DORADO: Opportunity Postponed
Lessons From Studies of Endothelin Receptor Antagonists in Treatment-Resistant Hypertension

David J. Webb

Treatment-resistant hypertension (TRH) describes a situation where blood pressure (BP) remains above target in spite of the concurrent use of 3 antihypertensive agents of different classes, with 1 of the agents a diuretic, and all ideally given at an optimized dose. TRH is a common clinical problem, perhaps occurring in 20% to 30% of participants in hypertension trials, and is likely to become increasingly common in the future because BP targets are reducing, and older age and obesity are 2 of the strongest risk factors for its occurrence. A number of interventions have been shown to reduce BP substantially in patients with TRH, and, with its growing prevalence and the excellent cost-effectiveness of current first-line treatments, it is increasingly becoming a valuable indication in its own right for newly licensed medicines.

One such intervention that has shown promise in this indication is the use of endothelin receptor antagonists (ETRAs). In a major study (DORADO) published last year, the ETRA darusentan, at doses of 50, 100, and 300 mg daily, was studied in 379 patients with TRH using a randomized, double-blind, placebo-controlled design. Comorbidities in these patients included type 2 diabetes mellitus and chronic kidney disease. Reduction in the coprimary end points of seated systolic and diastolic BPs at week 14 of treatment were 17/10, 18/10, and 18/11 mm Hg with increasing doses of darusentan but significantly less with placebo at only 9/5 mm Hg. The only major adverse effect of darusentan was edema and/or fluid retention, occurring in >25% of patients receiving darusentan but only 14% of those on placebo. Nevertheless, the authors describe this problem as generally manageable by increasing the dose of diuretic. These significant effects of darusentan on BP in TRH were very promising and justified pursuing the development program.

In the current issue of Hypertension, Bakris et al present the second of the 2 large clinical trials with darusentan in TRH, this time with an active control (DORADO-AC). This study, in 1453 patients with TRH, again used a randomized, double-blind, placebo-controlled design, with a similar case mix of patients, but here also included an active control agent, guanfacine at 1 mg daily, a central α-2 adrenoceptor agonist unfamiliar to many clinicians and now perhaps more commonly used for its potential benefits in attention-deficit/hyperactivity disorder. The doses used were the same as those in DORADO, as was the duration of treatment (14 weeks) and the coprimary end point. Seated BP at week 14 was reduced by 15/10 mm Hg with darusentan treatment, significantly more than by guanfacine (12/6 mm Hg) for both systolic BP and diastolic BP. However, very disappointingly for the investigators, placebo treatment unexpectedly reduced BP by 14/8 mm Hg at 14 weeks. This response was not different from that of darusentan for systolic BP and greater than that of guanfacine for diastolic BP. Because BP fell with placebo mainly after 8 weeks of treatment, a post hoc time-weighted analysis was performed, and in this situation darusentan outperformed both placebo and guanfacine. In addition, ambulatory BP monitoring was undertaken in this trial, and darusentan produced a greater reduction in mean 24-hour SBP and DBP at 14 weeks than either placebo or guanfacine. Nevertheless, there was no way of getting around the fact that darusentan did not meet its prespecified coprimary end points, and the manufacturer has subsequently put on hold further development of this agent in TRH.

The authors cannot provide an explanation for the late reduction of BP with placebo, but it does raise questions about BP end points in hypertension trials. Clearly, by using only the 14-week data for the primary end point, much valuable information on BP gained during prosecution of the trial has to be discarded. However, this is a common approach and should still give a robust outcome in a randomized, blinded, and adequately powered study such as this, and clinic/office measurements of BP currently remain central to clinical trials in this area. However, if the question is whether (and how well) the drug works to lower BP (and reduce cardiovascular risk), there is a strong case for using ambulatory BP monitoring as the primary end point for such studies. Ambulatory BP monitoring is particularly useful in excluding patients with white coat hypertension, who may serve to limit the apparent benefits seen with active treatment. Also, importantly, BP measured in this way shows little in the way of a placebo effect (true of DORADO-AC). In addition, ambulatory BP monitoring provides a better picture of how well the drug works across the full 24 hours after dosing, is a better predictor of cardiovascular risk than office BP, and may give useful prognostic information about the effect of the drug on BP variability (a further independent predictor of risk).

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So, what of ETRAs in hypertension? Endothelin 1 is a potent vasoconstrictor, a major physiological regulator of vascular tone, and, importantly, implicated in the pathophysiology of hypertension. Since the original study by Krum et al., it has been clear that this class of drug lowers BP. Newer studies, in proteinuric kidney disease, suggest an intrarenal role of ETRAs to reduce proteinuria and protect renal function. Indeed, in DORADO, although proteinuria was modest, it was substantially reduced (by >50%) by darusentan. There is a need for a new class of agents, beyond inhibitors of the renin-angiotensin system that provide renoprotection in chronic kidney disease, particularly one that does not affect serum potassium. There is now growing evidence that ETRAs may fulfill this role.

In DORADO, darusentan is described as a “selective endothelin antagonist,” but its selectivity is against endothelin 1 and not between the 2 receptors (ET\textsubscript{A} and ET\textsubscript{B}) that mediate its actions. Darusentan has only marginal selectivity for the ETA receptor, and, given the very flat BP response to increasing dose in DORADO, it is very likely being used at doses close to the top of the dose-response curve, which will not only block ET\textsubscript{A} but also ET\textsubscript{B}-mediated responses. Given that ET\textsubscript{B} receptors clear endothelin 1 from the tissues and circulation, promote endothelial NO release, and play a critical natriuretic role, there are grounds for hoping that ETA selective agents, which have so far been little explored clinically in hypertension, might produce promising results. Indeed, recently, ETRAs have been shown to improve endothelial function in patients with atherosclerosis and reduce arterial stiffness in patients with hypertension and chronic kidney disease. These additional benefits merit further investigation. Finally, it would be helpful to develop biomarkers to indicate which patients are likely to gain the most benefit from ETRAs and valuable to have a better understanding of how ETRAs cause fluid retention so as to maximize the benefits of treatment and to minimize any avoidable risk.

Disclosures
D.J.W. has provided advice on endothelin research to Abbott, Astra-Zeneca, GlaxoSmithKline, Pfizer, Roche, and Speedel.

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