Cardiovasc Drugs Ther (2014) 28:293–294
DOI 10.1007/s10557-014-6535-8

EDITORIAL

Clinical Benefits of Azilsartan Beyond Blood Pressure Lowering?

Editorial to: "Azilsartan Decreases Renal and Cardiovascular Injury in the Spontaneously Hypertensive Obese Rat" by A.H. Khan et al.

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Published online: 24 June 2014

Non-peptide antagonists of the angiotensin II type 1 (AT_1) receptor constitute a very useful and popular class of antihypertensive drugs. Azilsartan, a novel angiotensin II type 1 (AT_1) receptor blocker (ARB), was approved by regulatory authorities for treatment of hypertension and is the 8th ARB to appear on the clinical market [1]. Similar to other ARBs, azilsartan is highly selective for AT_1 receptors and has more than a 10,000-fold greater affinity for AT_1 versus AT_2 receptors. Like many other ARBs, azilsartan can also function as an inverse agonist and inhibit AT_1 receptor signaling that may occur even in the absence of angiotensin II. Based on clinical studies conducted to date, azilsartan appears to be characterized by a superior ability to control 24 h systolic blood pressure relative to other widely used ARBs [1]. In the current issue of the journal, Khan et al. report that azilsartan can decrease renal and cardiovascular injury in the spontaneously hypertensive obese (SHROB) rat [2]. Because the main reason for prescribing ARBs and other antihypertensive drugs is to control blood pressure and reduce the risk for target organ damage, the findings of Khan et al. are of potential clinical interest.

Given that many ARBs have been approved for the treatment of hypertension, the question often arises: Is there a particular ARB that is likely to yield better clinical outcomes than other members of the same class? ARBs can vary with respect to a variety of pharmacokinetic and pharmacological factors such as plasma half-life, potency for AT_1 receptor blockade, and the ability to lower blood pressure at maximum approved doses. To the extent that better blood pressure control is expected to afford improved clinical outcomes, one might anticipate better cardiovascular protection from ARBs that are the most effective in lowering blood pressure. However, this presupposes that ARBs with the greatest ability to reduce blood pressure are not accompanied by adverse effects that might offset the benefits provided by superior blood pressure lowering. One might also be motivated to favor the use of a particular ARB if it could do more than just lower blood pressure and could safely provide a significant degree of added organ protection beyond that achieved by blood pressure lowering. Like the SHROB rat model studied by Khan et al., patients with hypertension also have comorbidities like obesity, metabolic syndrome, diabetes, atherosclerosis, and or kidney disease. Although multiple risk factor intervention including non-pharmacologic strategies like diet and exercise can be useful for reducing the risk for some comorbidities, the presence of beneficial, pleiotropic effects beyond blood pressure lowering in a reasonably priced and safe ARB could represent a useful clinical bonus. If additional properties beyond blood pressure lowering were shown to have clinical value, such features would be reasonable to consider when deciding which angiotensin receptor antagonist to select out of the crowded field of currently available ARBs.

It is generally accepted that AT_1 receptor blockers can help protect against the progression of diabetic nephropathy and that some of this benefit may involve more than just blood pressure lowering. Nevertheless, the ability of ARBs to protect against target organ damage and improve clinical outcomes is still considered to be largely mediated by their ability to decrease blood pressure. In addition to lowering blood pressure, Khan et al. demonstrate that in the SHROB model, azilsartan medoxomil can protect against endothelial dysfunction as judged by its ability to improve vasodilatory responses to acetylcholine [2]. Impaired endothelial function might contribute to the pathogenesis of vascular disease and it is hoped that protection against endothelial dysfunction may promote improved clinical outcomes. Khan et al. also found that azilsartan medoxomil treatment improved left ventricular

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(LV) function, LV hypertrophy, and reduced cardiac fibrosis in the SHROB model [2]. However, the extent to which these cardiovascular benefits might be related to pleiotropic actions of azilsartan beyond the strong antihypertensive effects of the drug remains to be clarified.

Preclinical studies have indicated that azilsartan may have potentially beneficial effects on cellular mechanisms of cardiometabolic disease and on insulin action that could involve more than just blockade of AT_1 receptors and/or reduction in blood pressure. For example, a previous study reported that azilsartan is a pleiotropic ARB with antiproliferative effects in cultured vascular cells that may not strictly depend on AT_1 receptor blockade [3]. In addition, in studies in 3 T3-L1 cells, azilsartan has been found to promote adipocyte differentiation and stimulate expression of genes encoding peroxisome proliferator activated receptors (PPAR) α and δ, leptin, adipsin, and adiponectin more than valsartan [3]. Another study showed that in a rat model, azilsartan treatment reduced MPO and IL-1β levels, increased IL-10 levels, and reduced expression of MMP-2, MMP-9, COX-2, RANK, RANKL, and cathepsin K [4]. While intriguing, the clinical relevance of these additional actions remains to be determined. Meanwhile, the cardiovascular and renal benefits of azilsartan reported by Khan et al. in a rat model of hypertension and obesity are encouraging and are consistent with the known value of ARBs in patients with hypertension including in those with increased risk for diabetes and renal disease.

References

1. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manag. 2012;8:133–43.
2. Khan MA, Neckar J, Cummens B, Wahl GM, Imig JD. Azilsartan decreases renal and cardiovascular injury in the spontaneously hypertensive obese rat. *Cardiovasc Drugs Ther* 2014;28:this issue
3. Kajiya T, Ho C, Wang J, Vilardi R, Kurtz TW. Molecular and cellular effects of azilsartan: a new generation angiotensin II receptor blocker. J Hypertens. 2011;29:2476–83.
4. Araújo AA, Varela H, Brito GA, Medeiros CA, Araújo Lde S, do Nascimento JH, et al. Azilsartan increases levels of IL-10, down-regulates MMP-2, MMP-9, RANKL/RANK, Cathepsin K and Up-regulates OPG in an experimental periodontitis model. PLoS One. 2014;9:e96750.