The Addition of Uric Acid to rt-PA Therapy May Improve Outcomes in Patients With Acute Stroke

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Ángel Chamorro, MD, PhD, University of Barcelona, Barcelona, Spain, presented results from the Efficacy Study of Combined Treatment With Uric Acid and rt-PA in Acute Ischemic Stroke [URICO-ICTUS; NCT00860366], a Phase 3 investigator-driven, multicenter, randomized, placebo-controlled efficacy study to determine whether combined treatment with uric acid and recombinant tissue plasminogen activator (rt-PA) is clinically superior to rt-PA alone.

Although this study failed to reach its prespecified outcome of a 14% absolute improvement in excellent outcome, the results suggest that adding uric acid to rt-PA therapy is safe, may prevent early stroke worsening, may improve overall mRS score, and might facilitate full independence in patients with acute stroke.

Uric acid has been shown to have antioxidant properties in both animal and human studies. In the rat, uric acid administered early after a stroke reduces infarct volume, protects both cortical and subcortical brain areas, attenuates the inflammatory response, and extends the benefits of rt-PA [Romanos E et al. *J Cereb Blood Flow Metab* 2007]. Results of a Phase 2 study in patients with acute stroke treated with rt-PA showed that intravenous administration of uric acid in patients was safe, prevented an early decline in uric acid levels, and reduced the early increase in oxidative stress markers [Amaro S et al. *Stroke* 2007].

Participants were adult patients (n=421) treated with 0.9 mg/kg of rt-PA (alteplase) within the first 4.5 hours of stroke symptoms, a baseline NIHSS score >6 and <25, and a premorbid mRS score ≤2 before the ischemic event. Within 1 hour of their rt-PA infusion, patients were randomized to either uric acid (1 g; n=215), or placebo (n=206). NIHSS was assessed at 0, 2, 24, 48, and 72 hours, and again at Days 5 and 90. The Barthel Index and mRS were performed at Day 90. The primary study outcome was having an mRS score of 0 to 1 (2 for patients with a premorbid score of 2) at 90 days. Secondary outcomes included the proportion of patients with NIHSS ≤1 at 2 hours, ischemic worsening at 72 hours, and ordinal mRS, NIHSS, and the proportion of patients achieving a Barthel score of 95 to 100 at Day 90. Safety outcomes included incidence of symptomatic intracranial hemorrhage at 36 hours, the total incidence of gout, and death at Day 90.

Subjects were median age of 76 years (range, 66 to 82), ~50% men, and had comorbidities typical for this population of patients. The media NIHSS score was 13, median time to rt-PA was ~2.5 hours, and the median time to initiation of uric acid therapy was ~3 hours.

Full analysis data set was comprised of 411 patients (uric acid, n=211; placebo, n=200). The proportion of patients having an excellent outcome (ie, mRS 0-1 or 0-2 if premorbid mRS was 2) was 39.3% in the uric acid group and 33% in the placebo group (RR, 1.23; 95% CI, 0.96 to 1.56; p=0.099). Secondary outcomes favored the patients in the uric acid group but were not significantly different. The ordinal OR for mRS was 1.40 (95% CI, 0.99 to 1.98; p=0.057). The median mRS was 2 in the uric acid group and 3 in the placebo group (p=0.045). The percentage of patients with NIHSS score <1 at 2 hours or Day 90 was similar. Significantly more patients in the placebo group experienced ischemic worsening by Day 3 compared with uric acid (9.0% vs 3.3%; RR, 0.34; 95% CI, 0.14 to 0.85; p=0.021). The proportion of patients with a Barthel score >94 at 90 days was 48.3% in the uric acid group and 40.5% in the placebo group (p=0.057). There were no safety concerns, differences in the rate of bleeding, incidence of gout, or deaths between the groups.

Exploratory analysis showed that women (who naturally have lower levels of uric acid), patients with low baseline NIHSS values (≤10), and those with lower glucose levels had better outcomes with combination uric acid plus rt-PA treatment.

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