Effects of Endothelin Receptor Antagonism Relate to the Degree of Renin-Angiotensin System Blockade in Chronic Proteinuric Kidney Disease

To the Editor:

We thank Benigni and Remuzzi\(^1\) for their informative editorial relating to our study.\(^2\) They raise a number of pertinent issues. They comment that it would be interesting to know whether subjects included with focal segmental glomerulosclerosis (FSGS) had idiopathic or secondary disease, because there are currently few treatments available for this condition. We agree that specifically studying FSGS would be of great interest. However, all of the FSGS subjects included in our study had secondary disease. Idiopathic FSGS, more often than secondary, presents with problematic nephrotic syndrome (a specific exclusion for our study), whereas those with secondary FSGS often have asymptomatic but heavy residual proteinuria despite treatment. Indeed, of the 8 FSGS subjects studied, 4 had nephrotic-range proteinuria despite maximal achievable renin-angiotensin system blockade.

The suggestion of analyzing responses to treatment between those subjects receiving angiotensin-converting enzyme inhibitors (ACE-Is) alone with those receiving a combination of an ACE-I and angiotensin receptor blocker (ARB) is well received. We have done this for proteinuria and pulse wave velocity (see Figure). As can be seen, after administration of BQ-123 (selective endothelin-A receptor antagonist), the reduction in both was greater in those subjects receiving dual ACE-I/ARB treatment than in those on ACE-I alone. As suggested in the editorial, these findings support a role for endothelin antagonists to be considered in the multimodal regimen of the remission clinic.

Finally, Benigni and Remuzzi\(^1\) outline the importance of considering whether the presence of “aldosterone escape” could make a difference in the response to treatment with an endothelin antagonist. We agree that this phenomenon may be of crucial importance in those patients with residual proteinuria despite maximal inhibition of the renin-angiotensin system. However, although we can measure plasma aldosterone in our subjects, this would be of limited value. Because we are unable to measure aldosterone longitudinally, both before and after the initiation of renin-angiotensin system blockade, it will not be possible to identify those subjects exhibiting aldosterone escape. Furthermore, there currently exists no cutoff value for plasma aldosterone above which subjects are considered to exhibit escape.\(^3\) The introduction of aliskiren, the first licensed renin inhibitor, may overcome the problem of escape and residual proteinuria, but only to a degree,\(^4\) and there is growing evidence for endothelin antagonists to be of additional benefit.\(^2,5\)

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