Randomized, Placebo-Controlled Trial of IV Desmoteplase 3 – 9 hours from Stroke Onset in Patients with Diffusion-Perfusion Mismatch: Early Reperfusion Related to Dose and Therapeutic Response

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BACKGROUND: Thrombolytic therapy with IV rt-PA in a 3h time window is the only approved acute ischemic stroke therapy. Clinical trials of IV thrombolytics initiated beyond 3 hours in general samples of ischemic stroke patients have not proven effective. There has been great interest in MRI as a surrogate outcome and as a means to select patients for enrollment and to extend the time window for acute stroke therapy. Selection of patients with diffusion-perfusion mismatch, an approximation of the ischemic penumbra, is hypothesized to increase the likelihood of detecting clinical benefits in IV thrombolytic trials beyond 3 hours and to be superior to clinical selection criteria for identifying promising therapies to advance to Phase III trials. Early reperfusion on MRI is hypothesized to predict therapeutic effect of reperfusion therapy. Desmoteplase (DSPA) is a highly fibrin specific plasminogen activator with a long terminal half-life, lack of neurotoxicity, and due to some distinct pharmacological properties may have a good safety profile especially in the elderly.

METHODS: The **D**esmoteplase **I**n **A**cute ischaemic **S**troke (DIAS) trial, a randomized, placebo-controlled, double-blind, international, dose-finding Phase II study, enrolled 104 acute ischemic stroke patients. Patients scoring 4-20 on the National Institutes of Health Stroke Scale (NIHSS) and having perfusion > diffusion mismatch on MRI (by investigators' qualitative estimation) were selected and treated 3-9h after stroke onset. Scans were preformed on 1.5 T commercial scanners with single shot EPI capability and the required sequences were DWI (TE = 100 – 124 ms; b values = 0 and 1000 sec/mm^2), 3D TOF MRA, FLAIR, and PWI (T2*-weighted gadolinium bolus tracking). Sequence parameters were standardized within, and to the extent possible, across scanner type for parameters affecting SNR and spatial resolution. Repeat DWI, MRA, FLAIR, and PWI were acquired 4-8h after treatment and FLAIR at 30 days. Scans were analyzed centrally, blinded to treatment assignment and clinical data. DSPA or placebo was administered as an IV bolus. Safety endpoints included the rate of symptomatic intracerebral hemorrhage (sICH). Efficacy endpoints were the rate of reperfusion (defined as a reduction of MTT hypoperfusion volume ≥ 30% or improvement in MRA artery patency by 2 or more TIMI points) and clinical outcome (reduction by ≥ 8 points or scoring 0-1 on NIHSS, modified Rankin Score (mRS) 0-2 and Barthel Index (BI) 100-75). Patients were randomized among fixed doses of 25 mg, 37.5 mg, 50 mg or placebo. After 47 patients the dosing was changed because of excess sICH at higher doses. Subsequent patients were randomized to either placebo (n = 12) or lower, weight-adjusted, escalating doses of desmoteplase (DSPA): 62.5 µg/kg (n=15), 90 µg/kg (n = 15) or 125 µg/kg (n = 15).

RESULTS: All treatment groups were generally balanced on baseline variables. Median age was 68, median NIHSS was 12, and median time to treatment was 325 minutes. Pre-treatment mismatch $(VOL_{MTT}\text{-}VOL_{DWI})/VOL_{DWI} \geq 20\%$ was confirmed by the core imaging lab in 94% of patients. After 47 patients the study was temporarily halted and dosing was modified because the predefined threshold for sICH was exceeded. In the dose escalation part of the study, a linear, statistically significant dose response was observed for both 4-8h post-treatment reperfusion rates ($\chi^2 = 9.38$, df = 3, p = .025) and day 90 clinical outcome ($\chi^2 = 8.99$, df = 3, p = .029; TABLE). Better reperfusion appeared to translate into a reduction of day 30 lesion volume relative to pretreatment volume of DWI abnormality at 90 µg/kg and 125 µg/kg doses (TABLE). Reperfusion correlated with clinical outcomes in the total sample of patients.

CONCLUSION: The DIAS trial is the first randomized, placebo-controlled, double-blind stroke trial to use MRI diffusion-perfusion mismatch to select patients for thrombolytic therapy. In patients with diffusion-perfusion mismatch, a dose related effect of DSPA administered 3-9h from onset was observed on reperfusion rates 4-8h from treatment and on clinical outcome at 90 days. These results support the validity of mismatch as a selection criterion and reperfusion as an early marker of therapeutic response in thrombolytic trials beyond 3h and will have important implications for the design of future stroke trials. A confirmatory trial is in progress, and a Phase III trial of DSPA in mismatch patients is planned.

	MRI AND CLINICAL OUTCOME RELATED TO DESMOTEPLASE DOSE				
	Dose				
MRI outcome	**Placebo pooled**	**Placebo, part 2**	**62.5 µg/ kg**	**90 µg/kg**	**125 µg/ kg**
4-8 hr Reperfusion Responder	5/26 (19.2%)	2/10 (20.0%)	3/13 (23.1%)	7/15 (46.7%)	10/14 (71.4%)
Day 90 Combined Clinical Endpoint	6/27 (22.2%)	2/11 (18.2%)	2/15 (13.3%)	7/15 (46.7%)	9/15 (60.0%)
Day 30 % infarct volume change [median (range)]	72.1 (-90.1; 348.6)	18.6 (-90.1; 320.9)	70.6 (-22.8; 852.7)	-12.0 (-84.7; 37.1)	-27.2 (-83.4; 262.5)