Endothelin Receptor Antagonism
What Does the Future Hold?

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The endothelins are a family (ET-1, ET-2, and ET-3) of naturally occurring polypeptides, with ET-1 being the most clinically pertinent isoform. ET-1 was formally identified in 1988, at which time it was viewed mainly as a potent vasoconstrictor; however, the biological understanding of endothelin has since rapidly evolved, and it is now appreciated that ET-1 is not only a potent vasoconstrictor but also that it has a prominent role in fibrogenesis, inflammatory states, oxidative stress, atherosclerosis, salt and water balance, and pulmonary artery hypertension.1–3 ET-1 binds to 2 receptors: ETA and ETB. In general, stimulation of these receptors has opposing actions. For example, ETA stimulation is vasoconstricting, as well as being profibrotic and proinflammatory, whereas ETB stimulation is vasodilatory, antiproliferative, and natriuretic. The ETB receptor also subserves a clearance role for ET-1. The varying distribution of the endothelin receptors in different tissues is responsible for the mixture of actions attributed to endothelin. For example, the renal medulla contains the highest concentration of endothelin receptors in the body.4 The renal cortex is also heavily populated with endothelin receptors (50% of the density of the medulla). The ETA receptor predominates in the kidney, composing 70% of the receptors in both locations. Thus, the important roles of ET-1 and the ETB receptor are in regulating renal hemodynamics and tubular transport processes, as well as mesangial and vascular smooth muscle cell proliferation and mitogenesis.5

Likewise, ETA and ETB receptors are highly expressed in smooth muscle cells and foamy macrophages in atherosclerotic models. Stimulation of receptors in these locations is the basis of the proinflammatory and (pro)atherosclerotic actions of ET-1. As such, endothelin antagonism restores altered vasoactivity and reverses atherosclerotic lesion development in a number of animal models of atherosclerosis.5 Observations such as these, no doubt, provided the experimental underpinnings for the studies of Raichlin et al.6 The studies of Raichlin et al6 have been carefully performed and, as such, provide some interesting new information in addition to corroborating past findings with drugs in this class. As has often been the case with endothelin receptor antagonism (ERA), study design lessens the generalizability of positive findings and confounds interpretation of negative results. The uniqueness of these particular studies resides in the number of biological measurements undertaken over a fairly lengthy period of surveillance in what might be viewed as a relatively healthy population. The primary goal of these studies was to determine whether there was angiographic progression of coronary artery disease after 6 months of therapy with the ETA-selective endothelin receptor antagonist atrasentan.

As discussed by the authors, albeit in a rather perfunctory manner, “over the course of the study, no progression of angiographic coronary disease was observed.” This null finding should come as no great surprise based on the relatively short duration of the exposure to study medication, as well as the modest nature of the occlusive lesions submitted to study. In addition, routine coronary angiography is not as sensitive as intravascular ultrasound (which was not done in these studies) in determining the change in lumen size and wall morphology; thus, subtle changes in the composition of atherosclerotic plaque components may have gone unrecognized. Finally, to date there have been no studies comparing selective ETa with mixed ETA and ETB receptor blockade in atherosclerosis; thus, it is conceivable that the “best” therapy was not used in these studies.

It is also noteworthy in these studies that both peripheral cuff and direct aortic pressures were significantly reduced, even with pretherapy blood pressure (BP) values being in a relatively normal range. The BP reduction seen with atrasentan was in the range seen previously with the endothelin receptor antagonists bosentan (mixed ETA and ETB receptor antagonist) and darusentan (ETA receptor selective).7,8 This BP finding would suggest that at least a portion of the dose-response curve for BP reduction has been identified for atrasentan. The fact that this dose of atrasentan reduced BP also means that the adverse effect rates reported occurred at a physiologically active dose and, therefore, might reflect adverse effects that might occur with more general use of this drug.

This study was not designed as a dose-ranging study; thus, the best possible dose for the secondary outcome measures of lipids and glycemic control could not be identified. Mindful of the dosing limitations of this study, one is still hard pressed to interpret the findings, particularly as they relate to the reduction in triglycerides, which is disproportionate to what would have been expected from this degree of change in insulin sensitivity. This likely represents a play-of-chance observation relating to the rather large interpatient variability in the baseline triglyceride measurements.
The adverse effects attributable to atrasentan in these studies were similar to what has been observed previously with other ET\textsubscript{A} and mixed ET\textsubscript{A}-ET\textsubscript{B} receptor antagonists but much higher in their frequency. Headache, dizziness, and nasal congestion are a class effect for these drugs, which, in all probability, are vasodilatory in origin. Nasal stuffiness was particularly prominent, occurring in \(\approx 90\%\) of those treated with atrasentan.

In the studies of Raichlin et al.\textsuperscript{6} the lower and upper extremity and facial edema rates were very high, ranging from 50\% to 65\%; however, these rates are difficult to interpret in that the control group had similarly high rates of edema. As a point of comparison, the peripheral edema rate for darusentan (10 to 300 mg/d) ranges from 2\% to 17\%.\textsuperscript{9} The mechanism for peripheral edema with pure ET\textsubscript{A} and mixed ET\textsubscript{A}-ET\textsubscript{B} receptor antagonism remains very much undetermined, although it does appear to be dose dependent. In these studies with atrasentan, the drop in hemoglobin concentration is less than what might have been expected based on the edema rates. The reduction in hemoglobin concentration seen with endothelin antagonists is most likely dilutional in nature and is probably the explanation for what was seen with atrasentan. The significant adverse effect findings herein would suggest that a 10-mg dose of atrasentan is a “high-end” dose from a tolerance point of view.

What does the future hold for endothelin-receptor antagonists? The future of this drug class is not particularly bright. To date these compounds have only been approved for use in the patient with pulmonary artery hypertension. These compounds can reduce BP under a variety of circumstances, but in most such instances safer and better-tolerated compounds are available. The results from trials with these compounds in heart failure, chronic kidney disease, cerebral vasospasm, and erectile dysfunction have not matched the buildup from what seemed at the time to be promising in vivo and animal disease models results. Currently available endothelin-receptor antagonists have a prominent adverse effect profile and, as well, are encumbered by an overly restrictive label, relating to their teratogenicity (Food and Drug Administration Pregnancy Category X [same category as isotretinoin and thalidomide]) and propensity to dose-dependently cause transaminitis.

Pursuing development of drugs in this class will require “deep pockets,” because there remain innumerable unanswered questions, as well as the strong possibility that the risk/benefit ratio for their use may be overly weighted toward risk. There is a lengthy “to do” list as this class matures for indications other than pulmonary artery hypertension, which will include questions such as whether selective ET\textsubscript{A} receptor antagonism is superior to mixed ET\textsubscript{A}-ET\textsubscript{B} antagonism; whether there will be a differing dose range of selective and mixed ET\textsubscript{A}-ET\textsubscript{B} antagonists for BP-dependent and BP-independent tissue effects; whether the issue of liver enzyme changes (dysfunction) will be resolvable by careful dose selection and/or use of diphenyl propionic acid derivative compounds, such as amisentan and darusentan, which do not interfere with the canalicular bile salt export pump, as does bosentan; whether, in balance, the dose-dependent edema seen with these compounds will limit the reaching of a true effect dose; and, finally, whether a primary effect on BP supported by ancillary effect on lipids, glucose, and renal function define a “preferred” patient for use of these drugs, as suggested by Raichlin et al.\textsuperscript{6} from studies with the selective ET\textsubscript{A} antagonist atrasentan.

Disclosures

None.

References

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