

Stem cells in amyotrophic lateral sclerosis

Ready for prime time?

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Amyotrophic lateral sclerosis (ALS) is the neurodegenerative disease caused by systematic unraveling of the motor network, resulting in progressive loss of upper and lower motor neurons, leading to muscle wasting and weakness, culminating in ventilatory failure and death.¹ There are no treatments that prevent the inexorable course. Stem cells have been promoted as potential therapy for ALS based on their ability to self-renew and differentiate into multiple cell types with the ultimate goal of repairing or replacing injured cells. However, replacing injured cells does not have a high likelihood of successfully treating ALS. Even if stem cells differentiated into motor neurons, it would be difficult to imagine the new motor neurons reproducing the extensive connections lost among cortical neurons, or between specific cortical neurons and their spinal counterparts, or among spinal neurons, or between spinal neurons and their target muscles. Moreover, new motor neurons, if integrated into a diseased network, might be subject to the same pathologic processes that brought about the demise of the original motor neurons. A more attainable goal for stem cells in ALS is that they help extend the lives of spinal motor neurons. The presumptive rationale for transplanting neural progenitor cells (NPCs) in patients with ALS is based on the *in vitro* demonstration that such cells secrete protective growth factors and, *in vivo*, can differentiate into neurons and glia that can repair injured cells.² Transplantation of NPCs derived from a single 8-week human fetal spinal cord extended lifespan by 17 days when injected into the spinal cords of G93A SOD rats, a common model of ALS. In these studies, the grafts underwent extensive neuronal and to a lesser extent astrocytic differentiation, presumably mediated by graft intrinsic factors and the host microenvironment.^{3,4}

Stem cells have been transplanted into patients with ALS too often with limited preclinical data, limited or no evidence of safety, and without complete, systematic reporting of objective outcomes and adverse events. It is therefore gratifying when rigorously designed stem cell trials are reported. In this issue of *Neurology*®, Glass et al.⁵ report the results

of their phase 2 study to address the safety of injecting escalating doses of the human spinal cord–derived NPC line directly into the cervical and lumbar spinal cord of 15 immunosuppressed patients with ALS at 3 centers. The authors had reported previously on their phase 1 studies,⁶ and proceed cautiously, emphasizing safety, in this phase 2 trial. Severe surgical complications occurred in 2 of 15 patients. One developed spinal cord edema and paraparesis, and another developed intractable and incapacitating pain. These are serious complications even in a devastating disease such as ALS. The immunosuppressant medication regimen also caused side effects, albeit less than the surgical adverse effects: 2 participants stopped tacrolimus and mycophenolate because of headache and diarrhea, while 2 others stopped tacrolimus because of diabetes, a known side effect of tacrolimus. It is unclear from this study whether immunosuppression affects graft survival, and this merits clarification.

The authors report that the stem cell transplantation was not clinically beneficial. Postoperative ALS Functional Rating Scale–Revised (ALSFRRS-R) and forced vital capacity slopes of transplanted patients did not differ from slopes of 3 separate historical control groups. The use of any historical control group in assessing safety or efficacy can be limited by the difference in patient populations in the study vs those in the historical control group, as well as the changes in clinical care that may alter the natural history over time. The patients in this safety study were younger (49.5 ± 9.8 years) than the usual ALS clinical trial participant or new ALS clinic patient (55 years) and had longer disease duration when enrolled (25.5 ± 27.7 months compared to 18 months). There were fewer with bulbar onset (10% vs 20%) and they were progressing, on average, at a rate that was one-third slower than that of the usual clinical trial enrollee. Most would be expected to do better, individually, than average historical controls. It is not surprising that some did, and a few did not.

Defining clinical benefit in a disease as heterogeneous as ALS is difficult and this study was not powered to do so. The authors consider ways of improving clinical trial design to control for the

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heterogeneity. They discuss the potential usefulness of measuring the decline in ALSFRS-R slope during a 3- to 6-month lead-in period, to decrease variability by excluding rapidly progressing and slowly progressing patients from the clinical trial.⁷ A surrogate that could indicate that cell-based therapies have hit their target would be extremely useful. However, developing biomarkers as surrogates for cell-based therapies requires understanding of the specific mechanisms mediating clinical benefit. Growth factors have been proposed as such a surrogate, but even in ALS models transplanted with NPCs, it is not clear that the growth factors released in vivo are solely responsible for mediating the clinical benefit. Transplantation of ALS rats with NPCs engineered to produce increased amounts of glial cell line–derived neurotrophic factor (GDNF) and differentiate into astrocytes failed to maintain neuromuscular contacts or to prolong survival.⁸ Injection of the SOD1-G93A mouse with human NPCs producing either GDNF or insulin-like growth factor-1 attenuated motor neuron loss but did not affect overall survival.⁹ However, delivering GDNF to the neuromuscular junction of ALS rats with mesenchymal stem cells maintained neuromuscular contacts, and increased motor neuron survival and lifespan.¹⁰ Thus, in future ALS trials, injections of NPCs directly into the spinal cord ventral horn may require supplementation by intramuscular injections of GDNF-secreting stem cells to target the neuromuscular junction.

These are clearly early stages of evaluating the risks and benefits of transplanting neural progenitor stem cells in patients with ALS. The patients who volunteered for this study are to be thanked for their commitment, as are the authors for undertaking this extremely complex but important study.

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DISCLOSURE

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