Measuring Treatment Effect in Acute Stroke Trials

To the Editor:

We read with interest Bruno et al’s analysis of National Institutes of Health Stroke Scale (NIHSS) score in the trial of Org 10172 in acute stroke treatment (TOAST). They found the dichotomous variable, NIHSS score ≤2 at 3 months, to be associated with “very favorable outcome” at 3 months, defined as both Glasgow Outcome Scale of 1 and modified Barthel Index 19 to 20.

Prior work analyzing the NINDS recombinant tissue plasminogen activator (rt-PA) trial (the only conclusively positive clinical acute stroke trial) found NIHSS score ≤2 to be one of the most useful predictors of rt-PA treatment effect as well. Specifically, using the Classification and Regression Tree (CART) algorithm, the NINDS rt-PA Stroke Study Group identified all possible dichotomous end points that may discriminate between rt-PA treatment and placebo groups at 3 months (ie, long-term efficacy) and at 24 hours (ie, early rt-PA effect). Significant variables were identified in Part I of the NINDS trial, and then tested for validity in Part II of the trial. NIHSS score ≤2 at 3 months was a more powerful and sensitive measure of rt-PA long-term efficacy than the primary outcome measure of the trial (ie, the composite global statistic combining modified Rankin, Glasgow Outcome, NIHSS, and Barthel Index scores). Furthermore, NIHSS score ≤2 at 24 hours was the single most powerful discriminator of an early rt-PA effect.

NIHSS score ≤2 at 24 hours was also one of the best indicators of rt-PA long-term efficacy among the subset of patients with moderate-to-severe strokes (ie, baseline NIHSS ≥10), a cohort that has been the focus of the Interventional Management of Stroke (IMS) trials. In fact, this outcome was chosen as a secondary end point for the IMS trials based on this CART analysis. Again, in IMS I, NIHSS score ≤2 at 24 hours is the most sensitive measure of treatment effect at 3 months, compared with historical controls from the NINDS rt-PA trial (odds ratio 5.39; 95% Cl. 1.80 to 16.19).

Among dichotomous variables, NIHSS score ≤2 at 24 hours may be the best Phase I and II marker of early treatment effect in revascularization studies, and correlates well with long-term outcome. NIHSS score ≤2 at 3 months is also a useful outcome measure, as shown by NINDS and TOAST analyses. Recently, changes in distributions of relevant outcome measures, such as the NIHSS score and modified Rankin Scale score, have been proposed as potentially more powerful predictors of treatment effect than dichotomous variables. Determining the best end points for acute stroke trials is currently a topic of great interest.

Disclosures

The authors would like to report the following conflicts of interest: consulting for Genentech, Inc; Genentech supplies medication, and EKOS Corp and Concentric Corp supplies devices for an ongoing trial in which P.K. is involved. EKOS Corp has also provided grant support in the past for a completed trial.

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