

Endothelin Receptor Antagonists (ERA) in Hypertension and Chronic Kidney Disease: a Rose with Many Thorns

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Abstract: The discovery of endothelin created a lot of enthusiasm and paved new therapeutic avenues for the treatment of arterial hypertension. Endothelin plays a significant role in blood pressure regulation through pronounced vasoconstriction and modulation of sodium and water reabsorption in the kidneys. Endothelin receptor antagonists have been tested in many clinical trials in patients with arterial hypertension, heart failure, pulmonary arterial hypertension, systemic sclerosis, chronic kidney disease, and diabetic nephropathy. However, the results were usually disappointing, except in pulmonary hypertension and scleroderma digital ulcers. The future of ERAs for the treatment of arterial hypertension and chronic kidney disease does not seem bright, and only the combination with other classes of antihypertensive drugs might offer a way out.

Keywords: Endothelin, endothelin receptor antagonists, hypertension, chronic kidney disease, heart failure, pulmonary hypertension, pre-eclampsia, antineoplastic agents.

INTRODUCTION

The role of endothelial cells in the regulation of vascular tone and blood pressure homeostasis attracted wide scientific interest during the last three decades. Furchgott was the first to report in 1980 that acetylcholine-induced relaxation of vascular smooth muscle cells is mediated by the endothelium [1], and some years later himself and Ignarro identified nitric oxide (NO) as the endothelial mediator [2, 3]. The simultaneous discovery of prostacyclin by Vane and Moncada in 1982 [4] oriented cardiovascular physiological and pharmacological research towards the vasorelaxing properties of the vascular endothelium. However, endothelium-dependent vasoconstriction during anoxia was reported by Vanhoutte at about the same time [5], and an endothelium-derived constricting factor was characterized from cultured endothelial cells by Hickey [6]. The isolation of endothelin by Yanagisawa in 1988 [7] created a lot of enthusiasm and generated great expectations for the effective management of arterial hypertension.

ENDOTHELINS AND ITS RECEPTORS

Endothelins comprise a group of three peptides (ET-1, ET-2, and ET-3) with potent vasoconstrictive properties. The chemical structure of endothelins resembles the structure of sarafotoxins, which are venom neurotoxins produced in abundance in scorpions and snakes from the *Atractaspis* genus [8, 9]. Shortly after the discovery of endothelins, two subtypes of endothelin receptors were identified: ET_A and ET_B [10, 11].

Endothelin-1 (ET-1) is produced by prepro-ET-1. Prepro-ET-1 is cleaved to big ET-1, which in turn is being catalyzed to ET-1 by the endothelin-converting enzyme (ECE). ET-1 predominates *in vivo* and is considered among the most potent vasoconstrictive agents in nature. ET-1 results in strong and sustained vasoconstriction through activation of ET_A receptors, while the activation of ET_B receptors causes vasorelaxation *via* formation of NO [12].

ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS)

A quest for the discovery of effective and safe endothelin blockers resulted in the first compound at 1991 [13], only 3 years after the isolation of ET-1 and one year after the identification of its receptors. The first clinical trial was published in 1995 by the recently deceased Prof. Kiowski in patients with heart failure [14]. Shortly thereafter several endothelin receptor antagonists have been discovered, which were either selective ET_A or ET_B antagonists or mixed ET_A/ET_B antagonists.

It is therefore obvious that pharmaceutical advances preceded the physiological and pathophysiological research, before uncovering the role of endothelin in health and various disease conditions. It is thus not surprising that the majority of clinical trials were either neutral or negative. Currently only two endothelin antagonists are approved for clinical use: bosentan (a mixed ET_A and ET_B antagonist) and ambrisentan (a selective ET_A antagonist). These are the only survivors of a drug class (the ‘sentans’) originally comprised by dozens of compounds. According to both European and American guidelines, ERAs are recommended as first line agents in patients with mild-to-moderate pulmonary hypertension [15, 16]. ERAs are also indicated for the treatment of scleroderma digital ulcer.

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However, the forthcoming end of most drug patents within this category combined with many negative trials in several disease conditions and the risk of severe adverse effects during long-term therapy, cast significant doubts about the future of ERAs in arterial hypertension and other disease conditions (chronic kidney disease, diabetic nephropathy, heart failure, autoimmunity, cancer), apart from pulmonary hypertension and scleroderma ulcers.

Hepatotoxicity represents a major concern with ERAs, especially when sulphonamide is included in the chemical structure [17, 18]. Sitaxentan was withdrawn from the market due to 4 cases of fatal hepatotoxicity [19]. Although fatal liver failure was not reported with other marketed ERAs (bosentan and ambrisentan) [19], it has to be noted that bosentan is associated with frequent liver enzyme elevations (up to 10%) [20, 21], while ambrisentan seems more safe [22, 23].

ENDOTHELIN AND THE KIDNEYS

ET_A receptor activation, apart from vasoconstriction, promotes oxidative stress, inflammation, and proteinuria [24-26]. In contrast, ET_B receptor activation, apart from vasodilatation, inhibits sodium reabsorption in the renal collecting ducts [27]. ET_B blockade causes salt-sensitive hypertension [28, 29], and collecting duct ET-1 or ET_B knockout mice exhibit blood pressure elevation and sodium retention [30, 31].

Therefore, ET-1 seems to have opposing effects on blood pressure regulation by acting either in the renal cortex (promoting hypertension through ET_A activation) or in the renal medulla (promoting hypotension through ET_B activation). Another factor that has to be considered is the sexual dimorphism observed in the effects of ET-1 on the kidneys. Female animals seem to be protected by ETA-induced decrease in medullary blood flow observed in male animals [32], a factor that is implicated in angiotensin II-induced hypertension. This seems to explain why female animals are less susceptible in angiotensin II-induced hypertension [33].

ERAS IN CHRONIC KIDNEY DISEASE

The renal effects of ET-1 through ET_A receptor activation (promotion of hypertension, inflammation, oxidative stress, and proteinuria), render ET_A receptor antagonism an attractive option for the treatment of chronic kidney disease. Indeed, several trials have been performed in patients with renal disease using ERAs.

Recent studies showed that selective ETA receptor antagonism in hypertensive patients with chronic kidney disease results in reduction of blood pressure, proteinuria, arterial stiffness, and serum uric acid [34-36].

More data is available for the use of ERAs in diabetic nephropathy. It has been shown that selective ETA receptor antagonists lower urinary albumin excretion rate in patients with diabetic nephropathy already on RAS inhibition (ACE-inhibitors or ARBs) [37]. Moreover, the pronounced antiproteinuric properties of ERAs were confirmed in the ASCEND (A Study of Cardiovascular Events in Diabetes) study, a large trial with avosentan on top of RAS inhibitors in patients with diabetic nephropathy [38]. However, this trial was prematurely terminated after only 4 months of follow-up due

to a significant excess in cardiovascular events (heart failure and death) in the avosentan group. It has to be noted however that avosentan was used in this study in higher doses (25-50 mg) than the ones required (5-10 mg) to reduce albuminuria [39]. Moreover, diuretics were not used to compensate for fluid retention, caused by ERAs.

Finally, observational studies show that bosentan (a mixed ERA) appears to be safe and effective in scleroderma patients with renal crisis [40], and is currently under evaluation in an open prospective study for the treatment of scleroderma renal crisis.

ERAS IN HEART FAILURE

ET-1 is implicated in the pathogenesis of heart failure. The majority of studies with ERAs were conducted in patients with either chronic or acute heart failure. A pilot study of bosentan for 2 weeks in patients heart failure was very promising, with favourable effects on cardiac and pulmonary hemodynamics: reductions in pulmonary and mean arterial pressure together with reductions in pulmonary and vascular resistance by 10-30% were accompanied by increases in cardiac index by 13% [14]. This study was followed by several studies with mixed (bosentan, enrasentan) or selective (darusentan) ERAs in patients with chronic heart failure [41-45]. However, all studies failed to prove any significant benefit; instead, a significant increase in adverse effects was observed [41-45]. Similar disappointing results were obtained in acute heart failure by using intravenous tezosentan (a mixed ERA) in several clinical trials, which were characterized by lack of any significant benefit and increased frequency of adverse events [46-51].

ERAS IN ARTERIAL HYPERTENSION

Bosentan was the first molecule to be evaluated in patients with mild to moderate hypertension. Bosentan at a dose of 1,000 mg twice daily resulted in blood pressure reduction (11/6 mmHg) that was comparable to enalapril at 20 mg after 4 weeks of active therapy [52]. In addition, there was no reflex activation of the sympathetic or the renin-angiotensin system with bosentan. In terms of safety, bosentan was well tolerated, apart from a significant elevation of liver enzymes in some patients, which was asymptomatic and completely reversible upon bosentan withdrawal.

Despite the favourable effects of bosentan on blood pressure reduction, the risk of hepatotoxicity during life-long therapy for a disease like hypertension which is not acutely life-threatening, combined with the lack of superiority over existing antihypertensive drugs, the need for dosing twice daily, and most of all the significant vasorelaxation in the pulmonary vascular bed, moved the research towards the management of pulmonary hypertension, while the field of arterial hypertension was actually abandoned.

Darusentan, a selective ET_A receptor antagonist, was the only other ERA which was evaluated in a small clinical study of patients with moderate hypertension [53]. Darusentan at 100 mg reduced significantly both systolic and diastolic blood pressure (by 11 and 8 mmHg, respectively) after 6 weeks of therapy, without any significant adverse effect or signs of liver toxicity.

Erectile dysfunction is frequently encountered in patients with arterial hypertension [54, 55]. Animal data suggests that ET-1 is implicated in the pathophysiology of erectile dysfunction [56]. The use of ERAs in animals with erectile dysfunction yielded conflicting results [57, 58]. The only available study in humans is small and failed to show any significant improvement on erectile function with ERA [59].

ERAS IN RESISTANT HYPERTENSION

Data in both animals and humans point towards endothelin activation in severe hypertension [60, 61]. This observation prompted the design of clinical studies to evaluate the effects of ERAs in resistant hypertension, a condition defined as the inability to achieve blood pressure goals despite the optimal use of 3 antihypertensive drugs, including a diuretic [62]. Darusentan was tested in a small, randomized, placebo-controlled study in patients with resistant hypertension, and resulted in significant blood pressure reduction (11/6 mmHg) after 10 weeks of treatment, without any significant adverse effects [63]. This exploratory, dose-ranging study was followed by a larger study in 379 patients with resistant hypertension, randomized to 3 doses of darusentan (50, 100, and 300 mg) or placebo. A substantial reduction of systolic and diastolic blood pressure (up to 18/11 mmHg) was observed after 14 weeks of treatment in the active group, which was significantly higher compared to placebo (9/5 mmHg) [64]. Moving to the next step, a comparison study versus guanfacine was designed. Unexpectedly, office blood pressure at study end was not significantly different from placebo, and the study did not meet its primary endpoint. Of not, significant blood pressure differences favouring darusentan were observed during the study (at time-points before the end of the study), and more importantly ambulatory blood pressure reduction (a more reliable index than office blood pressure reduction) was significantly greater with darusentan [65]. However, Gilead has already announced the cessation of darusentan development based on office blood pressure measurements, despite the findings in ambulatory blood pressure and prior data.

ERAS IN PRE-ECLAMPSIA

A central role of ET-1 in pre-eclampsia has been recently suggested by experimental studies, in which ET-1 was identified as the final mediator inducing hypertension in response to placental ischemia [66, 67]. However, the clinical utility of this observation is limited because ERAs are contra-indicated in pregnancy due to teratogenicity [68]. Limited experimental data suggests that selective ET_A receptor antagonists might not be teratogenic in late gestation [69,70], which however should be considered with great scepticism.

ERAS IN ANTINEOPLASTIC DRUGS-INDUCED HYPERTENSION

Modern antineoplastic drugs targeting angiogenesis result in blood pressure elevation and frequently induce hypertension [71-73]. A reduction in NO bioavailability has been proposed as the mediating mechanism, however recent data in animals [74] and humans [75] suggests that angiogenesis inhibition results in substantial increases of ET-1 levels. Even more, a recent study reveals that hypertension is mediated by endothelin and not oxidative stress or NO [76]. Fur-

thermore, ERAs prevented the development of hypertension during angiogenesis inhibition in rats [74, 77]. Moreover, the potential anti-neoplastic properties of ERAs might be of additional benefit in these patients [78, 79].

ERAS IN PULMONARY ARTERIAL HYPERTENSION

Although an extensive description of ERAs in pulmonary arterial hypertension is beyond the scope of this review paper, a short summary seems necessary. Based on promising findings in experimental studies, two clinical trials with bosentan were conducted in patients with moderate to severe pulmonary hypertension (idiopathic or scleroderma-associated) [80, 81]. Both trials showed a significant improvement of symptoms and patients' quality of life, leading to the approval of bosentan for the management of moderate to severe pulmonary hypertension in 2002. Further studies proved the efficacy and safety of bosentan in patients with mild pulmonary hypertension, or pulmonary hypertension caused by HIV or congenital heart disease [82-84]. Similar beneficial effects were observed with ambrisentan in two large clinical trials and one long-term open study [85, 86]. Several other ERAs are under evaluation for the treatment of pulmonary arterial hypertension.

FUTURE DIRECTIONS

In our opinion, the future of endothelin inhibition for the management of arterial hypertension and chronic kidney disease lies in combination therapy with other classes of antihypertensive drugs.

A triple inhibitor of ECE, ACE, and neutral endopeptidase has been recently developed (Cgs 35601); however its use was limited by an increased risk for angioedema [87]. A combination of ET_A antagonists with angiotensin receptor blockers might be more promising than the combination with ACE-inhibitors in terms of safety, with similar antihypertensive efficacy. Indeed, such a molecule has been formed (PS433540), combining the properties of irbesartan with BMS193884 (a selective ETA antagonist) [88]. This dual angiotensin-endothelin A receptor antagonist (DARA) is orally active and potent, with favourable pharmacokinetic properties [89,90]. The results of the first randomized, placebo-controlled study in 114 patients with ambulatory-confirmed hypertension were reported in the 2008 meeting of the American Society of Hypertension [91]. DARA was found to be both effective and safe, with only one patient developing edema, while no liver toxicity was observed.

Another very attractive combination is the one that combines endothelin inhibition with neutral endopeptidase inhibitors. Animal data with such combinations point towards beneficial effects on albuminuria and cardiac remodelling [92,93]. In addition, this combination offers the potential benefit to overcome fluid retention, which frequently occurs with ERAs.

CONCLUSIONS

The discovery of endothelin generated great expectations for the management of arterial hypertension and other disease conditions characterized by vasoconstriction. The potent and long-lasting vasoconstriction induced by ET-1 (via ET_A

activation) combined with the effects of ET-1 on renal handling of sodium and water (via ET_B activation) point towards a significant role of ET-1 in blood pressure regulation. Several antagonists of endothelin receptors have been developed, either selective ET_A antagonists or mixed ET_A/ET_B antagonists. The subsequent conduction of numerous clinical trials in patients with arterial hypertension, heart failure, chronic kidney disease, and diabetic nephropathy however has not fulfilled our expectations and disappointing results were obtained. Problems in study design and the incomplete understanding of endothelin physiology might explain the negative outcome of the studies. Currently, ERAs are approved only for the treatment of pulmonary hypertension and scleroderma digital ulcers. ERAs in monotherapy for the treatment of arterial hypertension and chronic kidney disease seem to have reached a dead end, and only the combination with other classes of antihypertensive drugs might offer a way out.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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