Dual Renin-Angiotensin System Blockade for Nephroprotection: Still under Scrutiny

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Key Words

Renin-angiotensin system · Dual blockade · Diabetic nephropathy · Chronic kidney disease

Abstract

In experimental diabetic and non-diabetic chronic kidney disease (CKD), angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) combination therapy reduces proteinuria and prevents structural lesions more effectively than either drug alone. Consistently, in humans, a multidrug individually tailored antiproteinuric treatment based on combination therapy with maximum tolerated doses of ACEi and ARB (Remission Clinic protocol) reduced proteinuria and prevented end-stage renal disease (ESRD) more effectively than ACEi/ARB monotherapy, in particular in subjects with non-diabetic CKD. Fixed doses of an ACEi or renin inhibitor added to losartan failed to exert any additional renoprotective effect as compared with losartan monotherapy in patients at increased cardiovascular risk (ONTARGET study) or with type 2 diabetes and overt nephropathy (ALTITUDE study). The VA NEPHRON D study found that losartan and lisinopril combination therapy reduced by 34% the risk of predefined reductions in estimated glomerular filtration rate, ESRD or death as compared to losartan in 1,448 type 2 diabetes patients with overt nephropathy. Unfortunately, the treatment effect failed to

achieve the nominal significance ($p = 0.07$) because of premature trial interruption. Thus, the Remission Clinic protocol is the most powerful tool to prevent progression to ESRD in non-diabetic proteinuric CKD. Results of the ongoing VALID trial will show whether this approach can be safely extended to type 2 diabetes patients.

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Tens of trials have consistently shown that inhibitors of the renin-angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), more effectively than other non-RAS-inhibiting blood pressure-lowering medications, reduce proteinuria and delay or even prevent end-stage renal disease (ESRD) in both diabetic and non-diabetic proteinuric chronic kidney disease (CKD) [1]. Then, studies consistently found that reduction in proteinuria and renal or cardiovascular events were correlated (fig. 1) [2] and stronger RAS inhibition obtained by ACEi and ARB combination therapy could reduce proteinuria and delay ESRD even more effectively than ACEi or ARB monotherapy [3]. Consistently, several animal models of proteinuric disease documented that combined ACEi and ARB therapy reduces proteinuria and prevents and even regresses glomerulosclerotic, tubulointerstitial and vascular lesions more effectively

Fig. 1. Change in proteinuria from baseline and renal disease outcome in 2,387 patients with proteinuric CKD included in 11 randomized clinical trials. The asterisk indicates patients who were included in 2 studies that were too small and too short to detect a long-term treatment effect on GFR decline or ESRD events. Modified from Ruggenenti et al. [11].

than single drugs, in particular in experimental type 2 diabetes [4]. However, when proteinuria is minimal, as in patients at increased vascular risk included in the ONTARGET trial, dual-drug RAS inhibition has no effect over single-drug therapy on renal function loss [5]. Recently, the ALTITUDE trial tested the nephro- and cardioprotective effects of adding either the renin inhibitor aliskiren or a placebo to standard monotherapy with an ACEi or ARB in 1,515 type 2 diabetes patients with overt nephropathy [6]. Following its premature closure because of excess non-fatal strokes in the combination therapy arm, the US Food and Drug Administration contraindicated the concomitant use of aliskiren with ACEi or ARB in diabetes patients and warned that aliskiren should be avoided with ACEi or ARB in patients with moderate to severe renal impairment (<http://www.fda.gov/drugs/drugsafety/ucm300889.htm>).

Now, the premature closure for safety and futility reasons of the VA NEPHRON D [7] – a randomised trial testing the ACEi lisinopril plus ARB losartan combination therapy versus losartan monotherapy in 1,448 type 2 diabetes patients with overt nephropathy – led most diabetologists and nephrologists to definitely drop the dual RAS blockade as a harmful intervention in diabetes patients. However, at study closure dual RAS inhibition had already reduced ESRD events by 34% compared to losartan, a treatment effect never achieved before in type 2 diabetes. Risk reduction was associated with significantly higher proteinuria reduction and approximated the nominal significance ($p = 0.07$) over just 2.2 years of follow-up. Also in the RENAAL study, the larger antiproteinuric effect of losartan was associated with a similar (28%) ESRD risk reduction compared to placebo. Finding that treatment effect was still not appreciable at 2.2 years of follow-up, but became highly significant at the planned

3.2 years of follow-up [8], strongly suggests that also in the VA NEPHRON D trial ESRD event reduction could have become significant over the originally planned 5-year study period. Larger early glomerular filtration rate (GFR) reduction induced by dual RAS blockade diluted the treatment effect on the primary composite end point of GFR reduction, ESRD or death. However, early GFR reduction associated with RAS inhibition is known to predict slower GFR decline in the long term. Thus, the opportunity to demonstrate clinically relevant nephroprotection was unfortunately missed because of premature study closure dictated by adverse events, such as hypotension, hyperkalemia and acute kidney injury that could have been prevented by avoiding forced ACEi up-titration (up to 40 mg lisinopril daily in patients with an estimated GFR as low as 30 ml/min/1.73 m²) on top of full-dose losartan. Indeed, excess blood pressure reduction may precipitate cardiovascular events and acute kidney injury, in particular in elderly diabetes patients with diffuse atherosclerotic vascular disease and vascular stiffness. Moreover, complete RAS inhibition may blunt kidney vascular adaptation (autoregulation) to decreased perfusion pressure, with critically reduced glomerular pressure and filtration. Acute kidney injury and hyperkalemia may follow, in particular when kidney perfusion is further impaired by concomitant renovascular disease, a condition that may affect up to 20% of diabetes subjects, or overzealous fluid restriction or diuretic therapy, congestive heart failure, surgery, sepsis, bleeding and other intercurrent diseases.

In all the aforementioned studies, combined RAS inhibition was obtained by using recommended doses of both drugs. A different therapeutic strategy based on the combination of lower than recommended doses of an ACEi and an ARB has been suggested to effectively block

the RAS without excess blood pressure reduction and side effects. In a pilot, randomised clinical trial of 30 type 2 diabetes patients with overt nephropathy, 8-week combination therapy with 10 mg/day of enalapril and 50 mg/day losartan achieved larger proteinuria reduction than 20 mg/day of enalapril or 100 mg/day of losartan monotherapy. This effect, which was observed at similar blood pressure control across treatments and without appreciable changes in measured GFR and serum potassium levels [9], was likely mediated by decreased renal vascular resistance and an improved glomerular sieving function [10]. Now, the ongoing VALID trial is testing whether larger proteinuria reduction achieved by halved doses of an ACEi and an ARB may delay ESRD more effectively than full doses of each agent alone in 102 type 2 diabetes pa-

tients at high risk of events because of severe renal involvement (ClinicalTrials.gov: NCT00494715).

While waiting for the results, we suggest that ACEi and ARB combination therapy is not abandoned, since this regimen may be the most powerful tool to slow or prevent progression of chronic proteinuric nephropathies provided that treatment is individually tailored by careful dose titration to proteinuria and tolerability [3]. This approach, used in the context of the Remission Clinic protocol, allowed stabilising kidney function and preventing ESRD in 56 patients with CKD and nephrotic-range proteinuria, otherwise predicted to require renal replacement therapy within few years or months [3]. Ongoing studies will soon show whether this approach can be safely applied to the average population of patients that every day attend a renal clinic.

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