UKE Paper of the Month Mai 2018

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

Götz Thomalla, Claus Z. Simonsen, Florent Boutitie, Grethe Andersen, Yves Berthezene Bastian Cheng, Bharath Cheripelli, Tae-Hee Cho, Franz Fazekas, Jens Fiehler, Ian Ford Ivana Galinovic, Susanne Gellissen, Amir Golsari Johannes Gregori, Matthias Günther, Jorge Guibernau, Karl Georg Häusler, Michael Hennerici, André Kemmling, Jacob Marstrand, Boris Modrau, Lars Neeb, Natalia Perez de la Ossa, Josep Puig, Peter Ringleb, Pascal Roy, Enno Scheel, Wouter Schonewille, Joaquin Serena, Stefan Sunaert, Kersten Villringer, Anke Wouters, Vincent Thijs, Martin Ebinger, Matthias Endres, Jochen B. Fiebach, Robin Lemmens, Keith W. Muir, Norbert Nighoghossian, Salvador Pedraza and Christian Gerloff, for the WAKE-UP Investigators

The New England Journal of Medicine, 2018

ABSTRACT: BACKGROUND: Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase. METHODS: In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. We excluded patients for whom thrombectomy was planned. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis). RESULTS: The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P=0.003). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P=0.15). CONCLUSIONS: In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days.

STATEMENT: *The positive result of WAKE-UP is a milestone towards further improvement of the treatment of acute stroke, as the trial opens the window for treating many patients that have been excluded from thrombolysis until now. Treatment based on MRI-selection without knowing the time of symptom onset represents a paradigm change for acute stroke thrombolysis.*

BACKGROUND: The WAKE-UP trial was performed by a European consortium funding within the 7th framework programme, coordinated by UKE. Götz Thomalla and Christian Gerloff from the Department of Neurology coordinated the research project and the trial which built on their previous basic research on MRI as a surrogate marker of ischemic lesion age. Prof. Götz Thomalla is assistant medical director of the Department of Neurology and leader of the clinical stroke imaging research group at UKE. Prof. Christian Gerloff is the Head of the Department of Neurology.