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Allogeneic stem cells to improve long-term outcomes after stroke

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Stroke is a major medical concern, being the 2nd leading cause of death and the 3rd leading cause of disability worldwide. Acute reperfusion therapies can improve outcomes but currently are accessed by 1 in 20 patients with ischemic stroke in the US. The need exists for additional therapies accessible by a majority of patients[1]. One strategy in this regard is to develop new therapies that have a time window beyond the 3–6 hour window of current reperfusion therapies.

In this context, David Hess and colleagues[2] did the The MultiStem in Acute Stroke Treatment to Enhance Recovery Study (MASTERS) study, shedding light on potential pathways forward for cell-based therapies to treat acute stroke. These authors performed a phase II, randomized, double-blind, placebo-controlled, dose-escalation trial of an allogeneic adult stem cell, multipotent adult progenitor cells given intravenously 24–48 hours after stroke onset. No safety concerns were found, which is important because allogeneic cells have advantages over autologous cells, such as availability on demand and no need for human leukocyte antigen matching. The authors also found clear evidence of immune system modulation. However, this intervention did not improve the primary efficacy endpoint, a composite measure combining several dichotomized global scales. There are a number of strengths to this study and several lessons worth considering.

MASTERS aimed to improve stroke outcomes in a challenging population to study[3], with a time window beyond that of tPA and stent retrievers which target clots rather than brain tissue. Hess and colleagues[2] provide strong evidence that during the acute stroke admission, it is feasible and safe to transfuse very large doses of a cellular therapy--1.2 billion cells, touted by the authors as the largest single dose of intravenous cells ever studied in humans, a dose 10x higher than allogeneic cell doses effective in graft-versus-host disease[4]. The authors also provide clear evidence that the human immune system can be effectively modulated in the early days post-stroke, in association with reduced infections in some secondary analyses.

Another strength of the study was that follow-up of secondary endpoints was to one year after treatment, far exceeding the more common 90-day cutoff standard in acute reperfusion stroke trials. Curiously, 0 out of 9 efficacy measures differed between treatment groups at 90 days but 2 out of 9 did (uncorrected for multiple comparisons) at one year. This is concordant with the fact that treatments such as multipotent adult progenitor cells that

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promote neuroplasticity, whether directly or secondarily from effects of immunomodulation, take time to manifest clinically[5].

The study also reinforces several lessons in stroke clinical trials. Numerous negative acute neuroprotection trials in stroke have emphasized the importance of designing the clinical trial to match parameters of the animal studies that demonstrated efficacy[6]. In the MASTERS study,[2] the upper limit of the treatment window was expanded from 36 hours to 48 hours post-stroke to address slow enrollment (which in the end spanned >4 years), in the process shifting away from the time window when multipotent adult progenitor cells were most effective in animal studies. Indeed, post hoc analyses suggested greater efficacy among patients enrolled earlier in the 24–48 h time window.

Prior trials have also emphasized the importance of testing a biological model of treatment effects[7]. A new ischemic stroke sets into motion numerous biological cascades. Some brain tissue dies within minutes, but the ischemic penumbra remains salvageable for hours and is the target of reperfusion and neuroprotection therapies. Subsequently, a series of immunological events unfolds over hours to days, paralleling and interacting with repair-related processes that span days to weeks. Delayed neuronal death during the first few days post-stroke has also been documented[8]. Within this context, the authors suggest that multipotent adult progenitor cells may protect neurons from cell death. Greater insight into processes targeted by these treatments would improve interpretation of why no significant improvement in neurological outcomes was observed in the primary outcome of this trial. Greater discussion of models of mechanisms of multipotent adult progenitor cell treatment and a more extensive interpretation of current results in such a framework would have been welcomed, and might inform future trial design, e.g., for improved patient selection or biomarker testing. Also, global endpoints have high clinical impact when positive, but earlier phase trials might benefit from the increased granularity of modality-specific endpoints[9].

New therapies are needed that improve outcomes in a majority of patients with stroke. Cell-based therapies offer several attractive candidates in this regard. The study by Hess and colleagues[2] of multipotent adult progenitor cells is an important step forward and provides several key lessons for post-reperfusion acute stroke therapies.

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