Dose-Ranging Trial with a Recombinant Urokinase (Urokinase Alfa) for Occluded Central Venous Catheters in Oncology Patients

Steven R. Deitcher, MD, Giuseppe Fraschini, MD, Jonathan Himmelfarb, MD, Earl Schuman, MD, Thomas J. Smith, MD, Gregory A. Schulz, MS, Carolyn M. Firszt, MS, and Tamyra L. Mouginis, MD

PURPOSE: Recombinant urokinase (r-UK) is a high-molecular-weight urokinase produced in transfected, non-human, mammalian cells. A Phase II, randomized, double-blind, parallel, placebo-controlled, dose-ranging study was performed to compare the safety and efficacy of one or two instillations of three intraluminal concentrations of r-UK (5,000; 15,000; and 25,000 IU/mL) with a placebo for reestablishment of total function to occluded central venous access devices (CVADs).

MATERIALS AND METHODS: One-hundred eight patients with CVAD withdrawal or total occlusion were enrolled and randomized to treatment; 104 patients received at least one instillation of study drug and 101 patients completed treatment. All but one patient had cancer.

RESULTS: All three concentrations of r-UK were significantly superior to placebo in restoring total CVAD function (patency of all occluded lumens) after one or two instillations of study medication (25,000 IU/mL r-UK, 68% vs. placebo, 28% [P = .007]; 15,000 IU/mL r-UK, 69% vs. placebo, 24% [P = .004]; 5,000 IU/mL r-UK, 70% vs. placebo, 28% [P = .003]). Comparisons of the three r-UK concentrations indicated no difference after one or two instillations with regards to patency restoration. Treatment-emergent hemorrhagic events occurring within 72 hours after study drug exposure were experienced by four patients (17%) in the 25,000 IU/mL r-UK group, two patients (7%) in the 15,000 IU/mL r-UK group, no patients in the 5,000 IU/mL r-UK group, and no patients in the placebo group.

CONCLUSIONS: Efficacy and safety results of this study support further evaluation of a 5,000 IU/mL concentration of r-UK for treatment of occluded CVADs in adult and pediatric patients from 1 year of age.
instillation of r-UK. A total of 32 patients received treatment. Of these, 22 patients (69%) had their catheter successfully treated after a maximum of two instillations of study medication. One subarachnoid hemorrhage occurred in this study, but this was attributed to the patient’s chemotherapy (L-asparaginase). This was the only hemorrhagic event reported (3).

This Phase II study was designed to compare the safety and efficacy of three intraluminal concentrations of r-UK to a placebo in reestablishing function to occluded CVADs primarily in oncology patients.

MATERIALS AND METHODS

This Phase II, randomized, double-blind, parallel, placebo-controlled, multi-center dose-ranging study was conducted between May, 2000 and September, 2001 at 25 sites in the United States. The study was designed to compare the safety and efficacy of three intraluminal concentrations of r-UK (5,000 IU/mL; 15,000 IU/mL; and 25,000 IU/mL) to a placebo in reestablishing function to occluded CVADs (single or double lumen) primarily in oncology patients. Randomization was stratified by site. Information from the randomization schedule was incorporated into the drug packaging by labeling the proper blinded study medication kits with the subject numbers. Blind-breaker envelopes were provided to the sites for use in an emergency, although none were used during the course of the study. The protocol was approved by the Institutional Review Board/Independent Ethics Committee at each study site and all patients, or their legal guardians, provided written informed consent before enrollment.

Patient Population

Patients with any type of semi-permanent or temporary CVAD, excluding hemodialysis catheters, with either a withdrawal occlusion (inability to withdraw blood but able to infuse fluids) or a total occlusion (inability to either withdraw or infuse) were eligible for enrollment. There was no restriction on the duration of CVAD occlusion or catheter age. The CVAD must have been successfully used at least once to qualify. Patients were excluded from the study if the occlusion was suspected to be caused by incorrect catheter placement or drug precipitation or if they were pregnant or nursing, had sustained hypertension, less than 1 year of age or under 10 kg, or were at significant risk for bleeding. Patients with triple-lumen catheters and those receiving treatment intensity anticoagulation were excluded.

Patient Disposition

One-hundred eight patients with occluded CVADs presumed to be caused by a fibrin clot resulting in a withdrawal occlusion (inability to aspirate blood but ability to infuse solutions) or a total occlusion (inability to aspirate blood and infuse solutions) were enrolled and randomized to treatment. One-hundred four randomized patients received at least one instillation of study drug and 101 patients completed treatment. Patient demographics: 50 women, 58 men; 11 black, 95 white, 5 other (more than one race could have been recorded); mean age 23 years. Age categories: 1 year = 6 patients; 2–11 years = 45 patients; 12–18 years = 21 patients; >18 years = 36 patients. All but one patient had cancer. Of the 107 enrolled oncology patients, 58 patients (54%) had hematological malignancies and 50 patients (47%) had solid tumors. One subject had two primary cancers. Patients with single lumen withdrawal occlusions were predominant over all other types (65 of 108 patients, 60%).

Treatment

Treatments were administered intraluminally to all occluded lumens in a blind fashion and included one of three concentrations of r-UK (5,000 IU/mL; 15,000 IU/mL; or 25,000 IU/mL) or a matching placebo consisting of formulation excipients only. Study medication was slowly instilled at a volume to slightly overfill the occluded catheter lumen(s). If the fill volume of the CVAD was unknown, a set volume of study drug was administered based on catheter type. Treatment success was assessed by attempting to aspirate the study drug and residual clot with an empty, sterile syringe. Up to three (5, 15, and 30 minutes) attempts were made to aspirate the catheter after each instillation of study medication. If this was unsuccessful, any aspirated study drug was reinjected. If aspiration was successful, flushing of the lumen was attempted. If one instillation of study medication was not successful in establishing catheter function after 30 minutes, then a second instillation of the same study medication was administered in the same manner for the 5,000 IU/mL, 15,000 IU/mL, and placebo treatment groups. The second instillation in the 25,000 IU/mL treatment group (if required) was placebo.

Outcome Variables

The primary study efficacy endpoint was reestablishment of a functional CVAD after one or two instillations of study medication. A functional catheter was defined as the ability to both withdraw blood and to infuse solutions through all treated lumens of the catheter. The secondary efficacy endpoint was reestablishment of a functional catheter after a single instillation of study medication. The major safety endpoints were the incidence, causality, and severity of hemorrhagic and non-hemorrhagic adverse events within 72 hours of study drug exposure. Hemorrhages were classified as major (intracranial hemorrhage, retroperitoneal hemorrhage, any hemorrhage resulting in death, or overt bleeding associated with transfusion of 2 U of blood or a hemoglobin decrease of at least 2.0 g/dL) or minor (all other hemorrhagic events).

Statistical Analysis

Data were summarized with use of the Statistical Analysis System (SAS Institute, Cary, NC). All statistical tests were two-sided and conducted at the 0.05 level of significance. Efficacy analyses were performed on all randomized patients. Safety analysis was performed on all treated patients. Paired comparisons of catheter patency between treatment groups were made with use of a Cochran-Mantel-Haenszel test with investigative site as the stratification factor. A closed, step-down procedure was used for comparisons between placebo and each of the r-UK groups, starting with the 25,000 IU/mL concentration. Patients who were randomized but not treated were classified as failures for the i-


### Table 1
**Patency Results after One or Two Instillations of Study Drug (Stratified by Investigative Site, All Randomized Subjects)**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Subjects with Functional Catheters* (%)</th>
<th>Difference (%)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-UK 25,000</td>
<td>25</td>
<td>68</td>
<td>40</td>
<td>.007</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-UK 15,000</td>
<td>27</td>
<td>69</td>
<td>45</td>
<td>.004</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-UK 5,000</td>
<td>26</td>
<td>70</td>
<td>42</td>
<td>.003</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Placebo rates are slightly different for each comparison as they represent different weighted averages across sites.
† P-value from Cochran-Mantel-Haenszel mean score test with investigative site as the stratification factor.

### Table 2
**Patency Results after One Instillation of Study Drug (Stratified by Investigative Site, All Randomized Subjects)**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Subjects with Functional Catheters* (%)</th>
<th>Difference (%)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-UK 25,000</td>
<td>25</td>
<td>52</td>
<td>37</td>
<td>.010</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-UK 15,000</td>
<td>27</td>
<td>41</td>
<td>28</td>
<td>.023</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-UK 5,000</td>
<td>26</td>
<td>49</td>
<td>36</td>
<td>.003</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td>30</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Placebo rates are slightly different for each comparison as they represent different weighted averages across sites.
† P-value from Cochran-Mantel-Haenszel mean score test with investigative site as the stratification factor.

---

**RESULTS**

**Efficacy**

Tables 1 and 2 show that all three concentrations of r-UK (5,000 IU/mL; 15,000 IU/mL; and 25,000 IU/mL) were superior to placebo in restoring catheter function (patency) after one or two and after one instillation(s) of study medication. The differences in efficacy between the test concentrations and placebo were all statistically significant. Comparison of the three r-UK concentrations indicated no differences between the three concentrations after one or two and after one instillation(s) in the ability to restore catheter patency. Table 3 and the Figure show the cumulative patency rates for 1 hour after one or two instillations of study medication.

**Safety**

Table 4 shows that treatment-emergent hemorrhagic events occurring within 72 hours after study drug exposure were experienced by four patients (17%) in the r-UK 25,000 IU/mL group, two patients (7%) in the 15,000 IU/mL group, no patients in the r-UK 5,000 IU/mL group, and no patients in the placebo group. Of these, one subject (25,000 IU/mL group) had two events of major severity both of which were considered probably not related to study drug (subarachnoid hemorrhage status post a fall and injection site hemorrhage in the setting of thrombocytopenia requiring platelet transfusion). The remaining events were considered of minor severity, only one of which was considered possibly or probably related to study drug. No differences were detected among treatment groups in the incidence of non-hemorrhagic adverse events, nor in the seriousness or relationship of these events. No serious allergic-type reactions were reported. One subject death (not related to study drug, attributed to multiple organ failure status after bone marrow transplantation) occurred during the 30-day follow-up.

**DISCUSSION**

Fibrinolytic agents have been used successfully for more than two decades to restore patency of occluded CVADs. In an early study by Hur- tubise et al (2), 325 patients with occluded CVAD were treated with either intraluminal streptokinase (n = 266) or UK (n = 59). The first injection of a fibrinolytic agent restored patency in 77% of the occluded catheters. In 23% of the cases, two or more fibrinolytic injections were needed to obtain patency. Glynn et al (4) were uniformly successful in restoring function to occluded catheters in 20 patients by administering UK at a concentration of 2,500 IU/mL. Clearance of the catheter was achieved with the first infusion in 29 of 34 attempts (85.3%). In the remaining five instances, it was necessary to repeat the procedure 24 hours later. Lawson et al (5) successfully restored patency to 1,624 of 1,647 occluded catheters with 5,000 IU/mL UK for a success rate of 98.6%. Only one or two instillations of UK were required in the majority of patients. Wachs (6) reported a 98.1% patency rate when treating catheter occlusions in pediatric patients with UK at a concentration of 5,000 IU/mL. Cathflo Activase (Genentech, South San Francisco, CA) (alteplase) is a tissue plasminogen activator (t-PA) currently approved in the United States and indicated for the restoration of function to CVADs as assessed only by the ability to withdraw blood. Two pivotal trials were conducted to evaluate the ability of alteplase to restore function to improperly functioning CVADs. The first study was a placebo...
controlled, double blind, randomized trial in 150 patients with catheters that had been occluded for ≤ 24 hours (7). After the first 2-hour treatment, function was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < .0001$ compared with placebo). The second study was an open label trial in 995 patients with occlusions of any duration (8). Patients received a dose of alteplase (2 mg) and were assessed at 30 and 120 minutes. If patency was not restored after 120 minutes, patients could receive a second dose. Overall, 52.1% of patients had catheter patency restored at 30 minutes after the first administration of alteplase and 76.5% of patients had catheter function restored at 120 minutes after administration. A total of 209 remaining patients required and received a second 2 mg dose. Of these patients, 33% had catheter function restored at 30 minutes and 46% had function restored at 120 minutes after the second administration. Overall, 87.2% of patients had function restored after up to two doses and 4 hours of treatment.

Efficacy results of this study provide clear evidence of the superiority of r-UK over placebo. All test concentrations of r-UK achieved significantly greater catheter patency over placebo after one or two instillations of study drug involving up to 1 hour of active treatment. Comparisons between r-UK concentrations indicated no differentiation between concentrations. The 30-minute patency rates with r-UK in this study were comparable to the 30-minute patency rates reported with alteplase (8). The 60-minute patency rates in this study were comparable to the 120-minute patency rates reported with alteplase (8). This degree of comparability is particularly notable considering the fact that this study had more stringent criteria for “success” than the studies of alteplase (restoration of function to all treated lumens) and included catheters with both withdrawal and total occlusions of any age (7,8). If validated in larger trials, r-UK should be indicated for the rapid restoration of function to CVADs with single or multiple occluded lumens and lumens with withdrawal or total occlusion.

Efficacy and safety results of this study support the evaluation of a 5,000 IU/mL concentration of r-UK in further clinical trials of occluded CVADs in adult and pediatric patients from 1 year of age.

**LIST OF INVESTIGATORS AND PARTICIPATING SITES**

Victor M. Aquino, MD, University of Texas Southwestern Medical Center, Dallas, TX; Bach Ardalan, MD, University of Miami School of Medicine, Miami, FL; Frederick Ey, MD, Oregon Hematology/Oncology Associates, Portland, OR; James Feusner, MD, Children’s Hospital of Oakland, Oakland, CA; Jerry Z. Finklestein, MD, Pediatric Adolescent Hematology/Oncology Assoc., Long Beach, CA; James Garvin, MD, St. Joseph’s Hospital and Medical Center, Paterson, NJ; Paul Gaynon, MD, Children’s Hospital...
Table 4
Treatment-Emergent Hemorrhagic Events Occurring Within 72 Hours After Study Drug Start (All Treated Subjects)

<table>
<thead>
<tr>
<th></th>
<th>r-UK 25,000 N = 24</th>
<th>r-UK 15,000 N = 28</th>
<th>r-UK 5,000 N = 25</th>
<th>Placebo N = 27</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall*</td>
<td>4 (17)</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>.024</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hematuria†</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>.011</td>
</tr>
<tr>
<td>Injection site hemorrhage‡</td>
<td>3 (13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metrorrhagia¶</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage‡</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Only significant P (P ≤ 0.05) are presented.
* A subject who reported the same COSTART V term more than once was counted only once for that term. A subject who reported more than one hemorrhagic event was counted only once for “Overall”.
† P from Fisher’s exact test comparing the four treatment groups.
‡ Major hemorrhages were one subarachnoid hemorrhage and one injection site hemorrhage in the same subject.
¶ COSTART term is female specific; percentage is calculated accordingly.

References