Effectively Bridging the Preclinical/Clinical Gap: The Results of the ASTIN Trial

To the Editor:

Recently, the results of the Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN) were published. In this trial, 966 patients presenting within 6 hours of acute stroke received varying doses of either placebo or UK-279,276, a CD11b/CD18 inhibitor. Additionally, a subgroup of 204 patients was co-administered tissue plasminogen activator (tPA) when clinically appropriate. The trial was stopped early when interim analysis demonstrated futility in achieving the primary endpoint of increased functional improvement from the patient’s baseline as measured by the Scandinavian Stroke Scale (SSS) at 90 days. Post hoc analysis found that patients co-administered tPA and UK-279,276 exhibited a mean improvement of 1.6 points on the SSS, but this study was neither designed nor powered to achieve statistical significance in this group.

While the study utilized a novel approach to clinical trial design and management, there are limitations in the design of this study that, while stated by the authors, merit additional attention. The first of these is the study’s diminished emphasis on UK-279,276 administered alone, which was observed to demonstrate less efficacy in nonreperfused stroke.2,3 While future clinical efforts using UK-279,276 and similar agents such as UK-279,276 would be expected to demonstrate less efficacy in nonreperfused stroke.2,3

An alternative of limiting the patient population to intravenous tPA–treated patients was also discussed, with a goal to enrich the proportion of patients with reperfusion but not nonreperfused stroke.3,4 However, our own work with CD11b/CD18 knockout mice demonstrated that CD18 (-/-) knockout mice were protected in reperfused but not permanent stroke models.1

In the current case, preclinical work with UK-279,276 supported this claim. Early work with the agent using a reperfused intraluminal suture model with 2 hours of occlusion demonstrated benefit in the form of decreased infarct volumes and improved neurological outcomes, but failed to demonstrate benefit for UK-279,276 when used in a nonreperfused model.5,6 More recently, administration of UK-279,276 was shown to demonstrate no significant efficacy in a rat model of embolic stroke when the drug was administered alone, but led to significantly reduced infarct volumes and improved functional outcomes when co-administered with tPA, even when administered beyond the traditional tPA therapeutic window.7 These data further strengthened the claim that UK-279,276 predominantly acts by attenuating cerebral reperfusion injury and as such would be less likely to improve the neurologic functioning of patients with lesser degrees of reperfusion.

While future clinical efforts using UK-279,276 and similar drugs will likely refocus efforts toward subsets of patients who undergo either spontaneous, pharmacologic, or mechanical reperfusion, we feel this example further emphasizes the importance of effectively utilizing strong preclinical data to guide the design, nature, and aim of clinical stroke trials.8,9 We hope that closer collaborations formed between basic scientists and clinical researchers will continue to strengthen the link between preclinical observations and clinical applications in the development of neuroprotective drugs.

Response

Drs Sughrue and Connolly correctly point out that the preclinical data indicate that UK-279,276 might potentially be protective against cerebral reperfusion injury but might not have neuroprotective properties in the absence of reperfusion. When designing ASTIN we did debate including measures of cerebral perfusion and decided against it, mainly for logistical reasons: perfusion CT was not yet widely available, and overcoming the technical issues related to establishing tight interrater reliability of transcranial Doppler measurements appeared a difficult challenge at the time. However, we entirely agree that quantifying the degree of perfusion and using it as a covariate of interest is the way to go in future acute stroke trials.

The alternative of limiting the patient population to intravenous tPA–treated patients was also discussed, with a goal to enrich the proportion of patients with reperfusion. However, from a sponsor perspective the objective was not to develop an adjuvant therapy to intravenous tPA but to establish a neuroprotective therapy that could benefit the overall set of patients with ischemic strokes including those who spontaneously reperfused. The proportion of spontaneous reperfusion within the first 6 hours has been described as 19%;1,19 it seemed reasonable to allow inclusion of tPA– and non–tPA–treated patients.

Had we known prior to the start of ASTIN that >20% of patients would be cotreated with intravenous tPA rather than the <5% we anticipated, we would have probably designed a
different trial. One interpretation of the mean improvement of 1.6 points on the Scandinavian Stroke Scale in the tPA-treated subset of 204 patients is that it is a pure tPA effect and has nothing to do with UK-279,276: ASTIN does not allow any conclusions about interactions between UK-279,276 and tPA.

Given the limitations of the ASTIN trial, it is important to remember that absence of evidence is not evidence of absence for the mechanism of action in an appropriately chosen patient population. An interesting future research question might be whether an adjuvant therapy to intravenous tPA apart from potentially improving outcome might also allow to reduce the overall dose of tPA and thereby potentially add safety benefits. We are currently developing designs that would allow the continuous reassessment of the exposure-response and adaptive allocation to the most promising treatment combination.

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Stroke. 2004;35:e81-e82; originally published online February 26, 2004;
doi: 10.1161/01.STR.0000121164.29117.44

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