

# Combining Intravenous Thrombolysis and Antithrombotic Agents in Stroke: An Update

Laurent Derex, MD, PhD; Chloé Paris, PharmD; Norbert Nighoghossian, MD, PhD

Up until 2015, only intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) had proven to be effective for the treatment of ischemic stroke within 4.5 hours of the onset of symptoms.<sup>1,2</sup> Intravenous thrombolysis nonetheless has certain limitations linked to the risk of causing intracerebral hemorrhage and to an insufficient rate of cerebral arterial recanalization, particularly in case of a proximal occlusion.<sup>3,4</sup> Furthermore,  $\approx 15\%$  of patients exhibit a secondary clinical deterioration that may be caused by reocclusion after an effective thrombolysis that restored blood flow.<sup>5,6</sup> Mechanical thrombectomy, in association with intravenous thrombolysis, represents a therapeutic revolution that has been validated by several randomized trials in acute ischemic stroke related to a carotid or a proximal middle cerebral artery occlusion.<sup>7</sup> However, other intravenously administered therapeutic approaches might be used in case of a distal arterial occlusion or when the patient is admitted to a hospital that is not capable of delivering endovascular therapy. Thus, novel therapeutic strategies for ischemic stroke are undergoing evaluation, such as the association of thrombolysis by intravenous rtPA and an antithrombotic agent, with the aim of improving the rate and speed of recanalization and reducing the risk of reocclusion while also seeking to limit the rate of intracerebral hemorrhage.<sup>8</sup> By way of comparison, in case of myocardial infarction, the combined administration of thrombolytic, anticoagulant, and antiplatelet agents is frequently used, with a proven favorable effect on reperfusion and clinical outcome.<sup>9</sup>

The aim of this review is to present the current state of knowledge regarding the addition of antithrombotic agents to intravenous thrombolysis for acute ischemic stroke treatment, with the aim of enhancing the efficacy of the treatment.

## Alteplase and Aspirin

The combination of thrombolysis and an antiplatelet agent could potentially improve the rate of cerebral arterial recanalization as well as reduce the risk of reocclusion. The combination of antiplatelet and thrombolytic treatments has been shown to exert a synergistic effect on the reduction of mortality in myocardial infarction.<sup>9</sup> Aspirin inhibits platelet activation by blocking the synthesis of platelet thromboxane A<sub>2</sub>. This is the only antithrombotic agent that has proven to be effective at preventing early ischemic recurrence and at improving the prognosis for cerebral infarction. A randomized open phase 3 study, called ARTIS (Antiplatelet Therapy in Combination with RT-PA Thrombolysis in Ischemic Stroke), has evaluated the potential of a treatment associating 0.9 mg/kg of rtPA administered intravenously within 4.5 hours of the onset of stroke and 300 mg of aspirin administered as an intravenous bolus within 90 minutes of initiating the thrombolysis, as compared with a conventional intravenous thrombolysis.<sup>10</sup> Between July 2008 and April 2011, 642 patients were recruited at several Dutch hospital centers. This study was terminated prematurely because of a significant increase in the risk of symptomatic intracranial hemorrhaging in the group of patients who received the combination of rtPA and aspirin. Furthermore, the clinical outcome of the patients who had received rtPA and aspirin was similar to that seen for the conventional thrombolysis group. Thus, 54% of the patients in the rtPA and aspirin group and 57% of the patients in the rtPA only group had a modified Rankin Scale score  $\leq 2$  at 3 months ( $P=0.42$ ). Hence, early administration of aspirin did not provide a clinical benefit in patients treated with intravenous thrombolysis, while it significantly increased the risk of symptomatic intracranial hemorrhage.

According to the current guidelines, in order to limit the risk of an intracranial hemorrhagic complication, no antiplatelet treatment should be administered in the 24 hours that

From the Department of Neurology, Stroke Center, Neurological Hospital, Hospices Civils de Lyon, University of Lyon, Bron cedex, France (L.D., C.P., N.N.); EA 7425 HESPER, Health Services and Performance Research, Claude Bernard Lyon 1 University, Lyon, France (L.D.).

**Correspondence to:** Laurent Derex, MD, PhD, Department of Neurology, Neurological Hospital, Hospices Civils de Lyon, 59 Boulevard Pinel, 69677 Bron cedex, France. E-mail: laurent.derex@chu-lyon.fr

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follow treatment of an ischemic stroke by intravenous thrombolysis.<sup>11</sup>

## Alteplase and Heparin

Early administration of unfractionated heparin, low-molecular-weight heparin, or heparinoids is not currently recommended for the treatment of acute ischemic stroke.<sup>11</sup> This is contrary to the guidelines for the treatment of the acute phase of myocardial infarction, for which the association of rtPA and heparin has shown superiority over rtPA alone in terms of recanalization and prevention of reocclusion.<sup>12</sup>

A nonrandomized pilot study was carried out in 60 patients with acute ischemic stroke in order to evaluate the safety of the combination of low-molecular-weight heparin with intravenous thrombolysis by rtPA.<sup>13</sup> The control group could receive a standard anticoagulant treatment 24 hours after thrombolysis, while the evaluated treatment consisted of administration of 2850 IU of nadroparin every 12 hours initiated immediately after thrombolysis. The average National Institutes of Health Stroke Scale score was 13 for the 2 groups. In this study, there was no evaluation of the arterial status before and following intravenous thrombolysis. One patient (4%) of the standard anticoagulation group and 3 patients (8.6%) of the early anticoagulation group had a symptomatic intracranial hemorrhage ( $P$ =not significant). At 3 months, 36% of the patients in the standard anticoagulation group exhibited a favorable clinical outcome (ie, a modified Rankin score of  $\leq 1$ ) versus 45.7% of the patients in the early anticoagulation group. This favorable yet statistically nonsignificant trend indicates that additional studies may be warranted. Safety would be an important end point given the trend towards a higher risk of symptomatic intracranial hemorrhage in this pilot study.

## Alteplase and Inhibitors of Glycoprotein IIb-IIIa

Inhibitors of glycoprotein IIb-IIIa inhibit platelet aggregation by blocking the binding of fibrinogen to platelet glycoprotein IIb-IIIa receptors. Several molecules such as eptifibatide, tirofiban, and abciximab are currently indicated for the prevention of myocardial infarction in case of unstable angina or to prevent ischemic cardiac complications in case of percutaneous coronary intervention. These inhibitors of glycoprotein IIb-IIIa are undergoing research in the setting of acute ischemic stroke, although at present their use is not recommended for clinical practice.<sup>11</sup>

## Eptifibatide

Eptifibatide, which is a synthetic cyclic heptapeptide, reversibly inhibits platelet aggregation and it has a short

half-life. In association with intravenous thrombolysis, this agent increases the speed of recanalization in case of coronary artery occlusion.<sup>14</sup>

The aim of a multicenter phase 2 study, called CLEAR (Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA), was to evaluate the safety of a treatment initiated within 3 hours of a cerebral infarction that combines low doses of intravenous rtPA (0.3 or 0.45 mg/kg) and intravenous eptifibatide (75  $\mu$ g/kg by bolus, followed by a 2-hour perfusion at 0.75  $\mu$ g/kg per minute), as compared with conventional intravenous thrombolysis.<sup>15</sup> It was a randomized, double-blind study in which 94 patients were included between July 2003 and April 2007. Reperfusion was not evaluated in this pilot study. A symptomatic intracranial hemorrhage occurred in 1 patient (1.4%) of the group that received the rtPA/eptifibatide combination and in 2 patients (8%) treated with rtPA only ( $P$ =0.17). The safety of the combination of eptifibatide and low doses of rtPA led to further studies.

A randomized double-blind phase 2 study, CLEAR-ER (Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA—Enhanced Regimen) was hence carried out.<sup>16</sup> This study was funded by the National Institute of Health/National Institute of Neurological Disorders and Stroke, and sought to evaluate the safety and efficacy of concomitant administration of 0.6 mg/kg of intravenous rtPA and 225  $\mu$ g/kg intravenous eptifibatide (135  $\mu$ g/kg as a bolus, followed by a perfusion lasting 2 hours), as compared with a conventional intravenous thrombolysis initiated within 3 hours. Between July 2009 and October 2012, 126 patients were included in several American hospitals. Two patients (2%) who received eptifibatide and 3 patients (12%) in the conventional thrombolysis group had a symptomatic intracranial hemorrhage ( $P$ =0.053). At 3 months, the rates of serious events and mortality were similar between the 2 groups. The results of this study have hence confirmed that a combined rtPA/eptifibatide treatment is safe for clinical use. Additionally, 49.5% of the patients who received eptifibatide exhibited a favorable clinical outcome (ie, a modified Rankin Scale score  $\leq 1$  or equal to the initial modified Rankin Scale score) at 3 months versus 36% of the patients treated with intravenous rtPA only ( $P$ =0.23).

The CLEAR-FDR (Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA—Full Dose Regimen) study evaluated the safety of a treatment associating a standard dose of rtPA (0.9 mg/kg) and 225  $\mu$ g/kg of intravenous eptifibatide, administered within 3 hours of stroke onset.<sup>17</sup> This open prospective study included 27 patients between October 2013 and December 2014. The median age was 73 years and the median National Institutes of Health Stroke Scale score was 12. Thirty percent of the patients included in the study had a modified Rankin score  $>2$  before the stroke. A single case of symptomatic intracerebral hemorrhage was observed. The results of this phase 2 study of small sample size suggest

safety of the combination of full-dose rtPA and intravenous eptifibatide and support proceeding with a phase 3 trial evaluating full-dose rtPA combined with eptifibatide to improve clinical outcome after ischemic stroke.

## Tirofiban

Tirofiban, a nonpeptide antagonist, has been used in several clinical trials, alone or in association with a reduced dose of rtPA in patients with acute ischemic stroke.

Observational pilot studies have been carried out to evaluate the effects of a treatment associating a low dose of intravenous rtPA administered within the first 3 hours of stroke symptoms followed by an intravenous perfusion of tirofiban over 24 to 48 hours.<sup>18,19</sup> In a retrospective pilot study, 37 consecutive patients were treated with low-dose intravenous rtPA ( $24 \pm 9$  mg; range, 20–50 mg), followed by intravenous tirofiban. Tirofiban was given in a body weight–adjusted dosage starting with a bolus of  $0.4 \mu\text{g}/\text{kg}$  body weight per minute for 30 minutes followed by continuous infusion of  $0.1 \mu\text{g}/\text{kg}$  body weight per minute. Tirofiban was continued for at least 24 hours. Patients reached a Rankin Scale score of 0 to 2 in 63%. The death rate was 8% and 1 fatal hemorrhage was observed.<sup>18</sup> In a small open-label trial, 19 patients with acute middle cerebral artery occlusion underwent combined intravenous thrombolytic treatment using rtPA at reduced dosages and body weight–adjusted tirofiban for at least 48 hours. Middle cerebral artery recanalization occurred in 13 of 19 patients (68%) and no symptomatic hemorrhage was observed.<sup>20</sup>

The results of these small, open-label studies have suggested the feasibility of a combined treatment associating low-dose intravenous rtPA and tirofiban, but no randomized controlled trials have been performed.

## Abciximab

The combined administration of abciximab, which is a chimeric monoclonal antibody, and rtPA has only been reported in a limited number of patients with acute ischemic stroke. These observational studies have shown that a treatment combining a reduced dose of intravenous rtPA ( $0.45 \text{ mg}/\text{kg}$ ) and an intravenous perfusion of abciximab, administered in the 3 to 6 hours following stroke onset, does not appear to be associated with a high risk of major hemorrhagic complications.<sup>21,22</sup>

## Alteplase and Argatroban

Argatroban is a direct inhibitor of free and clot-associated thrombin. The safety of this agent has been demonstrated in patients with myocardial infarction, whether or not in association with thrombolysis or aspirin.<sup>23</sup> Argatroban has

the advantage of having a short half-life, which allows its anticoagulating action to be terminated rapidly in case of hemorrhage. Additionally, its activity can be controlled by measurement of the activated partial thromboplastin time.

In animal models of stroke, argatroban increased the efficacy of rtPA as a result of its favorable impact on microcirculation, on the speed of arterial recanalization, and on the prevention of reocclusion.<sup>24</sup>

A pilot study, ARTSS (Argatroban tPA Stroke Study), has evaluated the safety of a treatment associating  $0.9 \text{ mg}/\text{kg}$  of intravenous rtPA and argatroban administered as an intravenous bolus of  $100 \mu\text{g}/\text{kg}$  followed by a perfusion of  $1 \mu\text{g}/\text{kg}$  per minute over 48 hours.<sup>25</sup> Sixty-five patients (average age  $63 \pm 14$ ; median National Institutes of Health Stroke Scale score of 13) with a proximal intracranial arterial occlusion were included in this study between May 2003 and August 2010. The activated partial thromboplastin time target was 1.75 times the control under argatroban. A complete or partial arterial recanalization was seen in 55% of the patients at 2 hours and in 78% at 24 hours. Symptomatic intracranial hemorrhage occurred in 3 patients (4.6%) and 7 patients (10.8%) died within the first 7 days, mainly as a result of extensive cerebral infarction. These preliminary safety data regarding the association of argatroban and intravenous rtPA have led to additional studies.

The results of the randomized controlled multicenter ARTSS-2 study were recently published. This study aimed to evaluate the safety and the efficacy of a treatment combining a standard dose of intravenous rtPA and an intravenous bolus of  $100 \mu\text{g}/\text{kg}$  of argatroban in association with  $1 \mu\text{g}/\text{kg}$  per minute (low dose) or  $3 \mu\text{g}/\text{kg}$  per minute (high dose) by intravenous perfusion over 48 hours, as compared with conventional intravenous thrombolysis performed within 4.5 hours after the onset of stroke.<sup>26</sup> Ninety patients were randomized: 29 received rtPA only, 30 received rtPA and the low dose of argatroban, and 31 received rtPA and the high dose of argatroban. The rates of symptomatic intracerebral hemorrhage were similar in the 3 groups. At 90 days, 6 (21%) rtPA alone, 9 (30%) low-dose, and 10 (32%) high-dose patients had a modified Rankin Scale score 0 to 1. The relative risks (95% credible interval) for modified Rankin Scale score 0 to 1 with low-, high-, and either low- or high-dose argatroban were 1.17 (0.57–2.37), 1.27 (0.63–2.53), and 1.34 (0.68–2.76), respectively.

The results of these studies indicate that adding argatroban to rtPA is safe and that it can potentially provide a clinical benefit, thus justifying the evaluation of this association in a larger therapeutic trial.

## Alteplase and Inhibitors of TAFI

Thrombin-activated fibrinolysis inhibitor, also known as procarboxypeptidase B, is an enzyme synthesized by the liver for

**Table.** Summary of the Studies Evaluating the Combination of Intravenous Thrombolysis and Antithrombotic Agents in Acute Ischemic Stroke

	Dose of Thrombolytic Agent	Dose of Antithrombotic Agent	Design of the Study	Number of Patients	Main Outcomes
ARTIS <sup>10</sup>	rtPA 0.9 mg/kg	Aspirin 300 mg	Phase 3, multicenter, randomized, open, controlled vs rtPA	642	m-RS $\leq$ 2 54% rtPA/aspirin 57% rtPA s-ICH 4.3% rtPA/aspirin* 1.6% rtPA
Mikulik et al <sup>13</sup>	rtPA 0.9 mg/kg	Nadroparin 2850 IU	Pilot, nonrandomized, open, controlled vs rtPA	60	m-RS $\leq$ 1 45.7% rtPA/Nadroparin 36% rtPA s-ICH 8.6% rtPA/Nadroparin 4% rtPA
CLEAR <sup>15</sup>	rtPA 0.3 or 0.45 mg/kg	Eptifibatide 165 $\mu$ g/kg	Pilot, multicenter, randomized, double-blind, controlled vs rtPA	94	s-ICH 1.4% rtPA/eptifibatide 8% rtPA
CLEAR-ER <sup>16</sup>	rtPA 0.6 mg/kg	Eptifibatide 225 $\mu$ g/kg	Phase 2, multicenter, randomized, double-blind, controlled vs rtPA	126	m-RS $\leq$ 1 or equal to the initial m-RS 49.5% rtPA/eptifibatide 36% rtPA s-ICH 2% rtPA/eptifibatide 12% rtPA
CLEAR-FDR <sup>17</sup>	rtPA 0.9 mg/kg	Eptifibatide 225 $\mu$ g/kg	Phase 2, prospective, multicenter, open	27	m-RS $\leq$ 1 or equal to the initial m-RS 63% rtPA/eptifibatide s-ICH 3.7% rtPA/eptifibatide
ARTSS <sup>25</sup>	rtPA 0.9 mg/kg	Argatroban	Pilot, multicenter, open, uncontrolled	65	s-ICH 4.6% rtPA/argatroban
ARTSS-2 <sup>26</sup>	rtPA 0.9 mg/kg	Argatroban	Phase 2b, multicenter, randomized, controlled vs rtPA	90	s-ICH 13% Argatroban low dose 7% Argatroban high dose 10% rtPA

ARTSS indicates Argatroban tPA Stroke Study; CLEAR, Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA; CLEAR-ER, Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA—Enhanced Regimen; CLEAR-FDR, Combined Approach to Lysis Utilizing Eptifibatide and Rt-PA—Full Dose Regimen; m-RS, modified Rankin Scale score; rtPA, recombinant tissue plasminogen activator; s-ICH, symptomatic intracranial hemorrhage.

\* $P < 0.05$  statistically significant.

which the active form has an antifibrinolytic activity. Strategies that involve inhibition of thrombin-activated fibrinolysis inhibitor hence appear to be therapeutic options with the aim of boosting fibrinolysis and thus increasing the rate and speed of arterial recanalization. This new therapeutic approach is currently at a purely experimental stage. A murine thromboembolic model has been used to test the efficacy of a thrombin-activated fibrinolysis inhibitor administered alone or in association with a low dose of rtPA (5 mg/kg) as compared with a control group. Only the standard dose of rtPA (10 mg/kg) allowed for a significant reduction in the volume of the cerebral infarction as compared with administration of NaCl.<sup>27</sup>

Table provides a summary of the results of the studies that evaluated the combined administration of antithrombotic

agents and intravenous thrombolysis with rt-PA in the setting of acute ischemic stroke.

## Conclusions

The advent of mechanical thrombectomy has led to a new era in the treatment of cerebral infarction, although intravenous thrombolysis retains its indication in light of its greater availability and its widely demonstrated efficacy, particularly in the absence of a proximal arterial occlusion (a situation that precludes mechanical thrombectomy).

The approach combining intravenous administration of rtPA and an antithrombotic agent, an inhibitor of the glycoprotein IIb-IIIa such as eptifibatide, or a direct inhibitor

of thrombin such as argatroban, appears to be a promising direction in therapeutic research. It is hoped that this will increase the speed and rate of arterial recanalization while decreasing the risk of reocclusion, without leading to too much of a risk of symptomatic intracerebral hemorrhage.

More data are needed regarding the safety of the association of thrombolysis by intravenous rt-PA and an antithrombotic agent. The combined approach to lysis utilizing antithrombotic agents and intravenous thrombolysis may not ultimately prove best if an increased risk of symptomatic intracranial hemorrhage is observed.

An important limitation of the current research on combining antithrombotic agents with intravenous thrombolysis in acute stroke treatment lies in the fact that most trials have not used imaging to differentiate between small- and large-vessel occlusion, while the rate of recanalization is strongly influenced by the site of occlusion.

Therapeutic strategies associating antithrombotic agents and thrombolysis that are undergoing evaluation are complementary to rather than in competition with the development of mechanical thrombectomy. This noninvasive approach may be broadly applicable without delay, particularly in patients admitted to a center that does not have ready access to mechanical thrombectomy, pending a complementary endovascular approach if a proximal cerebral arterial occlusion persists.

## Disclosures

Dr Derex received honoraria for speaking from Boehringer Ingelheim. The remaining authors have no disclosures to report.

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