The Argatroban and Tissue-Type Plasminogen Activator Stroke Study
Final Results of a Pilot Safety Study

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See related article, page 770.

Developing new interventions for hyperacute stroke remains an important aim because current treatment options remain limited to alteplase, aspirin, hemicraniectomy, and stroke unit care. Over the last 20 years, drug developments have largely focused on fibrinolytic, neuroprotective, and anticoagulant strategies. Although the first is proven, the second and third remain without definitive data, although clinical research continues, as highlighted in the linked article by Baretto and colleagues who describe results from a small Phase II study of argatroban, an intravenous anticoagulant.1

After numerous neutral trials of unfractionated heparin,2 low-molecular-weight heparin,3,4 and low-molecular-weight heparinoids,5 it might seem strange to be testing another anticoagulant in the management of acute ischemic stroke. Meta-analyses of completed trials showed that anticoagulation did not alter functional outcome and that any apparent benefit in reducing early recurrence was offset by an increase in symptomatic intracranial hemorrhage.6–8 These findings were independent of the anticoagulant (type; dose—full, partial, or low; route of administration—intravenous or subcutaneous; and time to treatment) and patient characteristics (age, sex, stroke severity, stroke syndrome, and stroke etiology). Nevertheless, guidelines recommend the use of low-dose anticoagulation for the prophylaxis of venous thromboembolic events, although symptomatic intracranial hemorrhage and pulmonary embolism rates are similar with early treatment9 thereby questioning even this use.

Despite these problems with anticoagulation in acute stroke, this research field remains active for 2 reasons. First, there is a new generation of anticoagulants that selectively inhibits individual components of the coagulation cascade, in particular direct thrombin inhibitors and factor Xa inhibitors; hypothetically, these might may cause less bleeding than older nonselective agents. Second, anticoagulants might be useful as an adjunct to thrombolytics to augment recanalization and prevent rethrombosis, a strategy tested10 and used in patients with acute coronary syndromes.

Baretto et al studied intravenous argatroban, a direct thrombin inhibitor, in 65 patients with proximal intracranial arterial occlusion and moderate stroke severity who were given a standard dose of alteplase within 3 or 4.5 hours of ictus.1 Argatroban was administered open label without a comparator group as a bolus (100 μg/kg bolus given over 3–5 minutes) within 1 hour of tissue-type plasminogen activator (tPA) and then dose-adjusted from 1.0 μg/kg per minute to maintain the activated partial thromboplastin time at 1.75 times baseline over 48 hours. In practice, argatroban was started at a median of 51 minutes after tPA, and the target anticoagulation was reached at a median of 3 hours.1 Although recanalization (assessed using transcranial Doppler or CT angiography) occurred in 61% of patients (29 of 47) at 2 hours, significant intracerebral hemorrhage (the primary outcome) occurred in 6% (4 patients, and symptomatic intracranial hemorrhage in 4.6%, 3 patients). Seven (10%) patients died over the first 7 days. The investigators concluded that the combination of alteplase and argatroban was potentially safe and that further evaluation was warranted.1

The study is noteworthy in several respects. First, the lack of a parallel control group given alteplase alone means that, practically, it is impossible to assess whether combined therapy increases recanalization as compared with thrombolysis alone and whether this comes with an acceptable rate of symptomatic intracranial hemorrhage. In this respect, the authors originally planned to compare their findings with data from the control group in the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systematic tPA (CLOTBUST) trial.11 However, the relevance of historical controls can be questioned because CLOTBUST was an older trial with a different population of patients with stroke. Although the present trial was conceived in the early part of the last decade, it would have been far more relevant as a randomized controlled trial with a placebo comparator, that is, tPA+argatroban versus tPA+placebo.

Second, the findings in the first 15 patients have already been published.12 This reported 2 symptomatic intracranial hemorrhages plus 1 asymptomatic brain bleed, although the latter may have been incidental because anticoagulation does not appear to increase asymptomatic hemorrhagic transformation of the infarct.13 Third, the investigators took >7 years to complete the study; delays occurred due to regulatory issues, interim safety reviews, and recruiting in the absence of adequate funding. During the manuscript review process, it also became clear that the investigators had struggled with a stroke community that was negative to the aims of the study.
on the grounds that combined thrombolysis and anticoagulation would inevitably be unsafe.

What then of the future of argatroban? Monotherapy with argatroban seems of little interest because anticoagulation alone has not been found to be effective in multiple trials,1–8 as was also seen in the Argatroban Anticoagulation in Patients With Acute Ischemic Stroke (ARGIS-1) trial of argatroban versus control (without tPA).9 A larger randomized trial of argatroban on top of thrombolysis could be performed to further test safety and efficacy as suggested by the authors. However, the need for activated partial thromboplastin time monitoring and regular dose adjustment is a potential limiting factor; newer agents requiring no dose adjustment are replacing older ones that do need monitoring, as seen with the replacement of unfractionated heparin by low-molecular-weight heparin for the treatment and prevention of venous thromboembolism. In this respect, it might be preferable to use tPA with an existing anticoagulant that has a longer half-life, does not need monitoring, and can be reversed pharmacologically if necessary, that is, a low-molecular-weight heparin.

The wider lessons from this study are several; first, that randomized controlled trials should be the de facto design for early- as well as late-phase clinical studies. Comparison of an uncontrolled cohort with a historical group is no substitute for randomization between treatment and control groups. Excluding Phase I first-ever into human studies, uncontrolled Phase II studies should be resisted by investigators, funders, sponsors, and regulators. Second, we as a stroke community must not allow our preconceived beliefs to obstruct trialists just because we think we already know the results. There are too many examples in which trial results have overturned dogma built on little or no evidence. Finally, we must all support II studies should be resisted by investigators, funders, sponsors, and regulators. Second, we as a stroke community must

Disclosures
Dr Bath was Chief Investigator of the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST) trial of tinzaparin (Leo Pharmaceuticals) and a local investigator in the International Stroke Trial (IST-1) trial of unfractionated heparin. He has been on the Trial Steering Committee, Data Monitoring Committee, Advisory Board, and/or given talks at commercial symposia for AstraZeneca, Bayer, Biosite, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Lundbeck, Mitsubishi, M’s Science, Phagenesis, ReNeuron, Servier, Shire, and Takeda.

References

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