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Combining Antithrombotic and Fibrinolytic Agents: Can It Be Done?

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Over half of ischemic stroke patients who are treated with IV rtPA remain disabled at three months.[1-2] The reasons are many. IV rtPA's rate of recanalizing occluded arteries is not as high as we would like, especially for large arterial occlusions, which are opened only 30-40% of the time.[3-6] 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 approximately 20-30% 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 antithrombotics, 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 to 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Phase III ALIAS Trial of albumin, which also demonstrated interim futility, (personal communication, Michael D. Hill, unpublished data, 2012) and detailed results are pending for this as well.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 setting[13] prior to IV rtPA administration, the FAST-MAG Trial, is nearing completion of enrollment.

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The third strategy has been addressed in the recently published Phase III ARTIS (Antiplatelet Therapy in combination with RT-PA Thrombolysis in Ischemic Stroke) Trial from the Netherlands of aspirin as an adjunct to IV rtPA.[14] Zinkstok et al. 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 endpoint was three-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 two treatment groups. Key safety endpoints were sICH, severe systemic bleeding, and serious adverse events. Notably, subjects were not required to receive 24-hour CT scans, as is the standard of care in both the United States and in Switzerland. Investigators only performed CT scans in the setting of neurological deterioration.

The trial was terminated prematurely after inclusion of 642 patients due to more symptomatic intracranial hemorrhages (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 to 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 sICH among subjects in the aspirin arm than the non-aspirin arm, leading to more frequent CT 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 since the efficacy endpoints were assessed by blinded investigators, subjects were unable to remember their treatment allocation 70% of the time, and the effects 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 SITS-ISTR registry,[15] a pooled analysis of SAINT I and II Trials,16 and the ECASS II Trial[17] showed increased sICH risk without an effect on overall clinical outcome among subjects who were on antiplatelet medications prior to 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 NINDS Trial showed no modification of the treatment effect of rtPA among the subgroup on aspirin prior to 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 PROACT I, we witnessed high early recanalization rates (82%) when co-administering high dose IV heparin with IA pro-urokinase, 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 therapy 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 two hours, and is expected to be active for about 12 hours, in the Phase II 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 (APTT) levels in the Phase II ARTTS-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.[24-25] The CLEAR-ER Trial recently completed enrollment, and preliminary aggregate data suggests potential for safety (personal communication, Opeolu Adeoye, unpublished data, 2012); unblinded results are anticipated in early 2013. The ARTTS-2 Trial is currently recruiting.

Improving upon IV rtPA has been a challenge. It remains to be seen whether adjunctive 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 anticuagulated 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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