Effect of a Reduction in Uric Acid on Renal Outcomes During Losartan Treatment: A Post Hoc Analysis of the Reduction of End Points in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial

To the Editor:

We read with interest the recent article by Miao et al,1 which presents the results of a post hoc analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Study. The results suggest that losartan reduces serum uric acid (sUA), and this relates to the degree of long-term renal risk reduction and explains part of losartan’s renoprotective effect. We raise some issues.

sUA remained at its baseline of 6.7 mg/dL after losartan treatment. Because the placebo arm showed a rise in sUA (6.7–6.9 mg/dL), there was a mean group difference in sUA of −0.16 mg/dL in favor of losartan. The authors suggest that, after controlling for baseline and change in “other risk factors,” there is an almost linear relationship between the change in sUA and renal outcome (Figure 3 of Reference 1), with each 0.5 mg/dL reduction in sUA associated with a 6% reduction in the combined renal end point. However, we would argue that the CIs for each of the data points shown are too large for there to be any clearly observable trend, although it is statistically significant. Furthermore, the proposed relationship between the change in sUA and renal outcome would correlate to a modest 1.9% renal risk reduction for the change in sUA observed. The authors write that, “this is the first study that directly shows that the effect of losartan on sUA is associated with renal risk reduction.” This is perhaps an overinterpretation of these data. Although we agree that losartan slows the rise in sUA compared with placebo, the relationship of this “fall” to renal outcome remains unclear.

Through a series of statistical tests, the authors suggest that approximately one fifth of the overall renoprotective effect of losartan may be attributable to its “lowering” of sUA. This post hoc analysis is useful for looking at different treatment effects on sUA but is unable to provide this as a definitive mechanism for the renoprotection seen. Indeed, although losartan slows the rise in sUA and this may be linked to a beneficial renal outcome, it is unclear whether this is a direct effect of this drug on sUA or an indirect effect through blood pressure lowering, reduction in oxidative stress, or some other mechanism. sUA may be beneficial because it has powerful antioxidant properties2 in vivo, so here association is by no means synonymous with causation. Thus, the change in sUA may simply be a marker of some other drug effect or indeed a result of the outcome, per se. Indeed, this effect on sUA is not restricted to losartan and is also seen with endothelin receptor antagonists,3,4 which show promise as a novel therapy in chronic kidney disease.5

Disclosures

None.

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