Emerging Therapies

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European Cooperative Acute Stroke Study III
Support for and Questions About a Truly Emerging Therapy

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The results of the European Cooperative Acute Stroke Study III (ECASS III) provide an important advance for the field of acute stroke therapy. The study was well-designed and conducted. The trial provides unequivocal and straightforward evidence that treatment with intravenous (IV) tissue plasminogen activator (tPA) initiated 3 to 4.5 hours after the onset of ischemic stroke improves 90-day outcome and that the risk of symptomatic intracerebral hemorrhage is modest and acceptable relative to the derived benefit. ECASS III represents the most important advance in the acute stroke therapy arena since the publication of the National Institute of Neurological Diseases and Stroke tPA trial in 1995 that confirmed the benefits of IV in the <3-hour time window.1 The results of ECASS III will likely lead to swift regulatory approval of an extension of the IV tPA treatment window to 4.5 hours and a substantial increase in the number of patients with acute stroke treated up to this time point from stroke onset.2

The critiques by Ingall and Davis/Donnan provide details about the study and 2 perspectives on the results. We provide a third perspective. The ECASS III results can be looked at from 2 different depths of scrutiny. Superficially, the results clearly demonstrate that IV tPA improves 90-day outcome in patients meeting the inclusion/exclusion criteria of the trial. At a deeper level, these inclusion/exclusion criteria and the lack of some data from the ECASS III trial raise concerns about the generalizability of the benefits to the broad spectrum of the acute ischemic stroke population. Patients >80 years of age were not included in the trial nor were patients with baseline National Institutes of Health Stroke Scale scores >25 and prior stroke in diabetics. Such patients are not excluded from treatment with IV tPA in the 0- to 3-hour time window by the regulatory authorities in the United States and Canada. Should they be treated in the 3- to 4.5-hour time window? In the ECASS III paper, no information is provided about stroke subtypes nor the relationship of baseline severity to IV tPA treatment. It would be most useful to know whether particular stroke subtypes, a range of baseline stroke severity, or age at stroke onset predicts more or less response to treatment.2 Hopefully, this information was collected and appropriate analyses will be forthcoming in a companion paper.

A major concern about the ECASS III study is the imaging used to initially evaluate the study population, CT in 771 patients and MRI in 50 patients. What is lacking is information about the site of vascular occlusion or lack thereof that could have been determined by CT angiography or MR angiography and penumbral imaging data from CT perfusion studies or diffusion/perfusion MRI. It is understandable when this study was designed in 2003 why such advanced imaging was not required, but the lack of this information is problematic. We do not know what types of advanced imaging patterns likely predict a greater likelihood of response to treatment or potentially a lack of benefit. For example, would patients with an obvious baseline vascular occlusion on MR angiography or CT angiography or patients with substantial amounts of ischemic penumbra approximated by CT perfusion or diffusion/perfusion MRI be more likely to benefit from IV tPA than patients with no demonstrable vascular occlusion and/or a lack of substantial imaging confirmed penumbra? These questions are more pertinent in the 3- to 4.5-hour treatment window than in the <3-hour treatment window because it is clear that the extent of penumbra decreases over time and for IV desmoteplase given in the 3- to 9-hour time window, treatment was less beneficial without an obvious imaging-confirmed vascular occlusion or penumbra.3,4 Many larger centers routinely obtain advanced CT or MRI and they will be faced with the dilemma of how to use the acquired information from ECASS III for making treatment decisions. The other approach for interpreting the ECASS III results is to treat all patients meeting the inclusion criteria and not be concerned about such imaging information. This approach is counterintuitive because accumulating data from many sources suggest that identification of a vascular occlusion or substantial amount of penumbra does correlate with response to IV thrombolytic therapy.5,6 The answers to these vexing questions could come from addi-

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tional clinical trials or, to some extent, from treated case series compared with relevant historical controls.

The ECASS III study is clearly an important landmark in the history of acute stroke therapy and a reason for optimism that we can develop treatments that will benefit an increasing percentage of the ischemic stroke population. However, questions remain: do we only treat patients fulfilling the enrollment criteria used in the study, do we generalize the results to a more inclusive group of stroke patients in the 3- to 4.5-time window, and are there clinical and imaging-based subtypes of patients more or less likely to benefit from this treatment? Each physician involved in decision-making for patients with acute ischemic stroke will have to address these questions and presumably guidance will be provided by consensus recommendations, additional data from the ECASS III trial, and new clinical trials to be performed over the next few years.

Disclosures

None.

References


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