Desmoteplase in acute massive pulmonary thromboembolism

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Summary
Alteplase is standard therapy for patients with acute, massive pulmonary embolism. The novel plasminogen activator desmoteplase displays high fibrin specificity and selectivity for fibrin-bound plasminogen. In a preclinical model desmoteplase was twice as potent with a shorter lysis time and lower reocclusion rate. We conducted a phase II study comparing 125, 180, and 250 µg/kg bodyweight desmoteplase with 100 mg alteplase. Efficacy criteria were total pulmonary resistance (TPR), mean pulmonary artery pressure (mPAP), and Miller Index. Intention to treat analysis of 34 patients. The reduction of TPR after 24 hours was comparable between desmoteplase 180 µg/kg and alteplase (-48.0 ± 22.4 vs. –50.4 ± 16.3%; p = n.s. vs. alteplase; p = 0.0002 and p<0.0001 vs. baseline). The greatest effect was achieved with desmoteplase 250 µg/kg (-56.0 ± 29.4%; p = 0.0055 vs. baseline). Two hours after treatment PAP was reduced by 27.9 (p = 0.0004 vs. baseline) and 30.4% (p = 0.015 vs. baseline) with the higher doses of desmoteplase and 29.6% with alteplase (p = 0.0006 vs. baseline). Further PAP reduction after 6 hours was most pronounced in the desmoteplase 250 µg/kg group (-40.1 ± 18.0%; p = 0.0028 vs. baseline). The reduction of the Miller Index was greatest using desmoteplase 250 µg/kg (-41.6 ± 27.2%; p = 0.0003 vs. baseline). Safety did not differ among the 4 groups. The study results suggest that desmoteplase at doses of 180 and 250 µg/kg had similar or greater efficacy compared to alteplase 100 mg. Onset of action was faster, safety was comparable.

Keywords
Desmoteplase, alteplase, t-PA, massive pulmonary embolism, lysis, Miller Index, pulmonary artery pressure, total pulmonary resistance

Introduction
Pulmonary embolism (PE) ranges from asymptomatic, incidentally discovered emboli to massive embolism causing immediate death (1). The novel plasminogen activator, recombinant Desmos dus Salivary Plasminogen Activator α1 (rDSP α1-1 or desmoteplase), unlike other plasminogen activators, possesses a particularly high fibrin specificity. Preclinical studies comparing desmoteplase with alteplase in a rat model of PE have shown that desmoteplase was about twice as potent on a molar basis with a shorter lysis time and a lower reocclusion rate (2). While alteplase at 100 nmol/kg significantly decreased fibrinogen, plasminogen, and α₂-antiplasmin, desmoteplase at 100 nmol/kg only lowered α₂-antiplasmin significantly (2). Desmoteplase has a terminal plasma half-life of 4.5 hours (h), which supports the use of a desmoteplase single-bolus regimen (3). DESmoteplase in Pulmonary THromboembolism (DEPTH) was a multicenter, open-label, alteplase-controlled, randomized, parallel-group phase II trial to assess the efficacy and safety of various doses of intravenous desmoteplase in patients with acute massive PE.
Patients and methods

Study population
The study enrolled patients aged 18 to 80 years with clinical symptoms/signs of massive PE in the preceding 14 days, a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, and a pulmonary vessel occlusion ≥50% (Miller Index >17). Patients were excluded if they had an increased risk of bleeding (further specified in the study protocol). The study protocol was approved by the local ethics committee at each institution. Written informed consent was obtained from all patients according to the Helsinki declaration.

Study design
This study was a prospective, open-label, comparator-controlled, randomized phase II, dose-escalating trial. Patients were enrolled in seven centers in Germany, Hungary, and Russia (see the Appendix). Patients received either desmoteplase 125 µg/kg as an intravenous bolus over 1–2 minutes or alteplase 10 mg as a bolus and 90 mg as a 2-h infusion (randomization 1:1). Patients on alteplase weighing less than 65 kg received 1.5 mg/kg. Desmoteplase dosing was stepwise escalated to 180 µg/kg and finally 250 µg/kg based on assessment of safety and efficacy (total pulmonary resistance [TPR], mPAP, and Miller Index). Escalated doses were randomized 3 : 1 to desmoteplase : alteplase (Fig. 1).

All patients received an intravenous bolus of unfractionated heparin 70 IU/kg before thrombolysis, followed by an infusion of heparin of 15 IU/kg/h for at least 48 h, starting immediately after drug administration, which was subsequently adjusted to maintain an activated partial-thromboplastin time (aPTT) of 1.5 to 2.5 times the upper limit of normal, measured at least 4 and 24 h after starting heparin or adjustment of infusion rate.

Oral anticoagulants and antiplatelet agents were not allowed during the first 24 h after thrombolysis.

Definition of clinical endpoints
Efficacy parameters were TPR, mPAP, and Miller Index (local and central assessment). Safety parameters were major bleeding (life-threatening bleeding, a drop of haemoglobin ≥40 g/l, necessity of blood cell transfusion > 2 units or intracranial haemorrhage), death, or other serious adverse events.

Pulmonary angiography and pressure measurements: Right heart catheterization was performed to monitor changes in PAP, cardiac output

Table 1: Baseline characteristics of patients of the ITT population (n=34).
(CO), cardiac index (CI), and TPR over 24 h. A standard 5-French pigtail catheter was used for catheterization. Pulmonary angiography was performed with a non-ionic contrast medium. The occlusion rate was assessed by the Miller Index.

Statistical analysis
As this was an exploratory trial, no formal sample size calculation was performed.

Safety
The main safety parameters were overall and serious adverse events (AE) as well as major bleeding including intracranial haemorrhage and anaphylaxis. For each category, the frequency counts of events and patients with specific AE were calculated.

Efficacy
Efficacy parameters were TPR, mPAP, and Miller Index. The reduction in these parameters was described by the absolute and the percent change from baseline. Original values and changes were analyzed for each time point using standard summary statistic (including mean ± SD). For each parameter the percent change from baseline was compared between treatment groups using an analysis of covariance model (ANCOVA) with factor treatment (fixed effect) and baseline value as covariate. Within treatment groups percent change of efficacy parameters and fibrinogen were analysed using Student’s t-test. For all changes from baseline to a specific time point post-baseline, analyses are based on measurements available at that time point or the last post-baseline measurement prior to the time-point (last observation carried forward). A p-value of < 0.05 was considered nominal statistically significant. No adjustment for multiple comparisons was done due to the exploratory sense of the analyses.

All analyses were performed using SAS® Version 8.2, SAS Institute (4) or higher.

Table 2: Analysis of efficacy.

<table>
<thead>
<tr>
<th></th>
<th>Desmoteplase</th>
<th>Alteplase</th>
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<tbody>
<tr>
<td></td>
<td>125 µg/kg BW (n=7)</td>
<td>180 µg/kg BW (n=9)</td>
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<tr>
<td>Total pulmonary resistance (dyn·s·cm⁻⁵, mean ± SD)</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>661 ± 331</td>
<td>533 ± 245</td>
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<tr>
<td>Change vs. baseline after 2 h</td>
<td>−52 ± 249</td>
<td>−179 ± 111</td>
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<tr>
<td>Change vs. baseline after 6 h</td>
<td>−230 ± 270</td>
<td>−160 ± 183</td>
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<tr>
<td>Change vs. baseline after 12 h</td>
<td>−265 ± 272</td>
<td>−191 ± 192</td>
</tr>
<tr>
<td>Change vs. baseline after 24 h</td>
<td>−284 ± 260</td>
<td>−275 ± 218</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg, mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.6 ± 7.1</td>
<td>32.6 ± 6.6</td>
</tr>
<tr>
<td>Change vs. baseline after 2 h</td>
<td>−1.9 ± 7.9</td>
<td>−9.3 ± 5.4</td>
</tr>
<tr>
<td>Change vs. baseline after 6 h</td>
<td>−5.6 ± 4.9</td>
<td>−10.0 ± 8.5</td>
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<tr>
<td>Change vs. baseline after 12 h</td>
<td>−6.3 ± 3.5</td>
<td>−12.6 ± 6.8</td>
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<tr>
<td>Change vs. baseline after 24 h</td>
<td>−5.3 ± 4.1</td>
<td>−14.8 ± 7.1</td>
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<tr>
<td>Miller Index, local assessment (mean ± SD or %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.0 ± 3.0</td>
<td>22.9 ± 2.8</td>
</tr>
<tr>
<td>Abs. change between 2 to 12h</td>
<td>−3.0 ± 2.8</td>
<td>−5.4 ± 3.8</td>
</tr>
<tr>
<td>Rel. change between 2 to 12h (%)</td>
<td>−14.1 ± 13.9</td>
<td>−23.6 ± 15.6</td>
</tr>
<tr>
<td>Miller Index, qualitative assessment (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked improvement</td>
<td>1 (14.3)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>2 (28.6)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Mild improvement</td>
<td>3 (42.9)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>No difference</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Mild worsening</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Moderate worsening</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not indicated</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
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</table>

SD, standard deviation; BW, body weight.
Committee together with the sponsor decided to discontinue the study because of low patient enrolment, resulting in 34 patients enrolled. The study design required the use of pulmonary angiography, but this technique was no longer state of the art in the participating hospitals. Patient recruitment is depicted in Figure 1. Thirty-four patients were analyzed as the ITT (intention to treat) and safety population.

Results

Patient characteristics
Of 34 patients randomized, 22 patients were treated with desmoteplase (125 µg/kg n=7; 180 µg/kg n=9; 250 µg/kg n=6) and 12 with alteplase. Thirty-three patients (97.1%) completed the study. One patient treated with desmoteplase 250 µg/kg died from recurrent PE. The majority of the patients were randomized within 2–5 days after onset of the first symptoms of PE. For patient characteristics at baseline see Table 1.

Total pulmonary resistance
In all treatment groups, except that receiving desmoteplase 125 µg/kg, a comparable decrease in TPR was seen after 2 h (reduction by 33–34%) (Table 2). In the desmoteplase 250 µg/kg group, a further decrease in TPR was observed after 6 h (reduction from baseline 42.2% vs. alteplase 33.3%; p=0.016 and p=0.018 vs. baseline, respectively; p=n.s. vs. alteplase). In all treatment groups, the maximum effect was seen after 24 h. The reduction of TPR after 24 h was numerically comparable between desmoteplase 180 µg/kg and alteplase (−48.0 ± 22.4 vs. −50.4 ± 16.3%). The most prominent effect was achieved with
Mean pulmonary artery pressure (mPAP)
A reduction of mPAP of 27.9 ± 14.3% (desmoteplase 180 µg/kg), 30.4 ± 20.5% (desmoteplase 250 µg/kg) and 29.6 ± 21.8% (alteplase 100 mg) versus baseline was already seen after 2 h. The effect of desmoteplase 125 µg/kg was negligible (reduction 5.6 ± 21.9%). For absolute values see Table 2). Six hours after infusion of study medication, there was a further decrease in the desmoteplase 250 µg/kg group (-40.1 ± 18.0%), whereas desmoteplase 180 µg/kg (-28.7 ± 23.0%) and alteplase (-27.1 ± 38.1%) showed no further reduction. After 24 h, the maximum effect was achieved in all treatment groups. The reduction of mPAP by desmoteplase 180 µg/kg and alteplase was comparable (-43.9 ± 16.8% vs. -42.3 ± 13.1%; p=n.s.). The highest reduction was achieved by desmoteplase 250 µg/kg (-47.1 ± 20.5%; p=n.s. vs. alteplase). For a graphical display of the relative changes in mPAP, see Figure 3.

Miller Index
The Miller Index at baseline (local assessment) ranged from 20.5 ± 2.5 (desmoteplase 180 µg/kg) to 22.9 ± 2.8 (desmoteplase 180 µg/kg) or 22.9 ± 3.7 (alteplase 100 mg/kg) (see Table 2). The reduction of the Miller Index was greatest using desmoteplase 250 µg/kg (-35.0 ± 21.7%; p=n.s. vs. 125 µg/kg) and alteplase (-41.6 ± 27.2%; p=0.0041 vs. 125 µg/kg). The reduction of the Miller Index was lowest in the 125 µg/kg desmoteplase groups. For a graphical display of the relative changes in Miller index, see Figure 4.

Fibrinogen
The baseline fibrinogen levels were comparable among treatment groups and ranged from 11.3 ± 4.0 µM (desmoteplase 180 µg/kg) to 13.6 ± 5.4 (desmoteplase 125 µg/kg). In the desmoteplase groups no change from baseline of more than ±10% was observed (10.0 ± 27.3 %, 4.2 ± 19.8 %, and -9.5 ± 27.1 % for desmoteplase 125 µg/kg, 180 µg/kg, and 250 µg/kg, respectively; all p=n.s. vs. baseline). In contrast, fibrinogen concentration was remarkably reduced in the alteplase group -26.5 ± 16.8 % (p=0.0004 vs. baseline).

Safety profile
All patients except one completed the study. A 28-year-old man died. He was obese and had a history of PE. He received desmoteplase 250 µg/kg. Six days after administration of study medication, he suffered from recurrent PE due to deep venous thrombosis. The overall rate proportion of patients with adverse events ranged from 66.7% (desmoteplase 180 µg/kg; n=6) to 100% (alteplase; n=12).

Five patients experienced serious adverse events (SAEs) necessitating treatment. The most frequent drug-related SAE was haemorrhage at the catheter and injection site with drop of haemoglobin (desmoteplase 180 µg/kg, n=2, 22.2%; alteplase n=1, 8.3%). With desmoteplase, no anaphylactic or allergic reactions were observed. Two rashes were observed in patients who received alteplase.

Discussion
DEPTH is the first clinical study investigating the efficacy and safety of desmoteplase in patients with acute massive PE. The effects of desmoteplase 125 µg/kg on haemodynamic parameters were minimal, while doses of 180 and 250 µg/kg were similar to alteplase 100 mg. Haemodynamic improvement was achieved earlier (after 6 to 12 h after treatment with 250 µg/kg desmoteplase compared to alteplase (24 h). Overall safety did not differ among the four treatments, suggesting a favourable safety profile for doses of up to 250 µg/kg desmoteplase.

Previous pre-clinical studies in PE showed that desmoteplase was about twice as potent based on molarity or weight of the administered dose (2). However, at equal plasma levels, both plasminogen activators have a comparable thrombolytic potency, i.e. their specific activity in vivo is about equal. The results obtained in this phase II dose escalation study are consistent with these findings in that desmoteplase at doses of 180 and 250 µg/kg
bolus had a faster onset of action, and 250 µg/kg bolus desmoteplase tended to be more efficacious than 100 mg alteplase (10 mg bolus, 90 mg infusion over 2 h). Compared to previous clinical trials in acute ischaemic stroke (DIAS [5], DEDAS [6]), in which desmoteplase showed efficacy at doses of 90 and 125 µg/kg, the necessary effective dose was higher in the present study. In stroke patients (DIAS study), desmoteplase doses of up to 50 mg (corresponding to 714 µg/kg in patients with 70 kg) were tested, and symptomatic intracranial haemorrhage prompted investigators to reduce the dose to body weight adjusted 125 µg/kg (5). The high dose necessary for adequate response in DEPTH (with no intracranial haemorrhage) may reflect the larger thrombus burden in PE in comparison to stroke. However, doses of 500 and 750 µg/kg have been shown to be effective in patients with acute myocardial infarction without causing fibrinogen depletion (unpublished, mentioned in Hacke et al. [5]). Given that the highest dose tested was below this dose range and that adverse events including intracranial haemorrhage were not more frequent at the highest dose tested (250 µg/kg), this dose seems to be suitable for studies in patients with PE. The apparent paradox that these higher doses appear to be safe (concerning the risk of symptomatic intracranial haemorrhage) in PE and myocardial infarction but not in stroke may be explained by the fact that acute ischaemic stroke leads to an increasing loss of the integrity of the blood brain barrier (7), a feature being unique to the situation of patients with stroke.

Fibrinogen concentrations decreased substantially following alteplase treatment, whereas changes with desmoteplase treatment were minor. This finding confirms preclinical observations of negligible fibrinogen degradation with desmoteplase in comparison with alteplase, while the thrombolytic profiles of the two plasminogen activators were very similar (8). This difference has also a structural correlate: The kringle 2 domain, present in alteplase but not in desmoteplase, mediates alteplase binding to and activation by fibrinogen (9) and other non-fibrin activators and thus is a decisive factor in the limitation of the clot specificity of alteplase compared with desmoteplase.

Shortcomings of this study were the low number of subjects per treatment group (between 6 and 12 subjects); treatment of only six subjects with the highest desmoteplase dose; inhomogeneity of the number of subjects enrolled by center; inhomogeneity of baseline characteristics with regard to demographics; and a wide time window between start of treatment and onset of signs and symptoms of pulmonary embolism, which ranged between 6 h and 14 days. Furthermore because the study aimed to determine the optimal dose for the treatment of massive PE, it made use of surrogate endpoints only. A separate analysis was performed including only subjects with a Miller Index ≥17 at baseline (as assessed by the central imaging committee). However, the results did not yield different results compared with those observed in the ITT population.

Conclusions

In this patient population of PE, the efficacy of desmoteplase at doses of 180 and 250 µg/kg was similar or greater compared to alteplase 100 mg with a faster onset of action and a comparable safety. Desmoteplase 250 µg/kg appears to be a suitable dose for future studies in patients with massive PE.

Appendix

The following investigators participated in the DEPTH Trial: Principal investigator: U. Tebbe; Participating investigators, centers (included patients): U. Tebbe, Klinikum Lippe GmbH, Detmold, Germany (1); A. Grafit, Klinikum Dresden-Friedrichstadt, Dresden, Germany (24); H.F. Voeringer, DRK-Kliniken Köpenick, I. Med Klinik, Berlin, Germany (1); J. Neuzner, Klinikum Kassel gGmbH, Medizinische Klinik II, Kassel, Germany (1); L. Halmay, Szegedi Egyetem Intenzív, Osztály, Hungary (1); G. Luponvics, Zala Megyei Korhaz, Zala County Hospital, Zalaszentgyorgy, Hungary (4); A.I. Kirienkovic, City Clinical Hospital #1, Cardiology, Moscow, Russia (2).

References