Response to Letter Regarding Article, “Uric Acid Therapy Improves Clinical Outcome in Women With Acute Ischemic Stroke”

We thank Drs Heo et al for their comments on our article entitled “Uric acid therapy improves clinical outcome in women with acute ischemic stroke.”

In our study, a reanalysis of the Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischemic Stroke (URICO-ICTUS) trial, we showed that the administration of uric acid (UA) improved clinical outcome and reduced infarct growth significantly in women, but not in men. Thus, there was a 13% absolute increase in the rate of excellent outcome in women treated with UA compared with only 2% in men. Heo et al wonder whether this protective effect may be confounded by differences in baseline UA levels beyond sex-specific effects. Indeed, we concur with these colleagues that sex-specific traits, including baseline UA levels, could have affected stroke outcome in this trial.

In the URICO-ICTUS trial, baseline UA levels were available only for 142 (35%) of the 411 patients included in the efficacy analysis. As expected, women had lower concentration of UA than men at baseline, and UA levels were persistently lower in women allocated to the placebo group at 6 to 12 hours, 48 hours, and 90 days. Serum UA levels increased similarly in both sex groups, but women showed a greater allantoin to UA ratio at the end of therapy, suggesting a greater exposition to the effects of free radicals and a more efficient nonenzymatic oxidative consumption of the administered UA, because allantoin production in humans only results from free radical–mediated oxidation of UA. Likewise, we suggest that a naturally reduced endogenous antioxidant capacity in women would render this sex group more vulnerable to oxidative stress–mediated brain damage. In our study, women also had a reduced infarct growth after UA administration, and this effect was stronger in women with higher allantoin to UA ratio, suggesting the oxidative consumption of the exogenously administered UA as a plausible neuroprotective mechanism. Taking this together, we argue that women obtained greater clinical benefits after UA replenishment than men because of their greater need of antioxidants and more efficient mechanisms of UA oxidation.

URICO-ICTUS predefined several exploratory analyses to guide the design of future trials, which included the independent outcome effects of sex and baseline stroke severity, but not the effects of baseline UA levels. Accordingly, this post hoc analysis cannot be performed because many of the study participants did not have this information collected, limiting the statistical power and the interpretation of this effect.

As correctly pointed out by Heo et al, in the URICO-ICTUS trial, patients with mild to moderate stroke on admission who received UA obtained larger clinical benefits compared with the placebo group. These authors argue that this finding seemed to contradict the greater benefits obtained in women, regardless their more severe strokes at baseline. Alternatively, we think that this result highlights the high complexity of the factors determining stroke outcome, including sex and baseline stroke severity, among others as the concentration of glucose at stroke onset or the variability of comorbid conditions. We cannot exclude either that at each sex group, UA therapy was more effective within subgroups of individuals with less stroke severity at baseline. We agree with Heo et al that an additional larger trial is needed to validate the encouraging results of URICO-ICTUS and better establish which factors sway the response to this promising therapy.

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Disclosures

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