Dual inhibition of the renin system by aliskiren and valsartan

In 1898, Tigerstedt and Bergman discovered a powerful vasoconstrictor originating from the kidney, which they properly termed renin.1 This fundamental discovery started a mainstream of experimental and clinical research, leading up to the development of angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-II type-1 receptor blockers (ARBs), and renin inhibitors. Aliskiren is the first orally active renin inhibitor that has progressed to phase III clinical trials.2

In today’s Lancet, Suzanne Oparil and colleagues report the first large-scale (more than 1700 patients) randomised study of dual renin-system inhibition with the maximum recommended daily doses of aliskiren (300 mg) and the ARB valsartan (320 mg).3 At 8 weeks, aliskiren plus valsartan lowered blood pressure significantly more than either monotherapy or placebo (p<0·0001). When measured by conventional sphygmomanometry, the placebo-corrected blood-pressure-lowering activity of the combination averaged 12·6 mm Hg systolic and 8·1 mm Hg diastolic. Combination therapy provided additional systolic/diastolic reductions of 4·4/3·2 mm Hg and 4·2/2·5 mm Hg over aliskiren and valsartan monotherapy, respectively. Renin inhibitors do not lower blood pressure in normotensive individuals.2 An 8-h daytime ambulatory blood pressure of at least 90 mm Hg was therefore a prerequisite for entry in Oparil’s study. Only 45% of screened patients were randomised. The generalisability of these results is limited by the selective recruitment and the use of diastolic rather than systolic blood pressure as the main selection criterion and primary-efficacy variable.

More than 25 years ago, one of us reported for the first time escape of the inhibition of the renin system during long-term treatment with the ACE inhibitor captopril.4 ACE inhibitors, ARBs, and renin inhibitors interrupt the normal feedback suppression of renin secretion from the kidneys. The reactive rise in circulating active renin leads to greater generation of angiotensin I, which in turn increases the formation of angiotensin II via pathways dependent or independent of ACE. Non-ACE-dependent pathways of angiotensin generation, for instance via chymase5 or ACE,6 are upregulated during long-term ACE inhibition (figure). The increase in serum potassium also contributes to the increase in aldosterone secretion during chronic inhibition of the renin system.4 Renin inhibitors do not block renin-like enzymes, such as cathepsin D or tonins, which are present in the vascular wall and which release angiotensin I from angiotensinogen (figure). The idea of dual inhibition of the renin system has its rationale in limiting the escape during chronic inhibition of the renin system at a single step of the cascade. ARBs combined with ACE inhibitors shield the type-1 receptor against angiotensin II generated via non-ACE pathways. ACE inhibitors or ARBs, on top of renin inhibitors, protect against angiotensin generated
via renin-like enzymes. Renin inhibitors combined with ACE inhibitors or ARBs inhibit plasma renin activity even in the presence of a reactive rise in renin. In line with this concept, in Oparil and colleagues’ study, the combination of aliskiren with valsartan reduced plasma renin activity by 44%, despite a nine-fold increase in the renin concentration.

Oparil and colleagues report that the rates of adverse events and laboratory abnormalities were similar in all groups. However, they note that the proportion of patients with a transient increase of serum potassium above 5.5 mmol/L at any time post-baseline was higher in the combination group (4%) than in the aliskiren (2%) and valsartan monotherapy groups (2%) or in the placebo group (3%).

Hyperkalaemia can result in severe complications, such as paralysis, arrhythmias, and cardiac arrest. In patients with hyperkalaemia (>6.0 mmol/L) admitted to a teaching hospital, drug treatment in general and ACE inhibitors in particular were contributing factors in 63% and 15% of cases, respectively. Severe hyperkalaemia often remains unrecognised, with few symptoms prior to cardiac arrest.

Phase III trials of aliskiren with intermediate endpoints are in progress in high-risk patients with left ventricular hypertrophy, heart failure, or renal dysfunction. Because of the expected differences in blood-pressure between the groups randomised in these trials, interpretation will not be easy. No new class of antihypertensive agents should make it to routine use without hard outcome data. That necessity applies even more to dual inhibition of the renin system, which exposes patients to hyperkalaemia and renal insufficiency. Trials of the combination of ARBs with ACE inhibitors in patients with heart failure, kidney disease, or high-risk hypertension are complete or close to publication. In terms of blood-pressure reduction, Oparil and colleagues’ trial supports the concept of dual renin inhibition, with a renin inhibitor and an ARB. However, the additional blood-pressure reduction, over and beyond that provided by the single components, was not as large as might be expected from combining any two antihypertensive agents from different classes. One wonders therefore why Oparil opted to combine aliskiren with valsartan, rather than with a diuretic or a calcium-channel blocker, as recommended by current guidelines. Such agents decrease serum potassium, and counteract the increase in serum potassium on renin-system inhibitors. In the end, dual renin inhibition might find a niche in selected hypertensive patients at high risk with associated conditions or in treatment-resistant hypertension. However, because of the potential life-threatening side-effects, which require biochemical monitoring, this concept of treatment is unlikely to make it to general practice or even to primary prevention in specialist care.

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