Establishing Final Infarct Volume
Stroke Lesion Evolution Past 30 Days Is Insignificant

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See related article, pages 2765–2768.

Surrogate endpoints in acute stroke trials are manifold, albeit neither the optimum variable nor the optimum time point for assessment at present is known. They serve either as secondary end points or may serve as primary end points in phase 2a and 2b trials or proof of concept studies. Examples of frequently used surrogate end points are early neurological improvement at 24 hours (eg, in NINDS and ECASS 1), recanalization and/or reperfusion at 4 to 8 hours (eg, DEFUSE, DIAS and DEDAS) or >24 hours (eg, secondary end point in EPITHET). Trends toward benefit using clinical scales at phase II have been notoriously poor predictors of clinical outcomes in phase III trials on much larger samples.1,2 The optimum time point of reperfusion/recanalization assessment is still a matter of debate; however, imaging within 6 hours after a therapeutic intervention is considered as appropriate but also of limited practicality.

Modern imaging may be useful for sample size reductions either if used for patient selection, or as an outcome surrogate, or both. Imaging-guided phase II studies may answer the question of target biological activity in fewer than 200 patients, the sample size typical for phase II trials.3 Selection of patients by diffusion-weighted imaging is also optimally suited for using change in lesion volume compared to final infarct size as a direct measure of a therapeutic effect of the drug. Although optimizing sample selection may lead to smaller sample sizes,4 the greatest advantage of stroke MRI is the measurement of the pretreatment lesion against which to compare the final lesion. Such an approach to within subject variance should, by basic statistical principles, be more powerful than analysis of only the final lesion volume.2,4 It is also the most widely used imaging-based surrogate end point for effectiveness in clinical trials. Typically, lesion growth from baseline diffusion-weighted imaging to day 90 FLAIR or T2-WI has been used in the past as in the citicoline trials,5 as well as in the present (EPITHET, unpublished, stroketrials.org), while DEFUSE assessed a final image at 30 days.6

The choice of day 90 as an imaging end point has historical reasons, because day 90 usually is also chosen as a clinical end point in most acute stroke trials for practical reasons, although all experts in the field agree that even 1 year may not be enough to adequately assess long-term clinical outcome. Is better statistical power a sufficing quality criterion for an optimal surrogate parameter? Optimal feasibility and practicability in terms of loss to follow-up is also an important quality criterion. Consider the effect on a study with a sample size of n=100 (50 patients per arm), if 10 patients were lost to follow-up and have the last observation carried forward (as is general practice). This may be a “killer” not only for clinical end points but also for imaging surrogate end points where the final image usually is taken somewhere in between days 5 to 10 a period of maximum brain edema. In addition, if the surrogate end point is assessed rather late such as day 90 the likelihood of confounding adverse events unrelated to the intervention increases (eg, another stroke) as it does for a clinical end point.

In this issue of Stroke, Gaudinski and colleagues aimed to determine the optimum time point for assessment of lesion volume as a surrogate outcome parameter. In a retrospective study, they measured lesion volume in acute stroke patients over a course of 90 days, acutely, and at days 5, 30, and 90. Their patient sample of 45 patients acquired over 6 years of whom 18 met all inclusion criteria is a point in case that it is difficult to perform repetitive imaging in acute stroke patients. The sample of 18 patients had clinical and imaging parameters corresponding to an acute stroke intervention trial (average age and NIHSS 66 years and 11.5). In between all time points stroke volumes differed significantly except of baseline to day 30 or 90 respectively. However, the regression (meaning the “dynamics” of volume evolution) between day 30 and 90 did not differ at all with a regression slope close to 1.0 (Figure 2c in Gaudinski et al). In other words, the change in lesion volume from day 30 to 90 was in the range of 5%, which is in the range of inter-reader–variability in this as well as many other studies.7 Although this patient sample is small in absolute terms, it is not so small in the face of DEFUSE or EPITHET with 76 and 101 patients, respectively. Therefore, and because the data are robust, it appears preferable to use day 30 rather than day 90 stroke volume assessments as imaging surrogate end point in phase 2 and proof of principle studies.

Disclosures

None.

References


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