Recurrent Thrombolysis for Chronologically Separated Ischemic Strokes
A Case Series
Roland Sauer, MD; Hagen B. Huttner, MD; Lorenz Breuer, MD; Tobias Engelhorn, MD; Peter D. Schellinger, MD; Stefan Schwab, MD; Martin Köhrmann, MD

Background and Purpose—Recombinant tissue plasminogen activator is used for the treatment of acute myocardial infarction, pulmonary embolism, and acute ischemic stroke. With many years since approval of the drug and an aging population, chances increase that patients are treated twice for chronologically separated events.

Methods—We identified patients from the prospective Erlangen Stroke and Thrombolysis Database who received repeated thrombolysis for acute ischemic stroke. Baseline demographic data and clinical, laboratory, and imaging findings were analyzed. Functional outcome was assessed after 3 months.

Results—Eight patients treated twice and one patient with 3 treatments were identified. The median time span between first and second thrombolysis was 10 (3 to 48) months. All patients had a favorable outcome after the first treatment, and 67% of patients had a favorable outcome after the second thrombolysis. Neither allergic reactions nor other immunoreactive events were observed.

Conclusions—Repeated administration of recombinant tissue plasminogen activator for chronologically separate ischemic strokes does not appear to be associated with severe immune reactions. Larger case numbers are needed to evaluate safety and efficacy of repeated systemic thrombolysis. (Stroke. 2010;41:1829-1832.)

Key Words: tissue plasminogen activator ■ acute ischemic stroke ■ thrombolysis

Recombinant tissue plasminogen activator (rt-PA) is used for treatment of acute myocardial infarction, pulmonary embolism, and acute ischemic stroke. Development of antibodies against the recombinant protein has been described in various animal models1,2 and humans.3,4 However, their relevance for repeated application of the drug is unknown.3,4 Antibodies may influence efficacy of repeated treatment by neutralizing the active drug and may even harm patients in case of allergic reactions because of sensitization. With many years since approval and an aging population, the question of efficacy and safety of repeated thrombolysis will gain importance. We here report on 8 patients who were treated twice with rt-PA and one patient with 3 thrombolytic treatments, the first such case in the literature, for chronologically separated acute ischemic stroke.

Methods
The prospective Erlangen Stroke and Thrombolysis Database was established in 2006 and includes all acute ischemic stroke patients treated in our institution. For the present analysis, we extracted patients who received repeated rt-PA. To focus on patients with potential antibody formation and to exclude complications attributable to repeated thrombolysis in the context of subacute infarction, patients with a time interval of <3 months between treatments were excluded from analysis (n=3 with very early retreatment [<72 hours] for recurrent thromboembolism).

Demographic and baseline clinical data as well as neuroradiological data, including screening imaging modality, occurrence of symptomatic intracerebral hemorrhage, and site of infarction, were analyzed. Treatment and outcome parameters included the choice of treatment, immunologic complications, and functional outcome data assessed at 90 days using the modified Rankin Scale. Favorable outcome was defined as a modified Rankin Scale score 0 to 2 or recovery to the status before the acute stroke.

Results
Patient Characteristics and Outcome
Between January 2006 and January 2010, 9 of 496 thrombolysed patients were treated repeatedly with rt-PA for chronologically separated acute ischemic stroke. Eight patients were treated twice, and one was treated 3 times (Table; Figure). Median age at the time point of first thrombolysis was 64 (53 to 84) and 68 (54 of 84) at second thrombolysis. The median time interval between both rt-PA administrations was 10 (3 to 48) months. Median baseline National Institutes of Health Stroke Scale score was 6 (2 to 18) for the first and 12 (5 to 27) for the second thrombolysis. One symptomatic intracerebral hemorrhage was observed after the first thrombolysis but...
none after the second. All patients achieved a favorable outcome after the first treatment, and 6 of 9 (67%) patients recovered to a favorable outcome after the second thrombolysis. No hypersensitivity or other immune reactions were observed after repeated rt-PA administration.

**Discussion**

Longer time since approval of rt-PA and wider use in clinical practice combined with an aging population increase the possibility that the same patient is treated with thrombolysis more than once. However, there are very little data on efficacy and safety of repeated treatment with rt-PA.

Because alteplase is a purified human glycoprotein, studies in various animal models demonstrate antibody formation inducing altered pharmacokinetic properties as well as sensitization on re-exposure.1,2 Less immunogenicity of the recombinant endogenous protein is expected in humans. However, clinically relevant antibody formation against human recombinant proteins have been described in the past (eg, recombinant human insulin).3 Several studies investigated the development of antibodies against rt-PA after treatment for a variety of cardiac and noncardiac indications in humans.3,4 Reed et al screened 1.686 patients after rt-PA administration and identified only 3 patients (0.01%) who developed significant titers of antibodies.3 Conversely, Cugno et al showed significantly increased titers in 14% of cardiac patients after treatment.4 Hence, the overall incidence of post-treatment antibodies against rt-PA is still unclear. The highest antibody titer in the series by Cugno et al was found in a patient after 2 treatments. Thus, the risk appears to increase with subsequent exposures.4 No immunologic complications were encountered in the patient with a third exposure in our series, the first such case in the literature.

True anaphylactic reaction is rare in rt-PA–treated patients. Rudolf et al reported a case in which preexisting IgE antibodies against rt-PA lead to severe anaphylaxis in a

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**Table. Demographic, Clinical, and Neuroradiological Parameters As Well As Outcome Measures Before and After First and Second Thrombolysis**

<table>
<thead>
<tr>
<th>Age (First/Second Thrombolysis)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
<th>Patient 9 (Three Treatments)</th>
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<tbody>
<tr>
<td></td>
<td>62/64</td>
<td>84</td>
<td>76</td>
<td>71/72</td>
<td>81/83</td>
<td>62/64</td>
<td>53/54</td>
<td>64/68</td>
<td>62/63/65</td>
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<tr>
<td>Sex</td>
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<td>Female</td>
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<td>Male</td>
<td>Female</td>
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<td>Male</td>
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<td>150</td>
<td>90</td>
<td>270</td>
<td>60</td>
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<td>CT</td>
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<td>CT</td>
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<td>NIHSS baseline</td>
<td>4</td>
<td>9</td>
<td>12</td>
<td>2</td>
<td>18</td>
<td>6</td>
<td>2</td>
<td>18</td>
<td>3</td>
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<tr>
<td>Infarction site</td>
<td>MCA</td>
<td>PCA</td>
<td>MCA</td>
<td>MCA</td>
<td>MCA + ACA</td>
<td>MCA</td>
<td>MCA</td>
<td>BA</td>
<td>MCA</td>
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<tr>
<td>Thrombolysis (iv/ia/combined)</td>
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<td>iv</td>
<td>iv</td>
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<tr>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Immune reaction (yes/no)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Time between treatments (months)</td>
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<td>3</td>
<td>7</td>
<td>9</td>
<td>24</td>
<td>18</td>
<td>8</td>
<td>48</td>
<td>10</td>
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<tr>
<td>mRS before second treatment</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Time window (min)</td>
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<td>180</td>
<td>200</td>
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<td>170</td>
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<td>120</td>
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<td>CT</td>
<td>MRI</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
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<tr>
<td>NIHSS</td>
<td>19</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>18</td>
<td>7</td>
<td>27 (ventilated)</td>
<td>22</td>
<td>5</td>
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<tr>
<td>Infarction site</td>
<td>MCA</td>
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<td>MCA</td>
<td>MCA</td>
<td>MCA + ACA</td>
<td>MCA</td>
<td>MCA</td>
<td>BA</td>
<td>MCA</td>
</tr>
<tr>
<td>Thrombolysis (iv/ia/combined)</td>
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<td>iv</td>
<td>iv</td>
<td>iv</td>
<td>Combined</td>
<td>iv</td>
<td>iv</td>
<td>iv</td>
<td>iv</td>
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<tr>
<td>Symptomatic hemorrhage (yes/no)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>Outcome day 90 (mRS)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Immune reaction (yes/no)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>

NIHSS indicates National Institute of Health Stroke Scale; mRS, modified Rankin Scale; iv, intravenous thrombolysis; ia, intraarterial thrombolysis; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery.
patient without previous exposure to the drug.\textsuperscript{6} This has to be distinguished from anaphylactoid reactions and the development of orolingual angioedema, which is more common and occurs in up to 2\% of patients treated with rt-PA.\textsuperscript{7} It is caused by direct activation of the complement system and kinin cascades, with patients with angiotensin-converting enzyme inhibitor pretreatment being more susceptible.\textsuperscript{7}

Several smaller case studies reported on patients who received repeated thrombolysis mainly for early rescue treatment after failed intervention for myocardial infarction\textsuperscript{8} or pulmonary embolism.\textsuperscript{9} There is only one case of repeated rt-PA treatment for acute ischemic stroke in the literature.\textsuperscript{10} However, as in the above-mentioned nonstroke studies, retreatment in this case was performed shortly (90 hours) after the first thrombolysis\textsuperscript{10} too early for antibody formation to occur.

There are obvious limitations in our case series, the most important being the small number of patients presented, which does not allow firm conclusions on safety and efficacy of repeated thrombolysis in stroke. However, to our knowledge, this case series represents the first report on this topic. Thus, it

Figure. A 65-year-old patient with triple thrombolysis. A, CT before (left) and after (right) thrombolysis for isolated aphasia. Old lesion (right middle cerebral artery), otherwise normal. Complete recovery. B, CT 10 months later for acute aphasia, rt-PA at 120 minutes. CT before thrombolysis (left) normal, CT perfusion imaging (time to peak; middle) demonstrates hypoperfusion (left middle cerebral artery). Complete recovery, no new infarction on follow-up (right). C, CT 26 months after B for acute aphasia and hemianopia. CT before thrombolysis normal (left), CT perfusion (time to peak; middle) shows hypoperfusion (left posterior cerebral artery). Follow-up with new left posterior cerebral artery infarction (right).
may serve as a trigger for future research and gives an overview of the available literature. Another limitation is that no antibody titers were analyzed. This should be done in future studies.

Disclosures
H.B.H., P.D.S., and M.K. received travel grants from Boehringer Ingelheim. P.D.S. and S.S. are members of the advisory board and received speaker honoraria from Boehringer Ingelheim, the manufacturer of rt-PA. No funding was involved in the present study.

References
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