

Dual Blockade of the Renin-Angiotensin System: The Ultimate Treatment for Renal Protection?

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The prevalence of chronic renal diseases is increasing worldwide. There is a great need to identify therapies that arrest disease progression to end-stage renal failure. Inhibition of the renin-angiotensin system both by angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists is probably the best therapeutic option available. Several large, multicenter studies have indeed shown a significant reduction in the risk for doubling baseline serum creatinine or progression toward end-stage renal failure in patients who do and do not have diabetes and have chronic nephropathies that are treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. However, the number of patients who reach end-stage renal failure is still considerably high. Significant reduction of the incidence of ESRD is likely to be achieved in the near future for chronic nephropathies, provided that the degree of renoprotection can be improved. This goal may be attainable with a more complex strategy than with a single or dual pharmacologic intervention on the renin-angiotensin system. Strict control of BP and protein excretion rate, lowering of blood lipids, tight glucose control for individuals with diabetes, and lifestyle changes form part of the future multimodal protocol for treatment of patients with chronic nephropathies.

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Chronic kidney diseases are emerging as a global threat to human health. More than 1 million people worldwide are alive on renal dialysis or with a functioning graft (1). The incidence of renal failure has doubled during the past 15 yr, a trend that is likely to continue in the next decade (2). Contemporary treatment for ESRD is so costly that there is little chance that the vast majority of the world's population will have access to it. Less privileged countries simply cannot establish programs for regular renal replacement therapy for all chronic kidney patients because of its prohibitive cost (3). How could the global burden of chronic kidney disease be diminished in the future? At the present, there are no definitive cures for most acquired kidney diseases, and there is not reasonable expectation that gene therapy will be available soon enough to treat genetic forms of kidney diseases, such as polycystic kidney disease. Renal transplantation is limited by the organ shortage (4), a worldwide problem that is not likely to be resolved soon by xenotransplantation. The best that we can do at the present time is to concentrate our efforts on preventing progression of renal diseases.

Pathophysiology of Progressive Nephropathies

Experimental data from animal models have shown that a wide variety of glomerular insults result in a common pathway of increased glomerular hypertension, systemic hypertension,

glomerular permeability, and proteinuria. These diverse events seem to incite a vicious cycle of injury and inflammation, resulting in a similar pattern of progressive nephropathy, in which glomerular injury leads to proteinuria, interstitial inflammation, and, ultimately, scarring (5). A large number of studies established that progressive deterioration of renal function is the result of compensatory glomerular hemodynamic changes in response to nephron loss. In the widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arteriolar resistance, and increased glomerular blood flow (6). *In vivo*, angiotensin II enhances the vascular tone of both afferent and efferent glomerular arterioles and modulates intraglomerular capillary pressure and GFR (7). Besides these glomerular hemodynamic effects, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important. These findings have suggested that angiotensin II may alter permselective properties of the glomerular capillary barrier by mediating contraction of the foot processes, ultimately changing slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space (8). Abnormal protein trafficking through the glomerular capillary wall might contribute to progression of renal disease. Indeed, recent data support the possibility that the excessive protein load of podocytes can be a factor underlying progressive injury of these glomerular cells and through their release of TGF- β 1, ultimately allowing myofibroblast differentiation of mesangial cells (9). Moreover, excessive protein reabsorption by proximal tubuli provides further intrinsic toxicity to this nephron segment (5). Thus, both *in vitro* and *in vivo* protein overload causes increased production

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of vasoactive and inflammatory mediators such as endothelin-1, monocyte chemoattractant protein-1, normal T cell expressed and secreted (RANTES), a chemotactic cytokine for monocytes and memory T cells, and osteopontin (10). The activation of a variety of molecules, such as cytokines, growth factors, and vasoactive substances, may result in abnormal accumulation of extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis. The proinflammatory mediators promote local recruitment of macrophages and lymphocytes (11), which, in turn, can stimulate the transformation of interstitial cells into myofibroblasts. Proximal tubular epithelial cells can interact with interstitial fibroblast to promote fibrogenesis via release of profibrogenic molecules (12). In summary, there is robust experimental evidence that proteinuria is responsible for interstitial inflammation and subsequent fibrosis, thereby contributing to progressive renal function loss.

Renin-Angiotensin System Blockade for Renoprotection

In chronic proteinuric nephropathies, if the interstitial inflammatory reaction and the subsequent fibrosis were indeed a feature of protein overloading, then limiting protein traffic or the biologic effect of excessive tubular protein reabsorption should prevent or slow the progression of renal disease. This is precisely what happens in animals that are treated with angiotensin-converting enzyme inhibitors (ACE-I). The experimental demonstration that the blockade of angiotensin II with ACE-I slowed the progressive loss of renal function in a number of animal models of renal diseases, including diabetic nephropathy (13,14), offered the opportunity, for the first time, to devise a treatment strategy that was not limited to passively accompany patients to their destiny of dialysis but was aimed to preserve renal function as long as possible. The concept of renoprotection then emerged.

Clinical studies in patients with progressive nephropathies confirm the observations in experimental models that blockade of the renin-angiotensin system (RAS) affords renoprotection. ACE-I are highly effective in reducing proteinuria and slowing progression to ESRD in nondiabetic nephropathy. Their effect on slowing loss of GFR is tightly linked to the antiproteinuric effect. The Ramipril Efficacy in Nephropathy Trial provided definitive evidence that an ACE-I (ramipril) compared with conventional antihypertensive therapy more effectively slowed the rate of GFR at equivalent levels of BP control. The trial was divided into two levels on the basis of degree of baseline proteinuria (stratum 1, 1 to 3 g/24 h; stratum 2, >3 g/24 h). The stratum 2 arm was stopped early because of greater efficacy of ramipril on preserving GFR (mean decline in monthly GFR, 0.53 *versus* 0.88 ml/min for placebo). The ramipril group showed a slower rate of loss of GFR and a greater decrease in proteinuria (55% for ramipril *versus* no reduction for placebo). The reduction in proteinuria was inversely related to the reduction in GFR (15). The investigators also found that this effect was seen across degrees of renal insufficiency and that patients in the lowest tertile of GFR (10 to 30 ml/min) also benefited

from treatment with ACE-I without a significant increase in the risk for hyperkalemia (16).

RAS inhibition is effective in treating type 1 and type 2 diabetic nephropathy. ACE-I reduce the risk of progression of overt type 1 diabetic nephropathy to ESRD and in type 1 patients with microalbuminuria to overt nephropathy (17). The evidence that inhibition of the RAS was superior to conventional antihypertensive therapy in patients with type 2 diabetes was less clear until recently. It is important to consider type 2 diabetic nephropathy separately from type 1, as there are significant differences between the two. Both type 1 and 2 diabetic nephropathies are characterized by the appearance of microalbuminuria, which leads to overt proteinuria and progressive loss of GFR (18). However, a series of renal biopsies in patients with type 2 diabetes and proteinuria revealed that a significant proportion of these patients had glomerular lesions other than the classic lesions associated with type 1 diabetic nephropathy (19,20). ACE-I, which improve glomerular permeability in patients with type 1 diabetes as assessed by dextran clearances, do not do so in patients with type 2 diabetes (21). Furthermore, the superior effect of blockade of the RAS has been difficult to prove. Two recent studies demonstrated that angiotensin II receptor blockers (ARB) are superior to conventional therapy (22) and amlodipine (23) in slowing the progression of overt nephropathy. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study (22) compared the effect of losartan *versus* that of conventional therapy without RAS inhibitors in 1513 patients with type 2 diabetic nephropathy using a primary composite end point of the time to doubling of the serum creatinine, progression to ESRD, or death. Fewer patients in the losartan group reached the composite end point (43.5%) compared with placebo (47.1%), resulting in 16% risk reduction. Most of the reduction in the primary end point was due to renal components: 21.6% of losartan patients experienced a doubling in the serum creatinine compared with 26% of placebo, and 19.6% progressed to ESRD compared with 25.5% of patients who received placebo.

The Irbesartan Diabetic Nephropathy Trial (23) compared the effect of ARB to the effect of a dihydropyridine calcium channel blocker or of standard antihypertensive therapy in 1715 type 2 hypertensive patients. The primary end point was the same as that of RENAAL: Doubling of the serum creatinine, progression to ESRD, or death. The irbesartan group had a lower rate of progression to the primary end point (32.6%) compared with amlodipine (41.1%) or placebo (39%). The beneficial effect remained even after correction for the difference in BP between the treatment groups and placebo. The irbesartan group also had a 33% reduction in proteinuria compared with 6% for amlodipine and 10% for placebo.

Another recent trial examined the efficacy of two different doses of irbesartan (150 *versus* 300 mg) compared with placebo to prevent the progression of diabetic nephropathy in 590 patients with type 2 diabetes and hypertension, microalbuminuria, and serum creatinine <1.5 mg/dl (24). Fewer patients in the high-dose group developed nephropathy ($n = 10$) compared with the lower dose irbesartan group ($n = 19$) and the placebo group ($n = 30$). The combination of irbesartan groups achieved greater BP control than the placebo group, but after

adjusting for differences in BP, the beneficial effects of irbesartan persisted.

All three of these trials were performed with ARB and not ACE-I. This has raised the question as to whether such beneficial results in patients with type 2 diabetes would be seen with ACE-I as well. Unfortunately, for the reasons outlined elegantly by Hostetter (25), a large head-to-head comparison of ACE-I and ARB is unlikely to be made. The choice between an ARB and an ACE-I is made more difficult by the results of the Microalbuminuria–Heart Outcomes Prevention Evaluation (MICRO-HOPE) (26) Trial, in which ramipril reduced the risk for myocardial infarction, stroke, or cardiovascular death by 26% after 2 yr. Perhaps the more interesting question is whether the combination of ACE-I and ARB is more effective than either drug alone.

More Renoprotection with Dual Blockade of RAS

The evidence from clinical trials suggests that the current practice can at the best postpone ESRD for a few years and not avoid dialysis for most patients during their lifetime. Nevertheless, significant reduction of the incidence of ESRD is likely to be achieved in the near future for nondiabetic chronic nephropathies, provided that we can improve the degree of renoprotection. This goal may be attainable with a more complex strategy than with a single pharmacologic intervention on the RAS.

On the clinical ground, there are few trials that show that the combination of an ACE-I with an ARB affords greater renoprotection than each drug used alone. Preliminary studies in sodium-depleted healthy volunteers and in diabetic patients with normal renal function recorded greater reduction in BP and greater increases in plasma renin activity after the addition of losartan to enalapril treatment than after doubling the dose of enalapril (27). An additive antiproteinuric effect of ACE inhibition and angiotensin II receptor antagonism has been reported in normotensive patients with IgA nephropathy; systemic BP was not affected (28). The COOPERATE Study (29) compared a combined treatment of ACE-I and ARB, with monotherapy of each drug at its maximum dose, in patients with nondiabetic renal disease. Eleven percent of patients who receiving combination treatment reached the combined primary end point of time to doubling of serum creatinine concentration or ESRD compared with 23% of patients who were receiving trandolapril alone (hazard ratio, 0.38; 95% confidence interval, 0.18 to 0.63; $P = 0.018$) and 23% of those on losartan alone (hazard ratio, 0.40; 95% confidence interval, 0.17 to 0.69; $P = 0.016$). These studies were performed using a combination of drugs at full recommended doses, which may expose patients to some risks of symptomatic hypotension. In a prospective, randomized, crossover study of 24 patients with nondiabetic, chronic nephropathies, we evaluated the effects on BP, proteinuria, and renal hemodynamics of 8 wk of treatment with combined half-dose benazepril (10 mg/d) and valsartan (80 mg/d) as compared with those achieved by the full recommended dose of benazepril (20 mg/d) or valsartan (160 mg/d) alone. Despite comparable changes in BP and GFR, combined

therapy decreased proteinuria more than benazepril (-56 versus -45.9% ; $P = 0.02$) and valsartan (-41.5% ; $P = 0.002$) alone (30). These findings call for randomized trials that are intended to assess whether the antiproteinuric effect of combined ACE-I and ARB at half dose may in the long term confer more renoprotection than each treatments alone at full dose while achieving comparable BP control.

Multidrug Approach as Ultimate Treatment for the Progressive Renal Diseases

A significant number of patients who were treated with ACE-I/ARB showed only partial antiproteinuric response, and this heralds a progressive loss of renal function in most cases (15–17,22–24). An intensive, multimodal approach to the treatment of chronic nephropathies, which includes BP control, inhibition of the RAS, glucose control, and lipid control, should be more effective than standard approaches. Interest has been growing lately to the new treatment modalities. Data presented at the 62nd Scientific Session of the American Diabetes Association suggested that the association of an aldosterone-blocking agent, eplerenone to enalapril, reduced microalbuminuria in patients with type 2 diabetes to a greater extent than each drug alone, although hyperkalemia was a cause of withdrawal from the study for a significant number of patients (31). In the past several years, TGF- β has been recognized as a central player in the fibrogenic process of diabetic nephropathy (32,33) because of its activity of both stimulating matrix production and blocking matrix degradation (34,35). Experimental data suggest that anti-TGF- β antibody added to a background of chronic ACE inhibition therapy fully protects from the development of proteinuria and renal injury of overt diabetic nephropathy (36). Also, in a severe model of progressive nephropathy resistant to ACE-I, combining the ACE-I with a statin arrests proteinuria and protects from renal function and structure impairment (37).

The multidrug approach to chronic nephropathies has been formalized in an interventional protocol that has been named remission clinic (38). Patients with chronic kidney disease and proteinuria >1 g/24 h are initially treated with a low starting dose of an ACE-I, which then is increased up to the maximum dose. If the goals of BP $<120/80$ mmHg and proteinuria <0.3 g/24 h are not achieved, then an ARB is added at half-maximum dose. Again, the dose is increased stepwise. Throughout this up-titration of ACE-I or ARB, the addition of diuretics is usually needed for optimal BP control or prevention of hyperkalemia. If, after this step, target BP and proteinuria are still not achieved, then the next antiproteinuric drug to be added is usually a nondihydropyridinic calcium channel blocker. In those with LDL cholesterol >100 mg/dl, a statin is added, and in those with diabetes, glycemic control is reinforced to achieve hemoglobin A_{1c} $<7.5\%$. Both interventions (lipid reduction and tight glycemic control) are supposed to contribute to renoprotection (39,40). The multiple drug approach has been tested in >40 patients in our unit, and we could prove that it is feasible and effective. However, it is difficult to test in a formal study because any further addition of new or old drug to ACE-I or ARB in a multiple intervention trial would require a very large number of subjects and would be too costly for any company to

support (41). We probably should make better use of small but well-designed and rigorously conducted study with carefully selected marker of renal progression.

Looking for a more effective treatment, the role of lifestyle changes should not be overlooked. Smoking cessation *per se* may reduce disease progression by 30%, which qualifies as the single most important renoprotective measure (42). Physical activity has always been considered instrumental to the loss of excess weight, but it may have an intrinsic favorable effect, as documented by a small study in 20 patients who had chronic kidney disease and were assigned to 12-wk regular aquatic exercise or the armchair (43). During this short period of time, the body mass index did not change in either group. However, proteinuria decreased by 50% in those who performed aquatic exercise, whereas it did not change in the sedentary group.

Conclusion

The current therapeutic approach for proteinuric chronic nephropathies is based on blockade of the RAS with ACE-I and/or ARB that limit proteinuria and reduce GFR decline and risk for ESRD more effectively than other antihypertensive treatments. Full remission of the disease, however, is seldom obtained, particularly when pharmacologic intervention is started late. For nonresponders, treatment procedure to remission and/or regression must include a multimodal strategy to implement renoprotection.

So far, treatment of renal patients has been aimed at limiting or preventing progression to ESRD. Although we are trying to reduce the number of patients who reach ESRD, the real problem is patients who actually die before end-stage renal failure. Thus, for the future, the goal will be to concentrate not only on reducing the number of patients who reach end stage renal failure but also on those who are at risk for dying of myocardial infarction or other cardiovascular diseases before they reach end-stage renal failure. Why should nephrologists be involved in that? Because, these patients usually have microalbuminuria or some degree of renal dysfunction. Our efforts should be to find these patients and treat them before they develop cardiac or brain accidents.

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