Angiotensin II Blockade: A Therapeutic Strategy with Wide Applications

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Summary: Evidence now exists suggesting a pathologic role for angiotensin II in patients with cardiovascular disease and those with risk factors. Clinical trials such as the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE), the Heart Outcomes Prevention Evaluation Study (HOPE), the African American Study of Kidney Disease and Hypertension (AASK), and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study have clearly demonstrated that blood pressure reduction is important in hypertension and diabetes. If this can be accomplished with agents that block the renin-angiotensin system, then additional clinical benefit will be achieved. Clinical data on angiotensin-converting enzyme inhibitors (ACEIs) are well established, while emerging data on the use of angiotensin II receptor blockers (ARBs) continue to grow. There is evidence supporting the concept of angiotensin II escape in the presence of ACEIs. The question that remains to be answered is whether a combination of both agents (ACEIs and ARBs) can improve clinical outcomes. Ongoing clinical trials will answer this question.

Key words: angiotensin II, hypertension, diabetes

Introduction

The goal of identifying and treating hypertension is to reduce the risk of cardiovascular disease and its associated morbidity and mortality.¹ Uncontrolled hypertension has been established as a major risk factor for coronary artery disease,

stroke, end-stage renal disease, and heart failure.² Angiotensin II is well known to cause hypertrophy, fibrosis, and apoptosis at the level of the heart, kidneys, and vasculature. The benefit of interrupting the renin-angiotensin system is well established in heart failure and coronary artery disease.³ Until recently, no class of drug for the treatment of essential hypertension has prevented cardiovascular morbidity and mortality beyond the reduction in blood pressure achieved with diuretics and beta blockers.⁴ There is now clinical evidence suggesting that blocking the actions of angiotensin II at the level of the heart, kidneys, and vasculature, may confer benefits beyond lowering blood pressure.

Clinical Trials of Angiotensin II Blockade

The outcomes of several recent clinical trials support the practice of angiotensin II blockade. The Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE) randomized 9,193 patients with hypertension and left ventricular hypertrophy to receive either the angiotensin receptor blocker (ARB) losartan or the beta blocker atenolol for at least 4 years.⁵ Losartan prevented more cardiovascular morbidity than atenolol, with a similar reduction in blood pressure. The Heart Outcomes Prevention Evaluation Study (HOPE) enrolled 9,297 high-risk patients who had evidence of vascular disease or diabetes with normal ventricular function and randomized them to receive the angiotensin-converting enzyme inhibitor (ACEI) ramipril or placebo.⁶ Ramipril significantly reduced the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients. The mean reduction in blood pressure with treatment was extremely small (3 mmHg systolic/2 mmHg diastolic). There is controversy over whether these blood pressure readings reflect the actual peak reduction of blood pressure. Ramipril doses were given at night, while the blood pressure readings were taken in office-based practice during the day. This represents a large peak-to-trough ratio, so that some of the benefits of ramipril may have been related to blood pressure reduction. Svensson *et al.*⁷ recently reported 24-h blood pressure measurements in 38 patients enrolled in the HOPE study. Ramipril did not significantly reduce office blood pressure (8/2 mmHg, $p = \text{NS}$) or daytime ambulatory blood pressure (6/2 mmHg, $p = \text{NS}$) after 1 year of therapy compared with placebo. However, 24-h ambulatory blood

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pressure was significantly reduced with ramipril (10/4 mmHg, $p = 0.03$), mainly because of a more pronounced blood pressure-lowering effect during nighttime (17/8 mmHg, $p < 0.001$). Many patients in HOPE were normotensive; therefore it is likely that blockade of the renin-angiotensin system exerted additional benefit on cardiovascular outcomes beyond blood pressure lowering.

Angiotensin Blockade and Diabetes

An interesting finding in the HOPE study was a 34% reduction in new-onset diabetes in those patients taking ramipril. The reduction of new-onset diabetes in the presence of agents that block the renin-angiotensin system has also been demonstrated in the LIFE study (25% reduction losartan vs. atenolol) and in the Captopril Prevention Project (CAPPP) (21% reduction captopril vs. beta blockade and diuretics). The CAPPP study compared the effects of ACEIs versus conventional therapy on cardiovascular morbidity and mortality in hypertension.⁸ Both trials demonstrated reduction in new-onset diabetes when agents that interrupt the renin-angiotensin system were used to treat hypertension. There is increasing evidence that angiotensin II blockade by use of either ARBs or ACEIs improves insulin sensitivity, decreases hepatic clearance of insulin, and improves blood flow to the pancreas.⁹

Target Organ Protection

The concept of target organ protection with antihypertensive agents that intervene in the renin-angiotensin system also applies to the issues regarding nephropathy and end-stage renal disease. Brenner *et al.*¹⁰ recently reported the effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy (RENAAL). Patients with diabetes and hypertension ($n = 1,513$) were randomized to receive either the ARB losartan or placebo in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha blockers, and beta blockers). Losartan reduced the incidence of doubling of the serum creatinine concentration (risk reduction 25%, $p = 0.006$) and end-stage renal disease (risk reduction 28%, $p = 0.002$). These benefits exceed those attributable to changes in blood pressure alone. Similar data have been observed with the use of other ARBs.¹¹

The renal protective effects of angiotensin II blockade also extend to black Americans of African descent. This is an important issue in light of recent data suggesting that black American patients with heart failure may not derive as much benefit from ACEIs as white Americans of European descent with heart failure.¹² Agodoa *et al.* recently reported the effect of ramipril versus amlodipine on renal outcomes in hypertensive nephrosclerosis (AASK).¹³ Among 653 black American patients with hypertensive renal disease, ramipril provided a 48% greater reduction in risk of end-stage renal disease, decline in glomerular filtration rate, or death than amlodipine. Blood pressure reduction was similar in both groups ($p > 0.10$).

It is logical that interruption of the renin-angiotensin system offers renal protection and reduces the incidence of pro-

teinuria and end-stage renal disease in diabetes. There is a higher proportion of AT₁ receptors in the efferent than in the afferent arteriole. Activation of these receptors by angiotensin II causes glomerular hypertension, hyperfiltration, and proteinuria. The mesangial cells in the glomerulus also are rich in AT₁ receptors. Activation of these receptors by angiotensin II causes reduction in the filtration constant and release of renal cytokines, specifically transforming growth factor-beta (TGF- β). Production of TGF- β through AT₁ receptor activation is a strong stimulus of type 1 collagen synthesis leading to renal fibrosis. Multiple clinical trials involving patients with hypertension and diabetes have repeatedly demonstrated the benefits of renin-angiotensin system blockade in terms of improved clinical outcomes that are in addition to blood pressure lowering.^{14, 15}

What Is the Best Way to Block the Angiotensin Receptor?

Should we be using ACEIs, ARBs, or both? There is evidence supporting the concept of angiotensin II escape in the presence of ACEIs.¹⁶ Therefore, if we are to offer complete target organ protection from angiotensin II, not only will we have to block the production of angiotensin II with ACEIs, but we may have to use agents that block the receptors of angiotensin II. Current clinical trials are attempting to clarify this question. The recently released Valsartan in Heart Failure Trial (Val-HeFT) demonstrates some benefit in using combination therapy (ACEIs plus ARBs) in heart failure.¹⁷ Other ongoing clinical trials such as the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), Valsartan in Acute Myocardial Infarction (VALIANT), and Candesartan Cilexetil in Heart failure: Assessment of Reduction of Mortality and Morbidity (CHARM) are assessing the use of ACEIs plus ARBs in different cardiovascular disease entities.

Conclusion

Hypertension is generally an asymptomatic condition for which the benefit of treatment is the reduced risk of future heart attack, stroke, and end-stage renal disease. This simple statement represents a very large task. Blockade of the renin-angiotensin system is essential for accomplishing this goal.

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