan than with sitaxsentan and ambrisentan. However, bosentan has been used in thousands of patients since 2002 without causing permanent or fatal liver damage [57], and the two competitors still need to prove their safety over long-term administration outside clinical trials.

Pharmacokinetic interactions are probably relevant since combination pharmacotherapy is becoming the standard of care for patients with severe PH. As mentioned above, interactions with warfarin may be potentially harmful with sitaxsentan, less so with bosentan and absent with ambrisentan. Conversely, interactions with sildenafil could be a problem with bosentan, but apparently not with sitaxsentan or ambrisentan. The situation is becoming more complex with new classes of drugs currently entering clinical trials in the field of PH.

High-quality long-term studies and large-scale registers are required in order to gather more data on the safety and efficacy of the various endothelin receptor antagonists currently in use for pulmonary arterial hypertension.

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