MR Mismatch and Thrombolysis  
Appealing but Validation Required

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Since the initial description of the ischemic penumbra 30 years ago, the concept of rapid restoration of blood flow to threatened brain tissue has been the “holy grail” of acute stroke therapy. Despite its drawbacks, MR imaging of perfusion diffusion mismatch remains the most widely used and practical means of in vivo assessment.

There is accumulating evidence linking reperfusion with better clinical outcomes and attenuation of infarct growth in patients in patients with MR mismatch. However, validation that imaging effectively selects thrombolytic responders is still lacking. Both protagonists have highlighted areas of uncertainty in definition of MR mismatch. In our view, these include optimizing the ratio between PWI and DWI, choice of metric (we find Tmax, the time to peak of residue function, most useful), and choice of threshold to exclude benign oligemia (Tmax 4 to 6 appears to be better than Tmax 2). Another key question is the option of excluding large DWI volumes to reduce the risk of hemorrhagic transformation and poor outcome with thrombolysis. We consider that baseline core infarct volumes of >100 mL on DWI should be excluded.

As mentioned by both protagonists, there have been 3 key trials that have addressed the question of MR mismatch and thrombolysis, namely DEFUSE, EPITHET, and ECASS III. The former 2 provided biological evidence to support a strong relationship between reperfusion, attenuation of infarct growth, and improved clinical outcomes. Indeed in EPITHET, tPA significantly enhanced reperfusion in the 3- to 6-hour time window. Although neither EPITHET nor DEFUSE selected patients based on mismatch, these results do provide support for the concept of mismatch as a selection criterion in future trials. Of the 3 trials, only DIAS-2 actually used the principal of penumbral selection, with the “eyeball technique” at individual centers. How do we explain this unexpected result? As mentioned in part by our protagonists, possible explanations include the mild stroke severity in the DIAS-2 cohort, the use of CT perfusion (CTP) in about one third of cases, small sample size for a phase III trial, and the chance occurrence of late nonneurological deaths in the high-dose treatment group.

A particular issue arising from DIAS-2 is the use of the “eyeball technique” in penumbral selection. Without thresholding and standardization of the perfusion metric, the probability that most of the PWI images contain benign oligemia is high. In other words, many nonpenumbral patients would have been entered into the trial. To reduce error and truly operationalize penumbral selection uniformly across centers, automated online imaging is an urgent priority. We conclude that the potential of MR mismatch remains obvious, but a number of refinements are needed. Clearly, a large Phase III trial is required for validation of the principle of MR mismatch in treatment selection. To this end, our EXTEND trial is planned to commence during 2009.

Disclosures

None.

References


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