Dual Blockade of the Renin-Angiotensin System in the Progression of Renal Disease: The Need for More Clinical Trials

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There is clear evidence that pharmacologic blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) reduces proteinuria and slows the progression of renal disease in diabetic and nondiabetic nephropathies, a beneficial effect that is not related to BP control. Some patients exhibit a significant beneficial response, whereas others do not. The absence of response may be explained by the incomplete blockade of the RAS obtained with ACEI. In the search of new alternatives that could improve the antiproteinuric and nephroprotective effects of RAS blockers, the association of ACEI and ARB might prove useful. ARB produces a complete blockade of the RAS. Several studies have shown a more marked antiproteinuric effect of the dual blockade of the RAS versus ACEI or ARB alone. A recent study also demonstrated that this more marked antiproteinuric effect is associated with less progression of renal disease in primary nondiabetic nephropathies despite a similar effect on BP. Until now, there has not been any reference to a beneficial effect on progression of the dual blockade in type 2 diabetic nephropathy, which is the most frequent cause of ESRD. A multicenter, prospective, open, active-controlled, and parallel-group trial was designed to compare the effects of an ACE inhibitor versus an ARB or its combination on renal disease progression, proteinuria, and cardiovascular events in type 2 diabetic nephropathy.


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ingle-nephron hyperfiltration hypothesis, put forward by Brenner more than 20 yr ago, helped to explain the inexorable decline in renal function that is observed in chronic renal disease once the initial insult has disappeared. Angiotensin II is responsible for the increase in glomerular hydraulic capillary pressure by means of increasing systemic BP along with vasoconstriction of the efferent arteriole, thereby increasing filtration pressure in glomerular capillary walls. In experimental rat models with renal disease, a decrease of similar magnitude in systemic BP can be achieved either with angiotensin-converting enzyme inhibitors (ACEI) or with a combination of diuretics, reserpine and hydralazine, although only in those who are treated with ACEI is a reduction in glomerular capillary pressure and in progression of renal disease observed (1).

Besides these hemodynamic changes, many other experimental models of renal damage that result in severe proteinuria (e.g., nephrosis by adriamycin or immune-complex glomerulonephritis [2,3]) have implicated angiotensin as a mediator in most of the inflammatory mechanisms that are involved in the progression of chronic renal disease. In proteinuric nephropathies, protein trafficking through proximal tubular cells, besides damaging this tubular segment, stimulates the production of NF-κB, in part induced by angiotensin (4). NF-κB is present in all cellular types and plays a crucial role in inflammation and apoptosis. In experimental models of nephritis, activation of NF-κB results in an increase in expression of proinflammatory and profibrotic genes (5) such as endothelin-1; monocyte chemoattractant protein-1; RANTES, a chemotactic factor for monocytes and memory T cells; osteopontin; and the most powerful profibrotic molecule known, TGF-β1. This last molecule induces the deposition of collagen by inducing phenotypic transdifferentiation of epithelial tubular cells into mesenchymal myofibroblastic cells, promoting the synthesis of extracellular matrix proteins and inhibiting matrix degradation through a decrease in the activity of metalloproteases (6,7).

Recent publications emphasize the relationship between angiotensin II (AngII) and most of the proteins that conform the slit diaphragm between foot processes of podocytes (nephrin, podocin, Zo-1, CD2AP, and NEPH-1). It is likely that disturbances in the synthesis or expression of these proteins may play an important role in the pathogenesis of most proteinuric nephropathies. Furthermore, some studies showed that RAS blockade restores the expression of these proteins almost to normal values in experimental models of diabetic nephropathy (8,9).

Nephroprotection by Blockade of the RAS

Blockade of the RAS has been shown to reduce proteinuria and the rate of decline of GFR in proteinuric nephropathies, including diabetic nephropathy, thus far opening the only way for nephroprotection available at present, although it is only partial. In the 1980s, several small, short-term studies in patients who had diabetic nephropathy with and without hyper-
tension (10,11) showed a slower rate of decline of renal function when treatment with an ACEI, captopril, was given. In the study that was conducted by Lewis et al. (12) in patients with established diabetic nephropathy, treatment with captopril reduced by 50% the risk for doubling serum creatinine, although BP control was similar in both groups. In nondiabetic proteinuric nephropathies, treatment with ramipril instead of conventional antihypertensive drugs reduced significantly the risk for doubling creatinine and to reach ESRD, even after adjustment for BP control (odds ratio 1.78; 95% confidence interval 1.10 to 3.13).

Similar results have been achieved with AngII type I receptor (AT1) blockers. For instance, in the Irbesartan Diabetic Nephropathy Trial (IDNT), 1715 hypertensive patients with nephropathy secondary to type 2 diabetes were randomly assigned to treatment with irbesartan (300 mg/d), amlodipine (10 mg/d), or placebo. The risk for doubling serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$). These differences were not attributable to differences in the range of BP achieved. Another large, double-blind trial in patients with type 2 diabetes and nephropathy showed that treatment with losartan reduced the incidence of doubling of serum creatinine concentration (risk reduction 25%; $P = 0.006$) and ESRD (risk reduction 28%; $P = 0.002$) but had no effect on mortality of any cause.

Although only a few studies have compared the efficacy of ACEI and ARB, it seems to be similar (13,14). In the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial (13), the renoprotective effects of an ARB (telmisartan) and an ACEI (enalapril) in patients who had high BP and type 2 diabetes and had early-stage diabetic nephropathy was compared. The study demonstrated that telmisartan is as effective as enalapril in reducing the decline in GFR. It is known that healthy individuals show an age-dependent decline in GFR of approximately 1 ml/min per 1.73 m$^2$/yr, compared with a decline of 10 to 12 ml/min per 1.73 m$^2$/yr in patients with untreated type 2 diabetes and overt proteinuria (15). In the DETAIL study, the mean yearly decline of GFR in the telmisartan and enalapril groups was 3.5 and 3 ml/min per 1.73 m$^2$, respectively.

Some other conclusions could be drawn through analysis of the studies performed so far:

1. The relationship between proteinuria and nephroprotection is inverse and linear. The maximum antiproteinuric response is observed soon after starting treatment, usually within 6 mo, and identification of nonresponders allows implementation of additional measures.

2. The nephroprotective effect is not universal for all patients. In some studies, although not all of them, nephroprotection has been linked to DD genotype. Nonetheless, its relationship to reduction of baseline proteinuria is well accepted.

3. The antiproteinuric and nephroprotective effect of ACEI and ARB is dose dependent. Unfortunately, the optimal dosages for renoprotection seem to be different from those for BP control and poorly defined at the moment, because there are no dosage-escalation studies for these end points, except for some of the ARB (candesartan and losartan).

**Combined Treatment with ACEI and ARB**

Not all patients who are treated with ACEI or ARB show a clear antiproteinuric response. An insufficient response to ACE inhibition might be explained by incomplete blockade: At least 40% of AngII is produced via other non-ACE pathways, such as chymase (16). This incomplete blockade possibly explains the observation that plasma AngII levels return to normal after chronic ACEI treatment, a phenomenon that is known as ACE escape (17).

Theoretically, treatment with ARB may result in more complete blockade of the unfavorable actions of AngII mediated through AT1. Until recently, AT1 was considered responsible for most of the actions of AngII: secretion of aldosterone, vasoconstriction, and renal sodium reabsorption. Furthermore, AT1 plays a pivotal role in the pathophysiologic effects of AngII, such as profibrogenic and growth actions. This receptor is the predominant subtype in the adult kidney and is localized in glomeruli and renal tubules. Conversely, AT2 had no or only a marginal role in renal pathology, particularly in adulthood. However, several recent studies demonstrated the presence of the AT2 in adult kidney (18), with a range of effects related to kidney disease: regulation of the chemokine RANTES and the matrix protein osteopontin, mediation of the effects of kinin system on vascular cells, nitric oxide release, and prostaglandin E2 production. Esteban et al. (19) clearly showed that only combined therapy with AT1 plus AT2 antagonists blocked renal monocyte infiltration, NF-κB activation, and upregulation of related proinflammatory genes, showing that the blockade of AT2 is necessary to abolish completely the inflammatory process.

Finally, combining a drug (AT1 blocker) that stimulates kinogenase and intracellular bradykinin production with a drug (ACEI) that inhibits bradykinin degradation may provide a theoretical basis for significant augmentation of the bradykinin–nitric oxide–cyclic guanosine monophosphate pathway, with the resultant vasodilation, pressure natriuresis, cytotoxicity, and attenuation of glomerulosclerosis.

Therefore, treatment with both ACEI and ARB may offer synergistic blockade of the RAS that is not attainable with either drug alone. Preliminary studies in sodium-depleted healthy volunteers and in patients with diabetes and normal renal function recorded greater reduction in BP and greater increases in plasma rennin activity after the addition of losartan to enalapril treatment than after doubling the dosage of enalapril (20). Two large, open-label, clinical trials indicated that when an AT1 blocker is added to patients who are receiving an ACEI, the same degree of BP reduction is attained as when adding an AT1 blocker to other classes of drug, such as β blockers, calcium-channel blockers, or even diuretics (21,22).

In chronic proteinuric nondiabetic nephropathies, most studies have shown a superior effect of the combination of ACEI and ARB on proteinuria reduction in comparison with single therapy with ACEI or ARB. In one of the first reports published, the addition of 50 mg of losartan to previous therapy with an
ACEI in eight normotensive patients with IgA nephropathy and heavy proteinuria was associated with a more marked antiproteinuric effect than either drug alone, although there were not any significant additional antihypertensive effect (23). Laverman et al. (24) carried out a very interesting study in nine renal patients without diabetes and with median proteinuria 4.5 g/d, creatinine clearance of 80 ml/min, and mean arterial pressure of 102 mmHg. In the first 6-wk treatment period, the optimal antiproteinuric dosage of each drug was established. Losartan and lisinopril were used in randomized order, each preceded by a baseline period without medication. Afterwards, patients were treated with a combination using the optimal antiproteinuric dosages that were established for individual drugs. The antiproteinuric response of losartan was optimal at 100 mg, being larger than with 50 mg but not improving by titration up to 150 mg. Proteinuria decreased further at each up-titration step of lisinopril to $\sim75\%$ at the 40-mg dosage. Combination therapy reduced proteinuria more effectively than monotherapy ($P < 0.05$) and lowered mean arterial pressure to a level that was lower than the optimal dosage of losartan ($P < 0.05$) but not different from the optimal dosage of lisinopril. This study, although small in size, underscores the key question of the greater antiproteinuric effect that is attained by dual blockade compared with maximal antiproteinuric dosages of ACEI and ARB. Nonetheless, as described for trials in diabetic nephropathy, the question of whether the additive effect of combination therapy is not dependent on a greater reduction of BP remains open.

We studied 45 patients who had primary proteinuric nephropathies (urinary protein/creatinine ratio $3.8 \pm 2.4$ g/g) and normal or slightly reduced renal function (creatinine clearance 95 $\pm 33$ ml/min) and were enrolled in a 6-mo multicenter, prospective, open-label, randomized (1:1:1), active-controlled, and parallel trial (25). They received treatment with lisinopril (up to 40 mg/d), candesartan (up to 32 mg/d), and combination therapy at middle dosage (lisinopril up to 20 mg/d and candesartan up to 16 mg/d). After 6 mo, the urinary protein/creatinine ratio decreased in patients who were treated with lisinopril alone to $\sim50\%$, in patients who were treated with candesartan alone to $\sim48\%$, and in patients who were treated with the combination of both to $\sim70\%$. BP was reduced significantly from the first month until the end of follow-up for both systolic (SBP) and diastolic BP (DBP) compared with baseline but without any significant difference between groups at any time point. In this study, for the first time, it can be concluded that in chronic proteinuric nondiabetic nephropathies, dual blockade of the RAS with ACEI and ARB produces a beneficial antiproteinuric effect that is not attributable to more pronounced systemic BP reduction (25).

The COOPERATE trial (14) was the first long-term clinical trial to address the effect of dual blockade on primary renal end points. This was a double-blind, randomized, controlled study of 263 Japanese patients with nondiabetic proteinuric renal disease that was carried out in a single center. Patients were treated with 3 mg of trandolapril (dosage with maximal antiproteinuric response demonstrated), losartan 100 mg (maximal authorized dosage), or the combination of both drugs at the same dosage. Predicted follow-up was up to 5 yr, although it was ended prematurely after an intermediate analysis carried out at 3 yr of follow-up, because 23% of those who were on monotherapy reached the combined end point of doubling serum creatinine or creatinine clearance $<7$ ml/min, compared with 11% of those on dual blockade. There were no differences in SBP or DBP between groups at any point in follow-up. Covariates that affected renal survival were combination treatment, age, baseline renal function, change in daily urinary protein excretion rate, use of diuretics, and antiproteinuric response. The frequency of nonfatal adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group.

In the trials that have been conducted thus far, combined therapy was well tolerated. The most frequent adverse event has been hyperkalemia, which was managed easily with usual measures and only in rare instances was responsible for study dropout. As expected, this complication was more frequent in patients with reduced GFR (14,25). Some other adverse events, such as hypotension, cough, asthenia, and anemia, also have been reported. It is widely known that the RAS stimulates erythropoietin synthesis (26); therefore, blockade results in anemia. The effect is dosage-dependent in monotherapy and additive with dual blockade.

The effect of dual blockade of RAS in patients with diabetes has been investigated in short-term studies using surrogate end points for progression of diabetic nephropathy, such as antiproteinuric effects. The Candesartan and Lisinopril Microalbuminuria (CALM) study (27) was a prospective, randomized, double-blind trial in 199 patients with microalbuminuria, hypertension, and type 2 diabetes with 4 wk of a placebo run-in period and 12 wk of monotherapy with candesartan (16 mg once daily) or lisinopril (20 mg once daily), followed by 12 wk of monotherapy or combination treatment (16 + 20 mg once daily). At 24 wk, the mean reductions in DBP with combined treatment were significantly greater than with candesartan or lisinopril (16.3 versus 10.4 versus 10.7 mmHg; $P < 0.001$). Furthermore, the reduction in urinary albumin/creatinine ratio with combined treatment was greater than with candesartan and lisinopril (50 versus 24 versus 39%; $P < 0.001$). In patients with type 1 diabetes, Jacobsen et al. (28) performed a randomized, double-blind, crossover trial in 21 patients with proteinuria $>1$ g/d. The patients who were treated previously with ACEI received irbesartan 300 mg once daily or placebo. The addition of ARB induced a mean reduction in albuminuria of 37% and a reduction in 24-h BP of 8 mmHg SBP ($P = 0.11$) and 5 mmHg DBP ($P < 0.01$). Similar results were reported by the same author in type 1 diabetes in a randomized, double-blind, crossover trial of 18 patients who had albuminuria $>300$ mg/24 h and received 8 wk of placebo, 20 mg of benazepril, or 80 mg of valsartan and the combination (20 mg + 80 mg) in a random order (29). Treatment with benazepril, valsartan, or dual blockade significantly reduced albuminuria and BP compared with placebo. Benazepril and valsartan were equally effective. Dual blockade induced an additional reduction in albuminuria (43%) compared with any type of monotherapy and an additional
reduction in SBP of 6 mmHg and in DBP of 7 mmHg compared with both monotherapies.

In this and others studies in established diabetic nephropathies (30), dual blockade of RAS has been shown to reduce proteinuria significantly, but control of BP achieved was different in experimental and control groups. Although the differences in systemic BP were small, only a few mmHg, it raises the controversy as to whether the effect on urinary albumin excretion relates to more effective reduction of BP than to more complete blockade of the RAS.

No one trial has been published in diabetic nephropathy with direct comparison of ACEI and ARB in monotherapy and with combined treatment at equipotential dosage with a similar objective for BP control on the beneficial effect on renal disease progression. We are presently recruiting patients for such a clinical, open-label, randomized (1:1:2) trial to compare the effect of lisinopril (40 mg/d), irbesartan (600 mg/d), and combined therapy (lisinopril 20 mg/d and irbesartan 300 mg/d) on renal outcome after 3 yr of follow-up (primary composite end point of doubling serum creatinine, chronic kidney disease stage 5 according to Kidney Disease Outcomes Quality Initiative (K/DOQI), or death) in patients with diabetes and established nephropathy (microalbuminuria/creatinine ratio >300 mg/g) and chronic kidney disease stages 2 to 3 according to the K/DOQI. Proteinuria reduction and cardiovascular events are predefined secondary end points of the study. At the same time, we will study the effects of each treatment on plasmatic and urinary levels of TGF-β, oxidative stress, inflammatory parameters, fibrinolytic balance, and endothelial damage.

Conclusion

Combined therapy with ACEI and ARB results in a more complete blockade of the RAS than monotherapy, even when these drugs are given at maximal antiproteinuric dosage. In proteinuric nephropathies, whether diabetic or not, it reduces significantly baseline proteinuria. This effect is individual, because some patients do not respond and cannot be identified beforehand, independent of the severity of baseline proteinuria, and it is dosage dependent. Although it is possible and plausible that this effect might be independent of the effect on BP reduction, in most of the studies reported to date, the greater antiproteinuric effect has been associated with a greater reduction of systemic BP with combined therapy. The only published study that evaluated progression of renal disease and not only a surrogate marker, such as proteinuria, in nondiabetic proteinuric nephropathies demonstrated that dual blockade reduced significantly progression of chronic renal disease independent of BP. Until now, there has not been any reference to a beneficial effect on progression of the dual blockade in type 2 diabetic nephropathy, which is the most frequent cause of ESRD. We designed this multicenter, prospective, open, active-controlled, and parallel-group trial to compare the effects of an ACE inhibitor versus an ARB or its combination on renal disease progression, proteinuria, and cardiovascular events in type 2 diabetic nephropathy. The results of this trial will be available in 2009. Finally, in some pilot studies, a nephroprotective effect of blockers of aldosterone receptors have been shown (31). It could be of interest to compare the antiproteinuric and nephroprotective effect of ACEI and/or ARB, at least in patients with preserved GFR, with a blocker of the aldosterone receptor.

References


