Vascular Occlusion Enables Selecting Acute Ischemic Stroke Patients for Treatment With Desmoteplase

Jochen B. Fiebach, MD; Yasir Al-Rawi, MBChB; Max Wintermark, MD; Anthony J. Furlan, MD; Howard A. Rowley, MD; Annika Lindstén, BSc; Jamal Smyej, BSc; Paul Eng, PhD; Steven Warach, MD; Salvador Pedraza, MD

Background and Purpose—Desmoteplase is a novel and highly fibrin-specific thrombolytic agent. Evidence of safety and efficacy was obtained in 2 phase II trials (Desmoteplase In Acute Ischemic Stroke [DIAS] and Desmoteplase for Acute Ischemic Stroke [DEDAS]). The DIAS-2 phase III trial did not replicate the positive phase II efficacy findings. Post hoc analyses were performed with the aim of predicting treatment responders based on CTA and MRA.

Methods—Patients were grouped according to vessel status (Thrombolysis In Myocardial Infarction [TIMI] grade) for logistic regression of clinical response, applying the data from DIAS-2 as well as the pooled data from DIAS, DEDAS, and DIAS-2.

Results—In DIAS-2, a substantial number of mismatch-selected patients (126/179; 70%) presented with a normal flow/low-grade stenosis (TIMI 2–3) at screening, with the majority having a favorable outcome at day 90. In contrast, favorable outcome rates in patients with vessel occlusion/high-grade stenosis (TIMI 0–1) were 18% with placebo versus 36% and 27% with desmoteplase 90 and 125 μg/kg, respectively. The clinical effect based on the pooled data from DIAS, DEDAS, and DIAS-2 was favorable for desmoteplase-treated patients presenting with TIMI 0 to 1 at baseline (OR, 4.144; 95% CI, 1.40–12.23; P=0.010). There was no desmoteplase treatment benefit in patients presenting with TIMI 2 to 3 (OR, 1.109).

Conclusions—In this sample of patients with a mismatch diagnosed, proximal vessel occlusion or severe stenosis was associated with clinically beneficial treatment effects of desmoteplase. Selecting patients using CTA or MRA in clinical trials of thrombolytic therapy is justifiable.


Key Words: computed tomography angiography ■ desmoteplase ■ magnetic resonance angiography ■ occlusion ■ stroke
agent. Data from the first 2 phase II trials (DIAS, n=57; Dose Escalation of Desmoteplase for Acute Ischemic Stroke [DEDAS], n=37) suggested that desmoteplase is safe and efficacious.6,7 Whereas the DIAS-2 phase III trial (n=186) also supported the safety profile of desmoteplase, it did not replicate the positive efficacy findings of DIAS and DEDAS.7 These apparently discrepant results of the DIAS and DEDAS studies and DIAS-2 are difficult to explain by chance alone. Therefore, post hoc evaluations of the key variables of the studies were performed.8

Although the numerous similarities in the trial designs allow pooling of these data, there are some differences worthy of consideration. On review, it was apparent that 1 key variable differed significantly between DIAS, DEDAS, and DIAS-2; there was a higher percentage of patients presenting with intracranial vessel occlusion or high-grade stenosis in the DIAS and DEDAS phase II trials (57%) versus the DIAS-2 phase III trial (30%; P≤0.0001). Given that vessel occlusion appears to be the cause of ischemic stroke and restored patency, the key to good clinical outcomes, we decided to evaluate degree of vessel occlusion as a predictor of clinical outcomes in this data set. Thus, our primary purpose in the present analysis was to test the hypothesis that desmoteplase had a positive effect on clinical outcome at day 90 in patients with verified baseline intracranial vessel occlusion or high-grade stenosis.

Materials and Methods

Patients
Study designs of DIAS (NCT00638781), DEDAS (NCT00638248), and DIAS-2 (NCT01111852) were similar. Detailed inclusion and exclusion criteria, imaging assessment schedules, and trial profiles have been published previously.5-7

The 3 studies enrolled patients aged 18 to 85 years with clinical signs of hemispheric stroke. Treatment time window was 3 to 9 hours, and stroke severity ranged from 4 to 24 points on the National Institutes of Health Stroke Scale (NIHSS).8 Either CT (consisting of native CT, perfusion CT, and CTA [DIAS-2]) or MRI (consisting of DWI, T2*-weighted images, fluid-attenuated inversion recovery, MRA, and PWI [DIAS, DEDAS, DIAS-2]) was used to identify an ischemic region exceeding the initial infarct. Postprocessing of MRI perfusion data was performed according to local protocols at each site. Investigators adjudicated perfusion deficits visually without applying a certain threshold. Patients presenting with a site-determined visual mismatch between infarction and hypoperfusion were deemed to have potential to benefit from desmoteplase therapy, thus qualifying for randomization. The primary clinical endpoint in all 3 studies defined clinical response as a composite of ≥8 points of improvement (or ≤1 on NIHSS), a score of 0 to 2 on the modified Rankin Scale, and a Barthel Index score of 75 to 100 at 90 days.9-12

Procedures
All baseline CT and MRI examinations were evaluated qualitatively at each site for enrollment eligibility. The presence of PWI-DWI mismatch was evaluated in accordance with local practice. In DIAS-2, a central imaging reading group (M.W., S.P., J.B.F.) subsequently evaluated the imaging data independently and in a blinded fashion by quantitative perfusion deficit volume and infarct volume assessments. Vascular status at baseline was read in consensus by 2 central readers (S.P. and J.B.F.) blinded to all other imaging results and clinical information. In DIAS and DEDAS, the same procedures were performed by 1 blinded central reader (S.W.).

Four stages of vascular status were distinguished with either CTA or MRA, according to the modified Thrombolysis In Myocardial Infarction (TIMI) scale.13-15 TIMI grade 0 (complete occlusion) was defined either as lack of flow signal of a vascular segment and distal vessels by MRA or as lack of contrast filling of a vascular segment on CTA. TIMI grade 1 (high-grade stenosis or near-complete occlusion) was defined as severe or critical stenosis of a vascular segment by either CTA or MRA; significant reduction of flow signal distal to stenosis was also noted in MRA evaluation. TIMI grade 2 (mild to moderate stenosis) of a vascular segment was characterized by stenosis with normal distal flow signal on either CTA or MRA, and TIMI grade 3 was a normal open vascular segment with either imaging modality.

Statistical Analysis
Binary and dichotomized data are presented as frequencies and percentages; continuous data are presented as medians, mean values, and standard deviations (SD). Because findings on clinical outcome were similar for TIMI grade 0 and 1 and for TIMI grade 2 and 3, respectively, these were grouped as 0 to 1 and as 2 to 3 (Figure 1). In DIAS-2, patients with a baseline TIMI score of 0 to 1 were compared with patients with a baseline TIMI score 2 to 3. Sex and presence of diabetes were analyzed using the χ2 test; age, time window (onset to treatment), baseline NIHSS, and baseline infarct volume were analyzed using the Wilcoxon rank-sum test. The comparisons were performed within each imaging modality (CT, MRI) as well as in all patients. In addition, patients evaluated with CT were compared with those evaluated with MRI within the subgroup of patients presenting with TIMI 0 to 1.

Clinical outcome on day 90 was analyzed on both DIAS-2 data alone and on a pooled sample of patients randomized to either placebo or desmoteplase 90 or 125 µg/kg from DIAS, DEDAS, and DIAS-2. In DIAS-2, the predictive value of baseline infarct volume on clinical response at day 90 in each TIMI class was investigated using a logistic regression model including baseline infarct volume, treatment (desmoteplase 90 or 125 µg/kg versus placebo), TIMI class (0–1, 2–3), and the 2-way interactions. The predictive value of the final infarct volume at day 30 on the day 90 clinical response was investigated using a logistic regression model, with clinical response explained by day 30 infarct volume, treatment, and the interaction between treatment and infarct volume. The responder analysis of the pooled data was based on a logistic regression model including treatment, TIMI class, baseline infarct volume, and TIMI class-by-treatment and baseline infarct volume-by-treatment interactions. A reanalysis with baseline infarct volumes omitted from the model was performed, and odds ratios were calculated for the treatment effect within TIMI class. In addition, a similar analysis including treatment, baseline mismatch volume, and interaction between treatment and mismatch volume was performed with baseline mismatch volume dichotomized at 60 mL. The analyses were stratified for trial when pooled data were used.

Sample size calculations were performed with assumptions based on the obtained results from the pooled data in the TIMI 0 to 1 group and at different rates of patients (0%, 10%, 20%, 30%) presenting
Table 1. Desmoteplase In Acute Ischemic Stroke-2 Comparison of Gender, Age, Presence of Diabetes at Baseline, Time Window, and Baseline National Institutes of Health Stroke Scale in Thrombolysis In Myocardial Infarction 0–1 Patients Versus Thrombolysis In Myocardial Infarction 2–3 Patients for Computed Tomographic Angiography, Magnetic Resonance Angiography, and Combined Computed Tomographic Angiography and Magnetic Resonance Angiography

<table>
<thead>
<tr>
<th></th>
<th>CTA 0–1</th>
<th>MRA 0–1</th>
<th>Total 0–1</th>
<th>CTA 2–3</th>
<th>MRA 2–3</th>
<th>Total 2–3</th>
<th>CTA Total</th>
<th>MRA Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIMI</strong></td>
<td>0–1</td>
<td>2–3</td>
<td>0–1</td>
<td>2–3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>n=12</td>
<td>n=49</td>
<td>n=41</td>
<td>n=77</td>
<td></td>
<td></td>
<td>n=53</td>
<td>n=126</td>
</tr>
<tr>
<td>Age (y)</td>
<td>74</td>
<td>69</td>
<td>86</td>
<td>70</td>
<td>69</td>
<td>70</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11 (1)</td>
<td>15 (1)</td>
<td>12 (1)</td>
<td>13 (1)</td>
<td>12 (1)</td>
<td>13 (1)</td>
<td>12 (1)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2 (16.7)</td>
<td>13 (26.5)</td>
<td>12 (29.3)</td>
<td>16 (40.8)</td>
<td>14 (26.4)</td>
<td>29 (23.0)</td>
<td>0.477</td>
<td>0.302</td>
</tr>
<tr>
<td>Delay from symptom onset to treatment (min), mean, (SD) median</td>
<td>373 (103)</td>
<td>408 (90)</td>
<td>406 (96)</td>
<td>382 (81)</td>
<td>399 (98)</td>
<td>392 (86)</td>
<td>0.231</td>
<td>0.146</td>
</tr>
<tr>
<td>Total NIHSS score, mean, (SD) median</td>
<td>17.1 (4.6)</td>
<td>10.8 (4.8)</td>
<td>10.7 (4.6)</td>
<td>9.3 (4.6)</td>
<td>12.2 (5.3)</td>
<td>9.9 (4.7)</td>
<td>0.001</td>
<td>0.084</td>
</tr>
<tr>
<td>Baseline infarct volume (mL), mean, (SD), median</td>
<td>42.8 (32.3)</td>
<td>16.3 (20.2)</td>
<td>16.4 (24.4)</td>
<td>16.0 (20.0)</td>
<td>22.5 (28.3)</td>
<td>16.1 (20.0)</td>
<td>0.006</td>
<td>0.986</td>
</tr>
</tbody>
</table>

CTA indicates computed tomographic angiography; MRA, magnetic resonance angiography; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

without target mismatch. A 2-sided χ² test at the 5% level of significance with a power of 80% and equal distribution between treatment groups of patients without target mismatch was assumed. The response rate was assumed to be 0% for patients without target mismatch, and for patients with a target mismatch the response rate was assumed to be 16% for placebo and 40% for desmoteplase.

SAS version 9.1.3 (SAS Institute) was used for the statistical analysis. P < 0.05 was considered statistically significant.

Results

In DIAS-2, TIMI data were available from 179 of 186 treated patients (CTA, n=61; MRA, n=118). In total, 53 patients (29.6%) had vessel occlusion/high-grade stenosis (TIMI 0–1) at baseline, and 126 (70.4%) presented with normal flow/low-grade stenosis (TIMI 2–3). The demographic data were generally similar for TIMI 0–1 and TIMI 2–3 subgroups (Table 1). The only significant difference between the 2 TIMI groups was in initial stroke severity (median NIHSS score, 13.0 [TIMI 0–1] versus 9.0 [TIMI 2–3]; P=0.008; Table 1).

Further comparisons between the patients with a TIMI 0 to 1 and evaluated with CTA or MRA showed that CTA patients (n=12) presented with a median NIHSS score of 18.5, whereas MRA patients (n=49) presented with a median score of 10.0 (P=0.0004). This difference was associated with a significantly larger infarct volume at screening (median, 38.6 mL [CTA] versus 9.8 mL [MRA]; P=0.005). For patients presenting with TIMI 2 to 3 and evaluated with CTA or MRA, median baseline stroke severity (NIHSS score, 10.0 [CTA] versus 8.0 [MRA], P=0.053) and infarct sizes (5.1 mL versus 8.1 mL, respectively; P=0.45) did not differ.

Vessel status at screening had no influence on the distribution of patients across the time window: approximately 38% of each of the TIMI 0 to 1 and TIMI 2 to 3 patients were treated within 3 to 6 hours. Treatment of TIMI 0 to 1 patients with placebo, desmoteplase 90 μg/kg, or desmoteplase 125 μg/kg led to responder rates at day 90 in DIAS-2 of 18%, 36%, and 27%, respectively (Table 2). The responder rates in the pooled data of DIAS, DEDAS, and DIAS-2 were 16%, 38%, and 42%, respectively (Table 2). Infarct enlargement at Day 30 in DIAS-2 TIMI 0 to 1 patients, screened by MRI, was considerably less in responders than in nonresponders (Table 3).

The analysis of DIAS-2 data (MRI) could not show that baseline lesion volume or its interactions with treatment or TIMI class affected the clinical response at day 90 (χ²=0.002, P=0.967; χ²=1.49, P=0.222; and χ²=0.127, P=0.722, respectively). Infarct volume at day 30 predicted clinical response at day 90 in the total DIAS-2 MRI cohort (χ²=8.48, P=0.004) without interaction with treatment (χ²=1.721, P=0.190).

The pooled data from DIAS, DEDAS, and DIAS-2 consisted of 216 MRI-selected patients, of whom 73 patients were randomized to placebo, 68 patients were randomized to desmoteplase 90 μg/kg, and 75 patients were randomized to desmoteplase 125 μg/kg. A logistic regression analysis did not show that baseline lesion volume or baseline lesion volume combined with treatment (desmoteplase or placebo) affected clinical response at day 90 (χ²=0.034, P=0.853 and χ²=0.024, P=0.879, respectively).
Table 3. Desmoteplase In Acute Ischemic Stroke-2 (Thrombolysis In Myocardial Infarction 0–1) Infarct Size Changes by Magnetic Resonance Imaging from Baseline to Day 30 in Nonresponders Versus Responders (Composite Response) at Day 90

<table>
<thead>
<tr>
<th>Infarct Size Change (mL)</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>8</td>
<td>10.1</td>
<td>18.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Responder</td>
<td>2</td>
<td>-0.9</td>
<td>11.0</td>
<td>-0.9</td>
</tr>
<tr>
<td>Desmoteplase 90 μg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>5</td>
<td>22.9</td>
<td>23.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Responder</td>
<td>4</td>
<td>0.3</td>
<td>15.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Desmoteplase 125 μg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>11</td>
<td>17.6</td>
<td>17.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Responder</td>
<td>5</td>
<td>-0.8</td>
<td>6.0</td>
<td>-3.8</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

χ² = 0.28, P = 0.59, respectively). In the second model, with baseline infarct volume removed and treatment retained, TIMI class (0–1 versus 2–3) and its interaction with treatment kept in the model, the treatment effect in the TIMI 0–1 subgroup was borderline statistically significantly different from the effect in the TIMI 2–3 subgroup (test of interaction: χ² = 3.83, P = 0.05). The treatment effect (desmoteplase versus placebo) within the TIMI 0 to 1 group was statistically significant (χ² = 6.63, P = 0.010). There was no statistically significant treatment effect within the TIMI 2 to 3 group (χ² = 0.068, P = 0.794). The odds ratio for response between desmoteplase and placebo was 4.144 (95% CI, 1.40–12.23) for TIMI 0 to 1 patients and 1.109 (95% CI, 0.51–2.41) for TIMI 2 to 3 patients (Figure 2).

A hypothetical sample size calculation on the pooled data from TIMI 0 to 1 patients (all patients have a target mismatch) included in DIAS, DEDAS, and DIAS-2, showing 16% responders in the placebo group and 40% in the desmoteplase group (90 or 125 μg/kg), would result in the requirement of 54 patients per arm to find significance with 80% power at P < 0.05 (2-tailed). An increase of the proportion of patients without a target mismatch assuming that these patients are nonresponders would result in a higher sample size (Table 4).

Discussion

The post hoc analysis reported here showed an advantage in composite score for desmoteplase 90 μg/kg of 18% in TIMI

Table 4. Hypothetical Sample Sizes Based on Arbitrarily Assumed Response Rates; Thrombolysis In Myocardial Infarction 0–1 Group in Pooled Desmoteplase In Acute Ischemic Stroke, Desmoteplase In Acute Ischemic Stroke, and Desmoteplase In Acute Ischemic Stroke-2 Data

<table>
<thead>
<tr>
<th>Proportion of Patients Without Target Mismatch (%)</th>
<th>Assumed Placebo Response Rate (%)</th>
<th>Assumed Desmoteplase Response Rate (%)</th>
<th>No. Needed per Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.0</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>14.4</td>
<td>36</td>
<td>63</td>
</tr>
<tr>
<td>20</td>
<td>12.8</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>30</td>
<td>11.2</td>
<td>28</td>
<td>87</td>
</tr>
</tbody>
</table>

0 to 1 patients enrolled in DIAS-2, being consistent with the score of 22% when data from TIMI 0 to 1 patients were pooled from all 3 desmoteplase trials (DIAS, DEDAS, and DIAS-2). Analysis of all patients treated with desmoteplase 90 or 125 μg/kg in the 3 trials revealed a significant beneficial effect in patients with occlusion or high-grade stenosis (TIMI 0–1), resulting in an odds ratio of 4.144 for clinical response to desmoteplase.

The results of this post hoc analysis are based on a mismatch-selected population. In DIAS, DEDAS, and DIAS-2, patients were randomized if a 20% visual mismatch was present. Selecting based on vessel status carries a risk of randomizing patients without a mismatch. In DIAS-2, out of 228 imaging-screened patients (randomized and those who failed screening) with assessable perfusion imaging and angiography, 85% (52/61) of patients with TIMI 0 to 1 presented with a 20% visual mismatch versus 63% (105/167) in those with TIMI 2 to 3. This is in line with the results reported by Röther et al showing that 91% of patients with vessel occlusion on MRA have a 20% visual mismatch within a 6-hour time window. Similarly, pooled data from DIAS, DEDAS, and DIAS-2 (n=206, randomized MRI patients) showed that 44% presented with TIMI 0 to 1, and that the proportion of patients with vessel occlusion or severe stenosis increased with absolute mismatch volume. In 113 patients presenting with >60 mL mismatch volume, 66% had TIMI 0 to 1, and in the group of 80 patients presenting with >120 mL mismatch volume, 79% had TIMI 0 to 1 at screening. This suggests a strong correlation between vessel occlusion and mismatch.

Patients in DIAS-2 had significantly milder strokes than patients in DIAS and DEDAS, as indicated by lower median baseline NIHSS, and 20% to 50% smaller absolute core and mismatch volumes. However, exclusion of patients with normal CTA/MRA reduced the placebo composite responder rate preferentially, revealing a 9% (125 μg/kg) to 18% (90 μg/kg) absolute advantage for desmoteplase. It must be noted that in MRI-selected patients, the limited coverage of MRA carries a risk of not detecting distal vessel pathology.

The DIAS-2 trial was designed to have identical selection criteria as DIAS and DEDAS. The milder stroke severity in DIAS-2 can be explained by the heterogeneity of the perfusion algorithm that has been used at contributing centers. Thus, patients with limited infarction and benign hypoperfusion were considered for randomization. Recent studies show
that even the initial selection of arterial input function in the process of perfusion data after processing can significantly influence the perfusion map result by chance and, thus, cause a false-positive diagnosis of mismatch.16

The present study contributes to the validation of the “initial vascular patency” as a stroke imaging biomarker with therapeutic value.17 A similar observation was reported by Ma et al.,18 who investigated in 94 patients whether baseline vessel status evaluated by MRA can be the foremost factor to classify patients into subgroups for thrombolytic therapy within 3 to 6 hours of symptom onset. They concluded that patients not having initial occlusion on MRA might not need thrombolytic therapy. Optimal candidates for thrombolytic therapy were salvageable patients, classified as presenting with a combination of occlusion, PWI-DWI mismatch, and an initial DWI volume ≤100 mL.18 In addition, in the Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) trial, which targeted patients with angiographically proven middle cerebral artery occlusion, clinical outcome was improved after intra-arterial thrombolysis within 6 hours (40% recombinant prourokinase versus 25% placebo).19 This treatment response was associated with recanalization rates of 66% and 18%, respectively. Posttreatment vessel status information for pooled desmoteplase MRI data is lacking, rendering a comparison to PROACT-II recanalization rates impossible. Other studies did confirm good recanalization rates but did not reach positive clinical endpoints.

Use of the diffusion-MRA mismatch approach to triage and determine treatment has been proposed by Lansberg et al.20 The authors consider treatment if an infarct volume >15 to 25 mL was diagnosed with DWI and severe stenosis or occlusion was present. However, accurate assessment of infarct volume is not easy to obtain in the acute setting. Our results, focusing on either CTA or MRA to identify and localize vessel occlusion, support a more practical strategy through the simple exclusive use of severe stenosis or occlusion as a criterion to include patients.

One relevant limitation of this study is the lack of assessment of early recanalization attributable to the absence of early follow-up vessel examination in the protocol. This marker has been associated with a good outcome after treatment.21 However, the decision to focus a study protocol on vessel status alone is sufficient to predict treatment outcome or vessel status in combination with perfusion imaging would improve treatment outcome. The collection of data on perfusion imaging within ongoing randomized desmoteplase clinical trials and investigation of combined selection endpoints (verified vascular occlusion, perfusion features, or both combined) could help provide some answers. Nonetheless, using CTA or MRA in clinical trials of thrombolytic therapy appears to be an appropriate selection strategy.

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References

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