Multicenter Trials for Brain Trauma Questioned

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SCOTTSDALE, ARIZ. — The validity of large, randomized multicenter clinical trials involving treatments for traumatic brain injury was called into question by numerous speakers during the annual meeting of the Neurocritical Care Society.

Speaking on therapeutic hypothermia, Donald Marion, M.D., refused to condemn the treatment when its promise in small single-hospital studies was not borne out in a large, randomized, multicenter trial, the findings of which showed the regimen was no better than current therapies.

Dr. Marion, a neurosurgeon and senior research fellow at the Brain Trauma Foundation, New York, took aim at the process. "Are valid multicenter clinical trials for severe traumatic brain injury possible?" he asked in a leadoff presentation, which became the talk of a 3-day meeting. "I really think there is something about phase III trials that impacts the outcomes independent of the treatment you are trying to use."

Large, randomized, multicenter trials might be unsuited to the realities of neurocritical care for head trauma, according to Dr. Marion. The cases are too complicated "with multiple physiological variables that can affect outcome and, unfortunately, multiple critical care physicians making treatment decisions," he said, adding that patients with traumatic brain injury often have other severe injuries that further complicate their randomization.

Dr. Marion estimated that 15-20 drugs, including tirilazad mesylate, have failed multicenter trials in traumatic brain injury.

These physicians have strong individual biases that make complying with uniform protocols difficult, especially if the investigators are working at many different centers, he continued. Consistency within a center may make single-center studies a better measure of new treatments for head trauma, he suggested.

"My bias is very strongly that there is a lot of noise in multicenter trials that may have drowned out the potential benefit of a lot of therapies in the past," he said.

As chair of the hypothermia session, Michael N. Diringer, M.D., of Washington University, St. Louis, expressed surprise: "This is the first time I've heard someone argue we might want to think twice about how we interpret the results from multicenter trials," he said. "The ability to perform trials on very sick, very complicated patients across centers—to get everybody to do the same thing—is an enormous and maybe potentially impossible task."

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Stefan Schwab, M.D., also complained of inconsistent protocols as a major problem in his talk on therapeutic hypothermia for stroke. However, he disagreed with Dr. Marion's position. Studies have used different temperatures, times to cooling, duration of cooling, etc., according to Dr. Schwab of the University of Heidelberg in Germany. What is needed, he said, is one large, randomized, multicenter trial with agreed-upon protocols.

"In my view, just randomized trials can show whether there is significance," he said, arguing that small studies can be too selective. "Pick one right patient in one center and one right patient in another center and you come up with 20 right patients overall," he said.

Raj K. Narayan, M.D., of the University of Cincinnati, argued that therapeutic hypothermia should not be standard if it passes muster only in small studies. "Large randomized trials have some limitations, and certainly small trials have limitations. Just so long as we are all aware what those limitations are, large randomized trials are, in general, one of the strongest ways of figuring things out," he said.

For Maxwell S. Damian, M.D. of the University of Leicester, England, the issues raised by Dr. Marion are a concern as his group advances beyond its single-center study of hypothermia in combination with coenzyme Q10 for head trauma. "That actually has been influencing our multicenter trial," he said. "We are restricting it to people we know personally who have a similar regimen of hypothermia. It's a big problem—method." ■

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