Next Generation ARBs

Going Beyond Modulation of the Renin-Angiotensin System

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The renin-angiotensin system (RAS) is one of the multiple physiological systems that regulate cardiovascular homeostasis. Hence pharmacological modulation of the RAS by utilizing angiotensin converting enzyme inhibitors (ACE-I) and/or angiotensin II (AngII) type I receptor blockers (ARBs) is effective in the treatment of cardiovascular disorders, including hypertension, cardiac hypertrophy, and heart failure. Although ACE-I and ARBs are known to be beneficial beyond their blood pressure-lowering activity, blockade of the RAS has been suggested to reduce the relative risk for cardiovascular diseases by only 20% compared with therapeutic RAS blocking agents targeting other physiological systems. This indicates that multiple signaling pathways are clearly involved in pathophysiological mechanisms underlying hypertension and/or cardiovascular risk, and that modulation of the RAS alone is not sufficient to control these pathological conditions completely.

Hypertension is a multifactorial disorder, making simultaneous modulation of two or more pathways an effective treatment. Patients are thus usually given several antihypertensive drugs with distinct therapeutic targets concurrently. However, the increased number of pills to take, unfavorable drug interactions, and different dosing schedules for each drug can lead to poor adherence to this conventional approach. A potential alternative would be development of a single synthetic molecule that can modulate multiple therapeutic targets.

Nitric oxide (NO)-releasing ARBs: NO is a strong vasodilator that is endogenously produced by endothelial cells. In humans, NO regulates vascular tone. Therefore, dysregulation of the NO system contributes to the pathogenesis of cardiovascular disorders. Long-term clinical use of nitrates is limited by the occurrence of tolerance that develops in the process of biotransformation of organic nitrates to an active form. Hence, NO-releasing drugs that directly release NO, including NO-releasing ARBs, have been widely anticipated. Indeed, NO-releasing losartan and NO-releasing telmisartan have been synthesized and demonstrated to have superior cardiovascular effects when compared with those of the original ARBs in ex vivo and in vivo preclinical studies. Interestingly, however, clinical trials have not yet been reported for NO-releasing ARBs.

In this issue, Yahiro, et al. have examined the in vivo effects of another NO-releasing ARB (NO-releasing olmesartan). In contrast to previously reported NO-releasing ARBs, in vivo actions of the NO-releasing olmesartan were notably weaker than those of the original olmesartan although both compounds bound to AT1R with similar affinity in vitro. The authors speculate that the NO-releasing olmesartan might produce an excessive amount of NO that could antagonize its blood pressure-lowering effects.

Dual AT1R/endothelin receptor type A (ETA) antagonist (sparsentan: PS-433540): Endothelin is a potent vasoconstrictor peptide, and its effects on the cardiovascular system are mediated by two GPCRs, named endothelin receptor type A (ETA) and type B (ETB). Bristol-Myers Squibb has synthesized a number of dual AT1R/ETA antagonists, BMS-248360 is a first generation compound, showing high affinities for both AT1R and ETA (AT1R Ki = 10 nM, ETA Ki = 1.9 nM). Further optimization of the first generation compounds led to the synthesis of PS-433540, a second generation dual AT1R/ETA antagonist, which has an improved affinity for the AT1R (AT1R Ki = 0.8 nM, ETA Ki = 9.3 nM), and better pharmacokinetics in dogs and monkeys. After successful preclinical studies, PS-433540 was advanced to a phase II dose-ranging study. Although the blood pressure-lowering effects of PS-433540 in hypertensive patients were found to be greater than those of the ARB irbesartan, PS-433540 is apparently no longer being actively developed as an antihypertensive drug. However, there are indications that PS-433540 (sparsentan) reduces proteinuria in preclinical experiments, and Retrophin, Inc. has therefore begun a randomized, double-blind, phase II clinical trial of...
sparsentan in patients with focal segmental glomerulosclerosis (FSGS), for which currently no FDA-approved therapies exist (DUET; NCT01613118).

**LCZ696: a dual-acting angiotensin-receptor-neprilysin inhibitor (ARNI):** Neprilysin is a membrane-bound zinc metallo-proteinase that degrades endogenous natriuretic peptides. Natriuretic peptides regulate sodium and water homeostasis, and thus neprilysin inhibition followed by increased levels of natriuretic peptides exerts antihypertensive effects. However, neprilysin inhibition also leads to increased levels of vasoconstrictor peptides, including AngII. Therefore, dual inhibition of neprilysin and ACE is complementary and is more effective than inhibiting either one of these enzymes alone. Indeed, omapatrilat, a dual vasopeptidase inhibitor that inhibits both neprilysin and ACE, exhibits spectacular blood pressure-lowering activity. Unfortunately, however, clinical development of this compound has been abandoned because of severe angioedema observed in African American patients due to synergistic accumulation of bradykinin, substance P, and neurokinin as a result of the dual vasopeptidase inhibition.

To overcome this problem, Novartis developed LCZ696: a first-in-class dual-acting angiotensin-receptor-neprilysin inhibitor (ARNI). LCZ696 is a single molecule composed of the ARB valsartan and the neprilysin inhibitor produg AHU377 in a 1:1 ratio. Several phase II clinical trials have already been conducted in hypertensive patients. LCZ696 was shown to be safe and superior in reducing both blood pressure (especially in reducing systolic nocturnal blood pressure) and pulse pressure, compared with placebo or the ARB valsartan. Importantly, no angioedema was observed in these trials, indicating that LCZ696 could be an effective therapy with virtually no side effects. Compared with the standard treatment using ACE-I enalapril (PARADIGM-HF, NCT01035255), LCZ696 also demonstrated superior efficacy in reducing the risks of hospitalization or death in patients with heart failure with a reduced ejection fraction. Notably, some post-hoc analyses have suggested that these beneficial effects of LCZ696 in heart failure patients are greater than would be expected from its blood pressure-lowering activity alone.

Although further clinical studies are now required, these three important examples described above clearly suggest that next generation ARBs could be a significant breakthrough in the field of cardiovascular medicine.

**REFERENCES**