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Endothelin Receptor Antagonists in the Treatment of Pulmonary Arterial Hypertension

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Endothelin-1 in pulmonary arterial hypertension

Since its discovery in 1988, endothelin-1 (ET-1) has been increasingly recognized as an important mediator in the pathogenesis of pulmonary arterial hypertension (PAH) [1]. Although recent theories suggest that PAH may result from dysregulated proliferation and abnormal apoptosis of endothelial cells [2–4], the actions of ET-1 as a vasoconstrictor and its actions on the growth of endothelial cells, smooth muscle cells, fibroblasts, and pericytes probably contribute to the ongoing vascular remodeling seen in PAH. Endothelial cells are the principal source of ET-1, but the link between the abnormal endothelial growth pattern and excess synthesis of ET-1 in PAH is not understood at this time. ET-1, however, does have antiapoptotic effects on endothelial cells and smooth muscle cells [5,6], and these effects might in some way contribute to the abnormalities in apoptosis seen in PAH. Previous studies have established that plasma ET-1 levels are increased in PAH [7] and that pulmonary expression and synthesis of ET-1 is increased in PAH, particularly in the remodeled precapillary pulmonary microvasculature that is the site of the increased pulmonary vascular resistance in PAH [1]. With the recognition of these abnormalities, the development of clinically useful endothelin receptor antagonists was begun [8].

Receptors for endothelin-1

Two G protein–coupled receptors for ET-1, termed "ET_A" and "ET_B," have been described [9,10]. Activation of the ET_A receptor on smooth muscle cells, pericytes, and fibroblasts results in vasoconstriction and proliferation in vitro [11]. The in vitro effects of activation of the ET_B receptor on these cells are inconsistent, and vary with the cell type, the receptor-specific agonist used, and its concentration [12]. The relevant molecule for disease states, however, is ET-1, not an agonist, and the burden of evidence from experimental studies supports a much greater role for the ET_A receptor than for the ET_B receptor in the constrictive and proliferative responses of cells of mesenchymal origin to the levels of endogenous ET-1 seen in disease states [13]. In human pulmonary hypertension, two studies describe the increased expression of smooth muscle ET_B receptors, but the physiologic significance of this finding is unclear [14,15]. Those studies could not resolve the effects of the disease on the endothelial ET_B receptor.

In endothelial cells, ET_B receptors are abundantly present, particularly in the distal lung

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microvasculature [14]. There is no evidence for ET_A receptor expression on endothelial cells. The interaction of ET-1 with the endothelial ET_B receptor may moderate some of the detrimental effects of ET-1 within the circulation, in that it leads to release of the vasodilators and antiproliferative molecules nitric oxide and prostacyclin from the endothelium [16]. Also, clearance of ET-1 from the circulation occurs principally through the pulmonary endothelial ET_B receptor, which may offer another measure of protection in disease states by lowering ET-1 levels [17,18]. It has been proposed elsewhere that a diseased, dysfunctional endothelium in PAH might have reduced expression or dysfunction of the endothelial ET_B receptor [19,20]. Contrary to this hypothesis, the author and colleagues have demonstrated recently that most patients who have idiopathic PAH or PAH related to connective tissue disease have intact or only modestly reduced endothelial ET_B–mediated clearance, despite a reduced microvascular surface area from vascular remodeling [21]. Thus, in PAH, selective ET_A receptor antagonists, which preserve endothelial ET_B receptor vasodilatory and clearance activity, may offer more benefit than nonselective ET_A plus ET_B antagonists. This question will be resolved only by clinical trials.

Selectivity of endothelin receptor antagonists

The receptor selectivity of the various antagonists has been determined using standardized in vitro assays that allow comparison between compounds. The degree of selectivity also relates to the concentration of the antagonist, so even a selective antagonist will become relatively less selective at very high doses. Agents with an ET_A:ET_B selectivity ratio greater than approximately 2500:1 generally are considered to be selective, and, although it is not used clinically, BQ-123 (ET_A:ET_B, 2465:1) has served as a useful antagonist in studies of the effects of receptor selectivity. Three endothelin receptor antagonists are approved or are in the late stages of the approval process. All are orally active, and all carry some risk of hepatotoxicity (elevated transaminases and/or bilirubin levels), possibly through effects on the hepatic cytochrome P-450 enzyme system or other mechanisms [22]. Bosentan (ET_A:ET_B, 20:1) and ambrisentan (ET_A:ET_B, 77:1) are nonselective; sitaxsentan (ET_A:ET_B, 6500:1) is highly selective.

Clinical trials of endothelin receptor antagonists in pulmonary arterial hypertension

Table 1 summarizes all the studies listed below.

Bosentan

The initial study of bosentan in a cohort of seven patients who had PAH showed that an infusion could lower pulmonary vascular resistance. Several of the patients in this study died or suffered clinical deterioration during the second phase of the trial, possibly related to their poor clinical status at the time of entry into the trial. In this study, plasma ET-1 levels were measured serially after the administration of bosentan and rose, demonstrating that bosentan was blocking the endothelial ET_B receptor.

A subsequent randomized, double-blind, placebo-controlled 12-week trial showed that oral bosentan (62.5 mg twice daily for 4 weeks, then 125 mg twice daily) improved 6-minute-walk distance, pulmonary vascular resistance, and World Health Organization functional class in patients who had idiopathic PAH or PAH related to scleroderma [23]. All patients were in World Health Organization functional class 3 at baseline. The incidence of hepatotoxicity in bosentan-treated patients was 10% and resolved on discontinuation of the drug. Plasma ET-1 levels were not measured in this study.

This initial trial was followed by a larger 16-week, double-blind, placebo-controlled study, the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) [24]. Two hundred thirteen patients were assigned randomly to placebo or to bosentan (62.5 mg twice daily for 4 weeks, then either 125 mg or 250 mg twice daily). Almost all patients were in functional class 3 at baseline. As compared with placebo, bosentan-treated patients had improved 6-minute-walk distance, functional class, and delayed time to clinical worsening. There was a 9% incidence of hepatotoxicity in the combined bosentan group, with a greater risk of hepatotoxicity at the dose of 250 mg twice daily. The improvement in 6-minute-walk distance was apparent in the idiopathic PAH group but not in the patients who had PAH related to scleroderma. An echocardiographic substudy showed that bosentan improved right ventricular size and systolic function as well as left ventricular filling [25]. The BREATHE-1 study provided the first broadly applicable oral therapy for PAH.