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COMMENTARY

Possible benefits of azilsartan compared with other angiotensin II type 1 receptor blockers

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Eight types of angiotensin II (Ang II) type 1 (AT1) receptor blockers (ARBs; that is, losartan, candesartan, eprosartan, valsartan, telmisartan, olmesartan, irbesartan and azilsartan) have been developed and are available for clinical use worldwide.[1] ARBs are useful for preventing the development of cardiovascular disease dependent and independent of their blood pressure (BP)-lowering effects. Some of the benefits conferred by ARBs may not be class effects (common effects), and ARBs may also have molecule-specific effects (differential effects).[2] Although ARBs have many molecule-specific effects (for example, uricosuric effect and peroxisome proliferator-activated receptor-γ activity), the clinical significance of these effects remains controversial.[3] We also need to evaluate the differences in ARBs with respect to their BP-lowering effects in clinical trials.

Azilsartan, the newest ARB recently approved for treating hypertension (HTN), provides a significant BP-lowering effect.[4] In this issue of *Hypertension Research*, Takahara *et al.*[5] reported that 10 mg per day azilsartan was non-inferior to 8 mg per day candesartan cilexetil for controlling BP in Japanese patients with HTN, who were already being treated with 8 mg per day candesartan cilexetil. In Japan, 20 mg per day azilsartan and 8 mg per day candesartan cilexetil have been approved as the middle dose. The cost of 10 mg of azilsartan is 68 Japanese yen, which is about half the cost of 8 mg of candesartan cilexetil (140 Japanese yen). ARBs are relatively expensive compared with other types of antihypertensive medications, such as calcium channel blockers and angiotensin-converting enzyme inhibitors. The authors mentioned the benefit of replacing a currently used ARB with another ARB that possesses a similar BP-lowering effect at a lower cost. With regard to the stronger inhibitory effect of azilsartan compared with other ARBs, Rakugi *et al.*[4] reported that once-daily azilsartan (20–40 mg per day) provided a more potent 24-h sustained antihypertensive effect than candesartan cilexetil (8–12 mg per day) in Japanese patients with grades I–II essential HTN in a multicenter, randomized, double-blind study. In addition, several studies compared the antihypertensive efficacy of once-daily treatment with the maximum doses of azilsartan medoxomil, olmesartan and valsartan.[6,7] Treatment with 80 mg per day azilsartan medoxomil lowered 24-h BP significantly more than treatment with either 40 mg per day olmesartan medoxomil or 320 mg per day valsartan. Because the middle and maximum doses of each ARB are different, we should not make a final conclusion regarding which ARB has the strongest inhibitory effect in a clinical setting. As Takahara *et al.*[5] noted as a limitation of their study, they included patients in whom BP was well-controlled by 8 mg per day candesartan. Whether patients with uncontrolled BP would receive the same advantage with 10 mg per day azilsartan is not known. However, at this moment, better ARBs are available with respect to their inhibitory effect at the middle dose and cost.

In basic experimental studies, ARBs have clearly been shown to possess distinct molecule-specific effects.[1,2] While most ARBs have common molecular structures (biphenyl-tetrazol and imidazole groups), they also have slightly different structures. The common molecular structures are thought to be responsible for their class effects, whereas their slightly different structures may be important for promoting molecule-specific effects. Azilsartan, unlike candesartan, has a unique moiety, 5-oxo-1,2,4-oxadiazole, in place of a tetrazole ring. This feature of azilsartan may be responsible for its strong inverse agonism and high affinity for the AT1 receptor compared with candesartan and other ARBs in experimental studies.[8,9] Although this feature of azilsartan may be responsible for its superior BP-lowering efficacy, proving that the molecular effects of ARBs, as revealed in experimental studies, can influence the clinical outcome is difficult. Because ARBs have been used at relatively higher concentrations in experimental studies and the range of the dose of ARBs is limited in clinical treatment, recognizing significant differences between ARBs is not easy. Further studies will be needed to clarify these points so that we can clearly understand the beneficial effects of each ARB.

Takahara's study was an open-label trial but not a double-blind trial.[5] Eighteen patients in their study were allocated to start with 10 mg per day azilsartan but instead started with 8 mg per day candesartan cilexetil, which may have affected the outcome. The study was performed with a crossover design to compensate for this disadvantage. In addition, the study was also a randomized, crossover non-inferiority trial. They also

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performed both intention-to-treat and per-protocol analyses. An intention-to-treat analysis is a comparison of several treatment groups, including all patients who were originally allocated after randomization. A per-protocol analysis is a comparison of several treatment groups that includes only patients who completed the treatments to which they had been originally allocated. An intention-to-treat analysis can avoid various misleading artifacts, whereas a per-protocol analysis leads to a bias in the analysis. In non-inferiority trials, both intention-to-treat and per-protocol analyses should be performed. In these circumstances, they selected a better strategy for their statistical analysis.

In conclusion, Takahara's data clearly show that 10 mg per day azilsartan was non-inferior to 8 mg per day candesartan cilexetil for controlling BP.[5] Although we can expect that azilsartan has beneficial effects, we must be careful when comparing the abilities of ARBs and interpreting their clinical impact.

CONFLICT OF INTEREST

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