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Preventing renal disease progression: Can complete renin-angiotensin-aldosterone blockade work?

PERHAPS THE MOST daunting challenge for any primary care physician, nephrologist, or other internal medicine specialist is how to prevent the progression of chronic kidney disease.

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A MAJOR HEALTH CARE CRISIS

Ten to 20 million people in the United States have chronic kidney disease, with diabetic nephropathy and arterial hypertension accounting for two-thirds of cases. In 2007, the US Renal Data System[1] reported that, at the end of 2005, 341,319 patients were receiving dialysis and another 143,693 had received renal transplants.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiatives[2] has raised the level of awareness of chronic kidney disease among physicians and the general public. We have become more adept at diagnosing chronic kidney disease, in particular by calculating the estimated glomerular filtration rate, and we are starting to learn how to sort out the patients designated as having chronic kidney disease by this calculation but without "true" kidney disease. Nevertheless, the medical profession is still struggling to determine the best way to prevent progression in chronic kidney disease, and no single innovative approach currently exists. Should the emphasis be on the blood pressure target, the level of proteinuria reduction, the classes of medications to be used, or on other factors such as lipid control, vitamin D repletion,[3] or glycemic control?

WHY INHIBIT THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM?

Over the last 20 years, investigators have devoted much effort to controlling the adverse effects of the renin-angiotensin-aldosterone system on the renal vasculature and parenchyma. We now understand that this system is a complex cascade and that angiotensin II plays a key role.

Angiotensin II enhances the vascular tone of both the afferent and the efferent glomerular arterioles, helps regulate intraglomerular pressure and glomerular filtration, and stimulates the adrenal cortex to release aldosterone. In addition, it has several nonhemodynamic effects. In particular, it may alter the selective permeability of the glomerular capillary barrier by influencing podocyte morphology and by directing a reorganization of its actin cytostructure.

In theory, complete blockade might be better than partial blockade, but we need more data

Podocytes are highly differentiated pericyte-like cells that are essential for normal kidney function, but they have limited regenerative ability. Angiotensin II stimulation can lead to podocyte injury via mechanical stress due to increased intraglomerular pressure or an increase in cytosolic calcium,[4] formation of bridging between the parietal basement membrane and the glomerular basement membrane,[5] and extension of the extracapillary disease process to the glomerular-proximal tubular junction.[6] These alterations can

result in progressive atrophy, cell death, subsequent fibrosis, and irreversible loss in functioning renal parenchyma.

EVIDENCE FOR AND AGAINST COMBINATION THERAPY

In theory, by completely inhibiting the renin-angiotensin-aldosterone system in some patients with proteinuric chronic kidney disease (as Dr. Sheldon Hirsch suggests in this issue of the *Cleveland Clinic Journal of Medicine*[7]), we might be better able to prevent progressive renal injury than with an incomplete blockade of this system.

The rationale for complete blockade stems from evidence that long-term treatment with an angiotensin-converting enzyme (ACE) inhibitor results in the accumulation of angiotensin I, the escape of angiotensin II generation by ACE-independent enzymes (chymases), and the inhibition of angiotensin-(1–7) formation that partially antagonizes the effects of angiotensin II. In addition, aldosterone may injure the kidney by its rapid nongenomic effect on the renal vasculature, resulting in increased renal vascular resistance, with afferent and efferent vasoconstriction. Therefore, treatment with either an ACE inhibitor or an angiotensin receptor blocker (ARB) by itself may delay but not prevent end-stage renal disease for most patients with proteinuric chronic kidney disease.[8]

Hyperkalemia is a risk when using aldosterone antagonists with ACE inhibitors, ARBs, or both combined

Combining an ACE inhibitor and an ARB

Regimens in which an ACE inhibitor is combined with an ARB may achieve their therapeutic benefit of lowering proteinuria by modulating the compensatory events in kidney injury that stress "normal" nephrons, inhibiting the podocyte injury responsible for contiguous damage in the tubulointerstitial area, and limiting fibrosis and inflammation. However, few trials actually showed that combining an ACE inhibitor with an ARB leads to greater renal protection in the long term than with either agent alone, despite a greater chance of lowering the protein excretion rate.[9,10]

The COOPERATE study. The Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) study[11] evaluated the renoprotective effects of the combination of trandolapril (Mavik, an ACE inhibitor) and losartan (Cozaar, an ARB). Significantly fewer patients reached one of the end points (doubling of the serum creatinine concentration or end-stage renal disease) with the combined therapy than with either agent alone.

Kunz et al[12] recently performed a meta-analysis, which indicated that the combination of an ACE inhibitor and an ARB reduces proteinuria to a greater extent than either drug alone. However, the total number of patients in each trial was less than 30 on average, the duration of therapy rarely exceeded 1 year, and the effect on changes in the glomerular filtration rate or the need for dialysis was not reported.

ONTARGET. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET),[13] combination therapy had no clear benefit in the group at the highest renal risk (ie, with overt diabetic nephropathy), and it was associated with a trend toward worse results in the low-risk group. Most participants in ONTARGET did not have microalbuminuria or macroalbuminuria, and of interest, these patients without protein excretion were at increased risk for renal events, such as acute renal failure requiring dialysis.

Phillips et al[14] recently reported on the safety profile of patients with symptomatic left ventricular dysfunction treated with the combination of an ACE inhibitor and an ARB. Even in these nonrenal patients there was a significantly higher risk of worsening renal dysfunction (relative risk 4.87, 95% confidence interval 2.39–9.94) and hyperkalemia (relative risk 4.87, 95% confidence interval 2.39–9.94) with combination therapy.

Adding an aldosterone blocker to an ACE inhibitor, ARB, or both

There is little evidence that aldosterone plays a role in the progression of chronic kidney disease. However, several studies found that combining an aldosterone blocker with an ACE inhibitor, ARB, or both had an additional impact on reducing proteinuria and modulating the rate of change in the glomerular filtration rate.[15–17]

When aldosterone antagonists were added to an ACE inhibitor, an ARB, or both combined, proteinuria was reduced, but there was little effect on preserving the glomerular filtration rate.[17] However, most of the studies were small, with short observation periods. Hyperkalemia is a risk when using aldosterone antagonists in combination with ACE inhibitors and ARBs, especially in patients with glomerular filtration rates less than 30 mL/minute.[18]

Adding a renin inhibitor to an ACE inhibitor or an ARB

Few studies have examined combination therapy with either an ACE inhibitor or ARB plus a renin inhibitor, the newest class of agents that block this system.

Parving et al[19] recently reported the results of combining aliskiren (Tekturna, a renin inhibitor) with losartan in 599 patients with type 2 diabetes and nephropathy. At 6 months, the renin inhibitor showed a renoprotective effect that was independent of its blood-pressure-lowering effect in those who were receiving maximal recommended doses of the ARB.

OTHER FACTORS ALSO INFLUENCE PROGRESSION

Even though there is broad agreement that an approach that neutralizes the effects of the renin-angiotensin-aldosterone system on the kidney would lower blood pressure and protein excretion rates, whether it would change the natural history of chronic kidney disease and prevent progression is less clear. In reality, a number of factors other than the renin-angiotensin-aldosterone system are responsible for the progression of chronic kidney disease. These other factors may help explain why control of this system does not totally prevent deterioration of chronic kidney disease, although the rate may be slowed.

MORE QUESTIONS THAN ANSWERS

A number of provocative questions arise from Dr. Hirsch's discussion of complete renin-angiotensin-aldosterone system blockade to prevent disease progression:

- Will decreasing proteinuria to a specific target (< 500 mg/day) prevent progression?

- How low should the blood pressure target be set to modulate progression, and should it be the same in all age groups?
- Should complete blockade be applied all at once or in a stepwise fashion depending on the glomerular filtration rate, the level of proteinuria, or both?
- Which patients would benefit most from complete blockade?
- Is direct renin inhibition a critical component of complete blockade?
- What model of chronic disease management is required to avoid unexpected complications if this treatment approach is embraced?

Currently, therefore, there are more questions than answers. This strategy is an intriguing, opinion-based option, but for now it should only be applied to patients with proteinuria and evidence of early progression despite standard therapy who can be closely monitored, and it is not for the faint of heart. In view of the risks of hyperkalemia, hypotension, and perhaps even worsening renal function, more data from carefully designed trials are needed before the general medical community widely applies a complete blockade of the renin-angiotensin-aldosterone pathway to prevent progressive chronic kidney disease.

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