Desmoteplase After Ischemic Stroke in Patients With Occlusion or High-Grade Stenosis in Major Cerebral Arteries

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The beneficial effects of intravenous thrombolysis in ischemic stroke, reperfusion and improved outcome, have been directly correlated to time from onset to treatment. Recanalization of occluded intracranial arteries by tissue-type plasminogen activator (alteplase) has been shown to be effective only for the first few hours after symptom onset. Measured by transcranial Doppler monitoring, the effect of alteplase decreases over time, and treatment delay beyond 4.5 hours predicts lack of recanalization, especially in distal occlusions. Will the more fibrin-specific and longer acting fibrinolytics correct this problem in patients admitted beyond the accepted thrombolysis time window of 3 to 4.5 hours? A recent report (DIAS-2) has described the outcomes of intravenous desmoteplase to reverse occlusion or high-grade stenosis of major cerebral arteries (Desmoteplase in Acute Ischemic Stroke [DIAS]-3 trial) but failed to give support to this idea.

This first prospective, randomized, controlled phase 3 trial was designed to detect a possible benefit of a single intravenous bolus of 90 µg/kg of desmoteplase given 3 to 9 hours after onset in patients with confirmed major artery occlusion without substantial ischemic damage. Desmoteplase failed to improve functional outcomes at 90 days. It did not increase the rates of symptomatic brain hemorrhage, symptomatic brain edema, and death. On the other hand, significant (nominal P<0.05) improvements were observed in functional outcomes both in the desmoteplase group for the prespecified subgroup of patients with diffusion-weighted imaging lesions <25 mL and in the subgroup of patients treated >7 hours after onset of stroke symptoms after a prespecified ordinal analysis. In view of a superb safety profile, it should be noted that a previous DIAS-2 trial had tested also a higher dose, 125 µg/kg, in the same time window and observed elevated mortality, albeit predominantly unrelated to the study drug.

Although optimal sample size was estimated in power calculations and adjusted during the study period of DIAS-3, still 100 patients (21%) had to be excluded from the final analysis because of disagreements among study investigators on per-protocol imaging findings. In fact, the study inclusion criteria stated that patients had to have occlusion or high-grade stenosis assessed by magnetic resonance angiography or computed tomographic (CT) angiography in proximal cerebral arteries that corresponded to the acute clinical deficit. Eligible vessel occlusions were the middle cerebral artery M1 or M2, anterior cerebral artery, or posterior cerebral artery occlusions. The patients had to be excluded if there were signs of extensive early infarction on magnetic resonance imaging or CT in any affected area, an infarcted core involving >1/3 of the middle cerebral artery territory or >1/2 of the anterior cerebral artery or posterior cerebral artery territories. Other exclusion criteria were parenchymal hyperintensity on fluid-attenuated inversion recovery, T2*, or echo-planar imaging-T2 images or marked hypodensity on CT as indicators of subacute infarction or enhancement with morphological features suggesting that the lesion is >9 hours old. In the rating of the full analysis cohort (n=473), the centralized imaging committee had to exclude 8% (36) of the patients because of a lack of qualifying occlusion, another 8% (40) for ischemic lesion size >1/3 of the middle cerebral artery territory, 3% (12) for the presence of intracranial or subarachnoid hemorrhage, and finally 3% (16) for hyperintensity on fluid-attenuated inversion recovery or marked CT hypodensity.

Similar difficulties in applying study imaging criteria congruently by study investigators and central imaging committees are not exceptional. In a recent study on thrombectomy performed within 8 hours of symptom onset in ischemic stroke (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset [REVASCAT]), investigators observed discrepancies between central and investigator-adjudicated Alberta Stroke Program Early Computed Tomography Scores and vascular occlusion sites. Centrally adjudicated imaging studies had shown that 25% of patients had Alberta Stroke Program Early Computed Tomography Scores of ≤6 and 9% had occlusions in the M2 segment; both were
exclusion criteria. Clearly, this problem undermines the investigational success by degrading the effective sample sizes and calls for increased consideration in every future study where detailed imaging study entry criteria are important.

Patient selection by imaging modality has also been reported to play a role in detecting treatment effect in a planned post hoc subgroup analysis. The improved response to desmoteplase in patients with <25 mL of early ischemic injury on diffusion-weighted imaging suggests that magnetic resonance imaging is capable of identifying a subgroup of patients benefiting from desmoteplase therapy in the 3- to 9-hour time window. Remarkably, the CT-selected patients with small ischemic lesions did not seem to benefit. The issue on the role of baseline imaging modality–dependent therapeutic success (magnetic resonance imaging: better; CT: worse) lingers on and deserves attention when we aim at collecting uniform, balanced study cohorts using the 2 imaging modalities.

The late-time window is still being investigated by the ongoing European Cooperative Acute Stroke Study (ECASS) IV trial that is comparing intravenous alteplase with placebo administered at 4.5 to 9 hours after the onset of stroke or wake-up strokes. The imaging selection criteria include a significant penumbral mismatch, a perfusion volume (perfusion-weighted imaging) to infarct core (diffusion-weighted imaging) ratio of $\geq 1.2$, and a minimum perfusion lesion volume of 20 mL, using a computer-based analysis system (eg, RAPID; https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003609-80/AT#A). It will be interesting to observe whether this tissue signature with no primary requirement of vessel occlusions will predict beneficial tissue effects and functional recovery by alteplase in the late-time window.

The neutral results of DIAS-3 were attributable to the fact that the patients were not responders to the therapy after 3 hours from symptom onset. On the other hand, desmoteplase has not been studied in the optimal time window; for which, the real-life effect size of its potential acute therapeutic effect is not known. The responder rates reported in the time window of 3 to 9 hours in DIAS, DIAS-2, and Dose Escalation of Desmoteplase in Acute Ischemic Stroke (DEDAS) studies for Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1 vascular occlusion subgroups at day 90 were 16% to 18% for placebo but promisingly twice higher, 27% to 43% for the desmoteplase (90 or 125 µg/kg). In the DIAS-3 study, however, the responder rates (for the composite response: modified Rankin Scale response [scores, 0–2] and National Institutes of Health Stroke Scale [NIHSS] response [NIHSS decrease, ≥8 or NIHSS score, ≤1]) turned out neutral, 43% for the placebo group and 46% for the desmoteplase (90 µg/kg) group. Likewise, on angiographic outcomes, the recanalization response rates in patients with TIMI 0 or 1 occlusions were 42% for placebo and 49% for the desmoteplase group.

In the DIAS-3 trial, the fraction of patients reaching modified Rankin Scale score of 0 to 1 in the placebo-treated group (with admission NIHSS median of 12) was 35%, whereas in the pooled analysis of National Institute of Neurological Disorders and Stroke (NINDS), ECASS, and Assessment of Small Airways Involvement in Asthma (ATLANTIS) trials (with admission NIHSS median of 11), it was 29%. Stroke victims arriving late with small infarct cores despite occlusion or high-grade stenosis of a large cerebral artery are likely to possess good if not excellent collateral circulation, which may in part explain the remarkably benign clinical and recanalization responses of the DIAS-3 cohort, notably those in the placebo group. Better collaterals have been associated with smaller infarcts and larger mismatch volumes and found also to predict recanalization and good outcome. Without a strong improvement in the relatively frequent recanalization (desmoteplase 49% and placebo 42%; $P=0.18$), delayed fibrinolitics will have difficulty to show overall benefit in patients with good collaterals and small infarcts.

Desmoteplase was compared with placebo in a delayed time window, whereas tenecteplase, another fibrinolytic agent with a longer half-life and higher fibrin specificity than alteplase, has been investigated in direct comparison with alteplase. An Australian phase Ib trial compared tenecteplase with alteplase, showing significantly improved rates of reperfusion and clinical outcomes when imaging-based patient selection was in place. On the other hand, the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial assessed the efficacy and safety of tenecteplase versus alteplase within 4.5 hours of stroke onset in a population not selected on the basis of advanced neuroimaging. Neurological and radiological outcomes did not differ between the tenecteplase and alteplase groups. Underlying the discussed results, one explanation might be that they reflect a dominant, perhaps time-dependent, ceiling effect in the limited efficacy of pharmacological recanalization therapies of symptomatic occlusions of major intracranial arteries, which have been proven to be more amenable to treat with thrombectomy in combination with early intravenous fibrinolysis with alteplase.

In conclusion, the results from the DIAS-trial showed no benefit of desmoteplase beyond the therapeutic window in patients with large-vessel occlusions and small ischemic damage, although its pharmacological profile is more fibrin specific and long acting compared with alteplase. The results of the ECASS IV trial may help determine whether penumbra mismatch using a computer-based imaging analysis would successfully select patients who benefit from fibrinolytics in a prolonged time window.

Disclosures

Dr Caso has received speaker’s honoraria from Boehringer Ingelheim Pharmaceuticals and Pfizer BMS, and she is an advisory board member for Boehringer Ingelheim Pharmaceuticals. Dr Lindsberg reports no conflicts.

References


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