

ATHENS CARDIOLOGY UPDATE 2008

The Role of Double Renin-Angiotensin System Blockade

Haralambos Gavras, MD, FRCP

*Boston University School of Medicine,
Boston, MA, USA*

Blockade of the renin-angiotensin system (RAS) is now recognized as an effective means of lowering blood pressure (BP) and protecting hypertensive patients from end-organ damage. There are nowadays three pharmacologic approaches to blockade of the RAS: with angiotensin-converting enzyme (ACE) inhibitors, introduced in the 1970s, with angiotensin II (Ang II) AT₁ receptor blockers (ARBs), introduced in the 1990s, and with direct renin inhibitors, a new class whose first agent, aliskiren, was introduced in 2006. Clinical studies with the first two classes have shown that neither one achieves complete blockade of the RAS. With chronic use of ACE inhibitors, there is a gradual return of Ang II towards pretreatment levels because enzymes other than ACE (e.g., chymase and others) can cleave off two aminoacids from the decapeptide Ang I, even though there is no evidence of "escape" in terms of BP control. With ARBs there is a partial blockade of AT₁ receptors of variable degree and duration, depending on the affinity of each agent for the receptor and of the duration of the blockade (surmountable or insurmountable).

It has now been shown that an almost complete blockade of the RAS can be achieved by combination of an ACEI + ARB (Hypertension 2003; 41:31-36). There has been clinical evidence that a more complete blockade of the RAS may offer benefits in terms of end-organ protection even beyond those of optimal BP control, e.g. by arresting or reversing the progression of diabetic or other nephropathies (The Lancet 2003; 361:117-124). One such trial, the ONTARGET study of telmisartan + ramipril combination presented recently at the ACC meeting (Chicago, 2008), showed that combination of the two agents achieved a small additional BP lowering compared to monotherapy with either one. Not surprisingly, telmisartan tended to be better tolerated than ramipril. However, there was no advantage with the combination in terms of outcome; in fact, there was a trend to increased adverse reactions, especially renal impairment, which was puzzling. Nevertheless, these data are not much different from those reported in the past for treatment of acute myocardial infarct with valsartan and captopril alone or in combination (the VALIANT study). This is in contrast to two heart failure studies of ACEI + ARB combinations, the Val-HeFT and CHARM trials, in which the ARBs valsartan and candesartan, respectively, showed additional benefits when added to ACE inhibitor therapy.

A complete blockade of the RAS can also be obtained by combination of an ARB with a renin inhibitor. One such study (The Lancet 2007, 370: 221-229) demonstrated that combination of the ARB valsartan with the renin inhibitor aliskiren, produced a significantly greater BP decrease than either agent given as monotherapy. Such combination would be particularly desirable in cases, where total suppression of the RAS is desirable, but the patient is intolerant to ACE inhibition (because of cough or angioedema). Further outcome trials are needed to show whether ARB + renin inhibitor combination offers additional long-term advantages in terms of end-organ

Address for correspondence:
E-mail: hgavras@bu.edu

protection when compared to different drug combinations achieving the same degree of BP lowering.

BIBLIOGRAPHY

1. Gavras H. Historical evolution of angiotensin II receptor blockers: therapeutic advantages. *J Am Soc Nephrol* 1999;10 Suppl 12:S255-7.
2. Gavras I, Gavras H. Angiotensin II as a cardiovascular risk factor. *J Hum Hypertens* 2002;16 Suppl 2:S2-6.
3. Brunner HR, Gavras H. Angiotensin blockade for hypertension: a promise fulfilled. *Lancet* 2002;359:990-2.
4. Gavras H, Brunner HR. Role of angiotensin and its inhibition in hypertension, ischemic heart disease, and heart failure. *Hypertension* 2001;37(2 Part 2):342-5.
5. Gavras H. Effect of ramipril on cardiovascular events in high-risk patients. *N Engl J Med* 2000;343:65-6.
6. Gavras I, Gavras H. The antiarrhythmic potential of angiotensin II antagonism: experience with losartan. *Am J Hypertens* 2000;13(5 Pt 1):512-7.
7. Ribeiro AB, Gavras H. Angiotensin II antagonists: clinical experience in the treatment of hypertension, prevention of cardiovascular outcomes and renal protection in diabetic nephropathy and proteinuria. *Arq Bras Endocrinol Metabol* 2006;50:327-33
8. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75
9. Pfeffer MA, McMurray JJ, Velazquez EJ, et al, VALIANT Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906
10. Young JB, Dunlap ME, Pfeffer MA, et al, CHARM Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;110:2618-26
11. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007;370:221-9
12. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.