MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (The WAKE UP Trial)

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In up to 27% of ischemic strokes, symptom onset is unknown, particularly when in the setting of "wake up" symptoms, when a patient awakens from sleep with stroke-like symptoms. However, prior to this trial, other data had shown that a DWI hyperintense lesion on MRI with a corresponding lack of FLAIR hyperintensity on imaging (i.e., a DWI/FLAIR mismatch), was predictive of symptom onset within 4.5hrs prior to imaging, even in patients presenting with an unknown time of symptom onset. As such, this study was performed using this MRI-based imaging criteria (DWI/FLAIR mismatch) to evaluate the safety and efficacy of IV tPA in patients presenting with an unknown time of stroke symptom onset.

Methods: This was a randomized, double-blinded, placebo-controlled multicenter clinical trial, performed in 70 centers across 8 European countries. Both local investigators and a central image-review committee screen patients for eligibility. Inclusion criteria included 1) patients presenting with clinical signs of acute stroke, 2) age 18-80 years, 3) able to complete all ADLs prior to stroke onset, 4) a LKW > 4.5 hours prior to presentation (LKW prior to awakening OR unknown/unreportable LKW), and 5) an MRI brain on presentation with a DWI/FLAIR mismatch. Exclusion criteria included 1) presentation within 4.5 hours of LKW (i.e., a standard tPA window), 2) hemorrhage on MRI, 3) lesions > 1/3 the territory of the MCA, 4) NIHSS >25, 5) a planned thrombectomy, or 6) contraindication to tPA (other than time window). Eligible patients were then randomized 1:1 to receive either placebo or standard dose IV tPA. The primary outcome was a favorable functional outcome, or an MRS of 0-1, at 90 days. Primary safety end points were death and a composite outcome of death or dependence (score of 4-6 on MRS at 90 days). Secondary safety outcomes included symptomatic ICH and the incidence of PH2 hematomas. Data were analyzed via an intention-to-treat basis. Of note, this study was stopped early due to lack of funding.

Results: A total of 503 patients were randomized, with 254 randomized to IV tPA and 249 randomized to placebo. Baseline characteristics between the treatment groups were similar, other than a higher rate of intracranial ICA occlusions in the IV tPA group (Table 1). In terms of the primary outcome, treatment with tPA was associated with a favorable outcome in 53.3% of the tPA group vs. 41.8% of the placebo group (OR 1.61, *p*=0.02, Table 2). Death at 90 days in the tPA group occurred in 4.1% of patients vs. 1.2% in the placebo group (Adjusted OR 3.38; *p*=0.07), and death or dependency (MRS 4-6) occurred in 13.5% of the tPA vs. 18.3% of the placebo group (Adjusted OR 0.68; *p*=0.17, Table 3). Notably, a higher rate of PH2 ICHs occurred in the tPA group (4.0% vs. 0.4% in placebo, Adjusted OR 10.46; *p*=0.03, Table 3), and there was additionally a numerically higher # of symptomatic ICH in the tPA group, accounting for multiple definitions of "Symptomatic ICH" from prior trials.

Conclusions: Overall, this trial showed that treatment with IV tPA can improve functional outcomes at 90d, without a significant risk of death or disability, in patients with an unknown time of stroke symptom onset and with a DWI/FLAIR mismatch on MRI imaging at the time of presentation. Notably, the rate of ICH post tPA appeared generally similar to that in prior IV tPA trials. Ultimately, data from this trial has led to the "Wake Up" MRI-based protocols at many comprehensive stroke centers. Of note, there were some limitations to the study to consider. First, few patients had a presenting NIHSS of <10, so it is unclear if the results here are generalizable to this patient group. Further, since the trial ended early due to a lack of funding, additional sub-group analyses could not be sufficiently completed. There was also a numerically higher number of deaths in the tPA group that neared statistical

significance, and this data point may have reached statistical significance had the trial enrolled the targeted number of patients. Finally, patients pre-determined to receive thrombectomy were excluded, and 20% of patients in the trial would have qualified for DAWN or DEFUSE 3 enrollment criteria, so it is unclear if this group of patients would have obtained a greater benefit from thrombectomy, IV tPA, or both.

Summary Completed by Nathan Bicher, M.D.