Intravenous Recombinant Tissue-Type Plasminogen Activator in the Extended Time Window and the US Food and Drug Administration
Confused About the Time

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Since the earliest trials of intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) for treatment of acute stroke, the time window for clinical efficacy has been controversial. Preclinical studies suggested an increased hemorrhage rate when thrombolytics were administered at later time intervals after arterial occlusion. The first US pilot study of IV rt-PA demonstrated acceptable safety using a 90-minute time window at doses up to 1.08 mg/kg. In a subsequent study extending treatment to 91 to 180 minutes, more hemorrhages occurred with less apparent efficacy but outcomes were considered possibly better than the natural history. This formula was carried over to the pivotal National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial stratifying patients to treatment within 90 minutes and 91 to 180 minutes after stroke. A subsequent analysis showed the OR for favorable outcome at 3 months after rt-PA decreased with time from stroke onset approaching unity at 180 minutes. Other studies of IV rt-PA including European Cooperative Acute Stroke Study (ECASS), ECASS II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) enrolled patients up to 6 hours from stroke onset but failed to confirm the beneficial effect of IV rt-PA. Notably, none of these studies demonstrated a relationship between risk of symptomatic hemorrhage and time to treatment, although few patients within 3 hours of stroke onset were included. Based on the results of the NINDS rt-PA trial, the US Food and Drug Administration (FDA) approved IV rt-PA for treatment of acute stroke in 1996 but limited the approval to the study time window, 3 hours.

In 2004 a pooled analysis of 4 randomized IV rt-PA trials, NINDS, ECASS, ECASS II, and ATLANTIS, was published. Although few patients were added to the 0- to 3-hour group from studies other than NINDS, the larger number of patients in the 3- to 6-hour window demonstrated a benefit of IV rt-PA treatment up to 4.5 hours. In 2002 the European Medicines Agency approved IV rt-PA for use in its member states after reviewing the available evidence. The approval was conditional on performing a confirmatory study in Europe, but a placebo-controlled trial in the 0- to 3-hour window was not thought possible given the prevalent opinion in the community regarding the efficacy of IV rt-PA in this time window. Therefore, ECASS III, a placebo-controlled study investigating the benefit of IV rt-PA when administered within the 3- to 4-hour time window, was initiated and subsequently expanded to include patients up to 4.5 hours after stroke onset. At the same time, an observational registry of all patients treated with IV rt-PA under approved indication was commissioned. In 2008 the results of ECASS III including 821 patients demonstrated significant benefit of IV rt-PA compared with placebo (OR, 1.34; 95% CI, 1.02–1.76; \( P=0.04 \)). A large observational study of patients treated with IV rt-PA in 650 centers outside the United States found similar outcomes in patients treated 3 to 4.5 hours after stroke compared with those treated within 3 hours; however, patients treated in the longer window had lower stroke severity (median National Institutes of Health Stroke Scale 12 versus 10, \( P<0.001 \)), slightly younger age (68 versus 67, \( P<0.007 \)), and were more likely to have small vessel disease (10% versus 13%, \( P<0.001 \)). After adjusting for all imbalances in baseline variables, outcomes were better in the 0- to 3-hour group but differences were small. In ECASS III, a significant imbalance in baseline National Institutes of Health Stroke Scale favored the treatment group, but there remained a significant treatment effect after adjustment for all baseline imbalances. Compared with 0- to 3-hour patients in prior trials, outcomes in the ECASS III placebo group were better, at least partly due to the lack of enrollment of severe strokes and the treatment effect was not as robust consistent with results of prior meta-analysis. The effect of IV rt-PA was independent of stroke severity and showed a significant improvement in the treatment group in the overall distribution of Rankin scores. Benefit extended to multiple endpoints in both predefined secondary and post hoc analysis. Based on the ECASS III results, one additional patient has a favorable outcome for every 14 patients treated, a clinically important result.

After considering the results of these studies, the European Stroke Organization modified their acute stroke guidelines to recommend treatment with IV rt-PA for patients with acute
stroke within 4.5 hours of onset. The American Heart Association subsequently published an advisory also supporting treatment in this extended time window. In 2011, Boehringer Ingelheim gained approval for an extended time window to 4.5 hours for IV rt-PA in 15 European countries. Subsequently several other countries have followed suit in approving IV rt-PA within this longer time window.

Genentech, which markets alteplase in the United States, applied to the US FDA for a supplemental biological license to extend the time window for IV rt-PA treatment to 4.5 hours. This application was based on the ECASS III results and their own reanalysis of relevant patient information from ECASS II and ATLANTIS. Recently, the FDA denied the application effectively limiting approval in the United States to 3 hours. The details of the application and response from the FDA have not been released, but the denial appears to be largely based on the FDA’s opinion that the evidence from ECASS III and supporting data are not sufficient to justify extending the treatment window beyond 3 hours. The merits of this argument must await careful review of the FDA response and Genentech application, but the consequences of this action will undoubtedly resonate throughout the stroke community for some time.

Outside of the United States, the FDA action will probably not alter the landscape of IV rt-PA use because the European Medicines Agency (EMEA) and other governing bodies have already approved the extended time window. No new evidence has been presented that would precipitate a review of the prior decision. Within the United States, many vascular neurologists currently treat patients up to 4.5 hours from onset with IV rt-PA based on their own opinion of ECASS III and supporting data as well as personal experience. As a consequence, many stroke centers have incorporated this practice within their standard protocols. Subject to review of the FDA letter, it seems unlikely expert opinion will be altered by the FDA ruling. Most neurologists obtain consent by advising patients and families that treatment beyond 3 hours is not FDA-approved but in their opinion the benefits outweigh the risks. Until now, the FDA position was unknown because no opinion had been issued. With the recent developments, any consent process should probably specify that the FDA did not to approve this therapy based on their review of the available evidence. Stroke experts may disagree with this position and continue to advocate a benefit of treatment in this time window. Furthermore, given the perceived poor natural history of acute stroke, the FDA ruling is unlikely to deter patients or their surrogates from consenting to treatment. Less predictable is the situation in which consent cannot be obtained due to severity of neurological deficit and family unavailability. Within the 3-hour time window, the FDA approval confers an added sense of legitimacy and many physicians are willing to err on the side of treatment when it is not possible to obtain consent. Physicians may be reluctant to treat patients in the 3- to 4.5-hour time window without consent given the less robust benefit and the lack of FDA approval.

What effect will the FDA response have on use of IV rt-PA in the community? Although overall use has been increasing, the percent of all patients with stroke treated remains low. Nothing about the FDA opinion reflects on treatment within 3 hours of stroke onset, which remains approved by the FDA without change. By providing additional randomized placebo-controlled data in support of clinical benefit with IV rt-PA, the results of ECASS III reinforced the NINDS trial, which continues to be challenged in some quarters. However, ECASS III like all clinical studies has strengths and weaknesses and decisions regarding the relative weight of each must be decided on an individual basis. Outside of stroke centers, many neurologists and emergency department physicians may be reluctant to exceed the FDA guidelines both because of their respect for the FDA process and concern about medicolegal ramifications of adverse outcomes. In this era of healthcare cost containment, the FDA decision could result in restrictions of coverage for IV rt-PA therapy. The Centers for Medicare & Medicaid Services or other insurers; however, there is little precedent for such a policy change outside of devices or procedures. With the transition to new models of care, strength of evidence becomes central to decisions regarding protocol-driven treatment options. Hopefully, insurers will allow the medical community to guide appropriate use through at-risk arrangements and cost and gain-sharing models with sufficiently broad reach to realize downstream savings from greater recovery and reduced disability. Because decisions about thrombolysis are increasingly made by stroke neurologists remotely through telemedicine, thrombolysis in the community should follow the practice patterns in place at more comprehensive stroke centers.

At present, only a small percent of patients with stroke arrive at emergency departments in the 3- to 4.5-hour time window13 and the overall impact on acute stroke treatment is likely to be minor. Perhaps more of a concern is the group of patients arriving close to the 3-hour limit that might be aggressively evaluated and treated knowing that exceeding the 3-hour limit by a few minutes does not violate the accepted time window for treatment.

Endovascular therapy for acute stroke is also not approved by the FDA but commonly practiced in many stroke centers in the United States. Time windows for treatment vary by center but usually extend to 6 hours and in centers that select patients based on physiological information rather than on time, 8 hours or longer. Many of these same centers treat patients with IV rt-PA up to 4.5 hours either replacing endovascular therapy or using endovascular treatment as rescue therapy. The recent FDA decision may change this equation, increasing the use of endovascular therapy as a primary modality in patients beyond 3 hours. This holds true especially for subgroups that might be identified as responding poorly to IV rt-PA.17

A final consideration is the impact of the FDA decision on acute stroke clinical trials. In the absence of an FDA ruling, acute stroke studies might allow enrollment of patients treated with IV rt-PA up to 4.5 hours to accommodate the practice of many participating stroke centers. Whether institutional review boards would now approve extension of the treatment window with the FDA denial is less certain. The difference in approved practice in the United States and abroad also adds complications to international acute stroke studies. Endovascular therapy with placebo control groups may have differing lower time thresholds in the United States than elsewhere and treatment trials that include patients treated with IV rt-PA would differ in the composition of the 3- to 4.5-hour groups. Consideration of statistical approaches and protocol design must account for any potential biases or imbalances introduced.
Will further studies modify the FDA decision not to extend the time window for treatment? The Third International Stroke trial (IST-3)18 and accompanying meta-analysis19 do not provide clear support for the use of IV rt-PA between 3 and 4.5 hours despite randomizing 1177 patients in this time window in IST-3, far more than ECASS III. IST-3 is also not the final answer because the study was underpowered for subgroup analysis. The design aimed at enhancing enrollment at the expense of scientific rigor raises significant issues regarding the validity and general applicability of the results.20 Many stroke centers now use advanced imaging techniques beyond a standard head CT to select patients for thrombolytic therapy in longer time windows. Recent studies demonstrate improved outcomes associated with reperfusion when patients are selected with physiological imaging rather than time.21,22 Selection of patients based on imaging or perhaps some other criteria may increase the yield of thrombolytic therapy beyond 3 hours sufficiently to provide additional evidence of efficacy and gain FDA approval. Ongoing trials such as EXTEND (Extended Time for Thrombolysis in Emergency Neurological Deficits) and MR WITNESS (Multi-center Safety Trial of IV rt-PA in patients with un witnessed stroke onset), incorporate such advanced imaging in selection of patients for IV rt-PA and should help answer this important question. It would be difficult to complete a placebo-controlled trial in the 3- to 4.5-hour time window similar to ECASS III in the United States given the strong opinions and current practice of the stroke community. Therefore, it seems likely that until new evidence emerges, the use if IV rt-PA 3 to 4.5 hours after stroke will remain an area of controversy and confusion. At present, the American Heart Association advisory recommends treatment that the FDA does not. Unfortunately, it is the patients who will be most confused by these contradictory opinions making the process of informed consent in this time window extremely challenging. Guidance from the stroke community and leading organizations is necessary to help navigate these turbulent waters.

Disclosures
Dr Wechsler is on the data safety monitoring board of Desmoteplase in Acute Ischemic Stroke Trial (DIAS) 3 and 4 and is a consultant for Silk Rd Medical. Dr Jovin is a consultant/Advisory Board and Speakers Bureau at Stryker, a consultant/Advisory Board at Covidiem, and a consultant at Silk Rd Medical.

References

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