Response to Letter by Freeman et al Regarding Article, “Very Early Mobilization After Stroke Fast-Tracks Return to Walking: Further Results From the Phase II AVERT Randomized Controlled Trial”

Response:

In their letter, Freeman et al1 ask whether early mobilization is safe after thrombolysis. This is an important question. In a recent Australian review, we found that although protocols guided treatment in the majority of cases, only 53% of these specified when mobilization out of bed could begin. Of these, 33% permitted mobilization within 24 hours of treatment with recombinant tissue-type plasminogen activator (rtPA), whereas the remainder allowed mobilization 24 to 48 hours after treatment.2 Protocols to guide rtPA administration and subsequent care draw on evidence from clinical trials, expert opinion, and personal experience. Because safety was a major concern in early trials and intensive monitoring the norm, it is not surprising that bed rest became the dominant approach. Evidence of the risks and benefits of starting out of bed activity within hours of rtPA delivery is needed.

Freeman et al reported no safety concerns when they mobilized 10 patients between 12 and 24 hours after rtPA. They were interested in our experience from A Very Early Rehabilitation Trial (AVERT) Phase II, which tested mobilization <24 hours after stroke. In 2004, when Phase II started, rtPA was not standard care in Australia, so we excluded these patients from the trial. However, rtPA became routine and these patients are eligible for inclusion in AVERT Phase III if the physician approves. In the first 1000 patients (target n = 2104), almost 19% (n = 186) of patients, recruited from 18 different hospitals, have been treated with rtPA. Mean age is 71 years but ranges from 20 to 95 years. Mean National Institutes of Health Stroke Scale at recruitment is 11 (SD 7.5) and mean time from stroke to first mobilization is 17.8 (SD 5.8) hours with 20% of rtPA-treated patients starting mobilization <13 hours of stroke. The trial is ongoing. We expect to have approximately 380 rtPA-treated patients at trial end; approximately half will have received early mobilization. Safety monitoring is important and rtPA-treated patients are reported separately to the Data Safety and Monitoring Committee.

What can these data tell us so far? Physicians from Australia, New Zealand, Singapore, and the United Kingdom are willing to randomize patients they have treated with rtPA in full knowledge that they may be mobilized within hours of rtPA and frequently thereafter. At trial end, the demographics, safety, and functional outcomes of this subset of rtPA-treated patients will be known. It should be noted, however, that the study was not powered to answer any specific hypotheses related to rtPA-treated individuals. Furthermore, because physician approval dictates participation, information will be from a selected group, not the entire population of rtPA-treated individuals. To gain further insight into the factors that may influence clinicians’ decisions to either delay or allow mobilization after rtPA, we conducted a case–crossover study with hypothetical case vignettes.2 In this study, individual factors were introduced or modified and we studied the influence this had on decision-making. Severe stroke, neurological decline, infection, drowsiness, and confusion significantly influenced the decision to start or delay mobilization. Whether these factors drive decisions in the clinic is yet to be tested.

Pilot trials suggest that early and frequent mobilization is a promising treatment. This needs confirmation in larger trials and the benefits or risks of applying the intervention after rtPA remains uncertain. Phase III AVERT completion will provide robust data from a relatively large, but select, group of patients treated with rtPA. This may help refine protocols, but further research may be needed.

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Disclosures

J.B. declares modest financial conflict of interest. She has received some support to attend conferences to present work related to AVERT and has been a Chief Investigator on all grant applications.

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