Patients With Mild Ischemic Stroke Benefit From IV-rtPA

Written by Phil Vinall

There has been considerable debate regarding the use of intravenous recombinant tissue plasminogen activator (IV-rtPA) in patients with mild stroke symptoms. It has been unclear whether the potential benefits of improvement in neurologic outcomes outweigh the potential risks of hemorrhagic stroke, increased impairment, and death. Pooja Khatri, MD, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, presented results from a post hoc analysis of data from a subset of patients from the Third International Stroke Trial [IST-3; ISRCTN25765518], indicating that patients with mild stroke symptoms (ie, those having a National Institutes of Health Stroke Score of 0 to 5) may benefit from IV-rtPA.

IST-3 was a Phase 3 randomized open-label trial that compared IV-rtPA administered within 6 hours of symptom onset to a placebo control. A total of 3035 patients were enrolled from 12 countries outside the United States, of which 612 had mild stroke symptoms [IST-3 Collaborative Group. *Lancet* 2012]. Among those with mild strokes who were treated with IV-rtPA or placebo, there were no differences in the primary endpoint of being alive and independent (Oxford Handicap Score [OHS], 0 to 2) at 6 months (73% vs 75%, respectively; odds ratio [OR], 0.85; 99% CI 0.52 to 1.38). Mild stroke patients treated with IV-rtPA also had a higher risk of symptomatic intracranial hemorrhage compared with control patients (3% vs 0%, respectively).

Khatri and her colleagues performed a post hoc analysis on the IST-3 data to examine the effect of IV-rtPA in a more restricted subset of IST-3 patients with mild stroke. This subset included patients of any age in the IST-3 who had a mild stroke, received IV-rtPA <3 hours after symptom onset, had a pretreatment blood pressure <185/110 mm Hg, and met all other National Institute of Neurological Disorders and Stroke tissue plasminogen activator study criteria. The primary outcome was being alive and independent at 6 months (OHS, 0 to 2). Key secondary outcomes included an ordinal analysis of OHS and the proportion of patients who were alive and independent with a favorable outcome at 6 months (OHS, 0 to 1). Outcomes were adjusted for age, time to randomization, and presence of ischemic change on baseline scan.

About 20% (n=612) of subjects enrolled in the IST-3 trial had a mild stroke. Of these, 106 met the restricted criteria for the post hoc analysis. Among these patients, IV-rtPA was associated with an increase in being alive and independent at 6 months versus control, with an OHS of 0 to 2 (84% vs 65%, respectively; adjusted OR, 3.31; 95% CI, 1.24 to 8.79; p=0.02). The IV-rtPA effect on having a favorable outcome was not significant as compared to control (60% vs 51%, respectively; adjusted OR, 1.92; 95% CI, 0.83 to 4.43, p=0.13; Table 1). There were no reports of symptomatic intracerebral hemorrhage in any of these 106 patients with mild stroke who received IV-rtPA.

Limitations of this study include the highly restricted subset and sample size, which is too small to reliably estimate the risk of symptomatic intracerebral hemorrhage. However, this post hoc analysis showed that the use of IV-rtPA—in patients with a mild stroke and a pretreatment blood pressure <185/110 mm Hg who can be treated within <3 hours after symptom onset—was associated with an increase in odds of being alive and independent at 6 months. As such, a new Phase 3 trial of IV-rtPA in patients with mild stroke has been initiated: "A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke" [PRISMS; NCT02072226]. PRISMS is expected to enroll 950 patients with a mild stroke, defined as a National Institutes of Health Stroke Score of 0 to 5, from 75 centers in the United States. It is hoped that the PRISMS trial will provide definitive data regarding the efficacy of IV-rtPA in patients with a mild stroke.

Table 1. Outcomes

Outcomes	OHS	Subjects, %		Adjusted Analysis		Unadjusted Analysis	
		IV-rtPA[a]	Control[b]	OR (95% CI)	p	OR (95% CI)	p
Alive + independent	0-2	84	65	3.31 (1.24-8.79)	0.02	2.79 (1.03-7.91)	0.03
Alive + favorable outcome	0-1	60	51	1.92 (0.83-4.43)	0.13	1.44 (0.62-3.34)	0.35
Ordinal analysis	0-6	—	—	2.38 (1.17-4.85)	0.02	1.98 (0.99-3.96)	0.05

IV-rtPA=intravenous recombinant tissue plasminogen activator; OHS=Oxford Handicap Score; OR=odds ratio.

[a]n=55.

[b]n=51.