Emerging Therapy Critiques
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Combining Antithrombotic and Fibrinolytic Agents
Can It Be Done?

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More than half of ischemic stroke patients who are treated with IV recombinant tissue-type plasminogen activator (rtPA) remain disabled at 3 months.1,2 The reasons are many. The IV rtPA rate of recanalizing occluded arteries is not as high as we would like, especially for large arterial occlusions, which are opened only 30% to 40% of the time.1–6 When rtPA does effectively lyse a thrombus, it is sometimes too late; permanent tissue injury may have already occurred.7,8 Moreover, even when rtPA restores blood flow expeditiously, reocclusion occurs in ≈20% to 30% of patients.9–11

Enhancing thrombolysis with adjunctive agents is a logical next step. Strategies under investigation include increasing recanalization rates through endovascular therapies or ultrasound assistance, increasing the resilience of ischemic tissue using neuroprotective strategies, and limiting the likelihood of reocclusion (and possibly improving recanalization) by adding antithrombetics, such as antiplatelet or anticoagulant agents. Definitive studies have been disappointing to date.

The first strategy was recently addressed by the phase III Interventional Management of Stroke (IMS-III) Trial, which demonstrated interim futility of adjunctive endovascular therapy compared with IV rtPA alone in a broad population of moderate and severe acute ischemic stroke subjects.12 Detailed results, including subgroup analyses, are pending.

The second strategy was recently addressed by the phase III Albumin in Acute Ischemic Stroke (ALIAS) Trial of albumin, which also demonstrated interim futility (personal communication, Michael D. Hill, unpublished data, 2012), and detailed results are pending for this as well. Another phase III trial of neuroprotection strategy to enhance IV rtPA is testing the use of magnesium in the prehospital setting13 before IV rtPA administration, the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) Trial, is nearing completion of enrollment.

The third strategy has been addressed in the recently published phase III Antiplatelet Therapy in combination with rtPA Thrombolysis in Ischemic Stroke (ARTIS) Trial from the Netherlands of aspirin as an adjunct to IV rtPA.14 Zinkstok et al14 tested the hypothesis that adding acute IV aspirin (300 mg) to standard dose IV rtPA may improve outcomes in an open-label randomized trial of 800 planned subjects. The primary efficacy end point was 3-month favorable outcome (modified Rankin Score of 0–2) as assessed by a blinded investigator. The study was powered to detect a 10% absolute difference in favorable outcome between the 2 treatment groups. Key safety end points were symptomatic intracranial hemorrhages (sICH), severe systemic bleeding, and serious adverse events. Notably, subjects were not required to receive 24-hour computed tomography scans, as is the standard of care in both the United States and Switzerland. Investigators only performed computed tomography scans in the setting of neurological deterioration.

The trial was terminated prematurely after inclusion of 642 patients because of more sICH (7.4% vs 0.7%; P=0.006) and no evidence of higher favorable outcome (54% vs 57%; P=0.42) among those in the aspirin arm compared with controls. In fact, outcomes were numerically worse in the aspirin arm. As the authors acknowledge, a key limitation of the trial was the open label approach. Investigators might have been more alert to the possibility of sICH among subjects in the aspirin arm than in the nonaspirin arm, leading to more frequent computed tomography scan monitoring and thereby more detection of sICH. Underscoring this possibility is the fact that the control arm had one of the lowest sICH rates reported in an IV rtPA cohort (0.7%). Nevertheless, we agree with the authors that these potential reporting biases regarding sICH are unlikely to have affected the overall results because the efficacy end points were assessed by blinded investigators, subjects were unable to remember their treatment allocation 70% of the time, and the results were numerically in the wrong direction, despite enrollment of 80% of the planned sample size.
The ARTIS Trial provides definitive evidence of the added risk without added benefit of the combination of antiplatelet and fibrinolytic agents. This supports recent large-scale registry and post hoc analyses. The large Safe Implementation of Treatments in Stroke—International Stroke Thrombolysis Registry (SITS-ISTR), a pooled analysis of Stroke–Acute Ischemic–NXY Treatment (SAINT) I and II Trials, and the European-Australasian Acute Stroke Study (ECASS) III Trial showed increased sICH risk without an effect on overall clinical outcome among subjects who were on antiplatelet medications before IV thrombolytic administration. However, it is important to note that the ARTIS Trial should not deter us from treating patients who are already on antiplatelet medications at the time of determining eligibility for thrombolysis. The appropriate comparator for this conclusion is the group of patients on antiplatelet agents who were not treated with IV rtPA. The National Institute of Neurological Disorders and Stroke (NINDS) Trial showed no modification of the treatment effect of rtPA among the subgroup on aspirin before randomization (which consisted of 26% in the rtPA and 18% in the placebo arms).1

Acute reperfusion strategies that combined antithrombotic and fibrinolytic agents seem to be a double-edged sword, increasing rates of both recanalization and hemorrhagic transformation. For example, in Prolyse in Acute Cerebral Thromboembolism (PROACT) I, we not only witnessed high early recanalization rates (82%) when coadministering high-dose IV heparin with IA prourokinase, but also saw unacceptably high hemorrhagic transformation rates (70%).18 The benefits of combining other classes of antithrombotics and systemic thrombolysis, such as GPIIb/IIIa inhibitors and direct thrombin inhibitors, remain to be seen. This combination strategy has been hypothesized to lead to faster and more complete recanalization, in addition to preventing reocclusion, in the setting of ischemic stroke based on the cardiac literature. For example, eptifibatide in conjunction with IV rtPA increases the speed of recanalization of occluded coronary arteries.19 In the brain, achieving recanalization more quickly is likely to translate into higher rates of good clinical outcome.20 This agent acts by reversibly binding GP IIb/IIIa receptors and is therefore short-acting. It is currently being administered for 2 hours and is expected to be active for about 12 hours in the phase II Combination Therapy of rt-PA and Eptifibatide to Treat Acute Ischemic Stroke (CLEAR-ER) Trial.21 As another example, argatroban in combination with IV rtPA leads to more complete recanalization after acute coronary occlusion.22 This drug is also short-acting and selectively inhibits free and clot-associated thrombin. It is being tested as a 48-hour infusion that is individually titrated to activated partial thromboplastin time levels in the phase II Argatroban TPA Stroke Study (ARTTTS-2) Trial.23 Completed phase II trials of both drugs have suggested reasonable safety profiles in the setting of thrombolysis for acute ischemic stroke, and they are now being evaluated in additional dose escalation studies.24 The CLEAR-ER Trial recently completed enrollment, and preliminary aggregate data suggest potential for safety (personal communication, Opeolu Adeoye, unpublished data, 2012); unblinded results are anticipated in early 2013. The ARTTTS-2 Trial is currently recruiting.

Improving on IV rtPA has been a challenge. It remains to be seen whether antithrombotics, among other approaches, can safely enhance the efficacy of IV rtPA. In the meantime, the conventions established by the NINDS Trial, including treating those already on antiplatelet therapies and not treating those actively anticoagulated with IV rtPA, and not adding antithrombotic or antiplatelet drugs within the first 24 hours of IV rtPA, are the only proven clinically effective approaches.

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References
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