Editorial

Neural transplantation

ROY A. E. BAKAY, M.D.

Chicago Institute of Neurosurgery and Neuroresearch; and Department of Neurological Surgery, Rush Medical College, Rush University Medical Center, Chicago, Illinois

In this issue, Dr. Kondziolka and colleagues present their Phase II randomized trial of neural transplantation for subcortical stroke. Eighteen patients with completed stroke of 1 to 6 years in duration and fixed neurological deficits that had remained stable for at least 2 months were entered into a randomized, observer-blinded trial. Patients received either 5 or 10 million human neuronal cells (LBS-Neurons), which were implanted along five tracts in 25 sites. After surgery the patients participated in a stroke rehabilitation program (seven patients per group). Four additional patients only underwent stroke rehabilitation and served as the control group. Patients who underwent surgery received cyclosporin A (CsA). The primary end point was the European Stroke Scale (ESS) motor score at 6 months. Secondary outcomes included the Fugl-Meyer Stroke Assessment, Action Reach Arm Test, and Stroke Impact Scale scores, as well as the results of neurocognitive and neuropsychiatric testing. The ESS motor scores and the Fugl-Meyer scores did not significantly differ from control or baseline values. Scores on the hand-movement portion of the Action Reach Arm Test, the Stroke Impact Scale, and the Everyday Memory Test improved in comparison with baseline values.

Thus, although there were some measurable improvements in certain patients, this study did not find evidence of significant benefits to motor functions as determined by the primary outcome measure and, therefore, the treatment must be characterized as a failure. To the therapeutic nihilist this is just another failed cell therapy, but such an opinion misses the bigger picture.

Cellular therapy in the central nervous system (CNS) is in its infancy and will be a major contributor to the future treatment of a number of diseases of the CNS. As with other therapies, there have been early failures and there will continue to be failures until we learn proper methods. The underlying principles are sound. The biggest problem is an incomplete understanding of neurobiological host repair mechanisms, which is needed so that the repair and circuit reconstruction required to normalize function can be augmented. This incomplete understanding is not for lack of trying. There has been an exponential growth in the number of papers on neurotransplantation for all varieties of neurological diseases including Alzheimer disease, multiple system atrophy, spinal cord injury, brain injury, epilepsy, chronic pain, CNS malignancy, genetic defects, ischemia, and stroke.

If there is so much activity in the basic sciences, why invest in clinical studies? Why not just wait until the basic scientists solve all the problems? Unfortunately, basic scientists will never solve all the problems because the models they create are not the disease; in addition feedback from the clinical sphere is necessary to drive basic research. No clearer example could be demonstrated than work performed in neurotransplantation for Parkinson disease (PD). No one could have predicted the overwhelming placebo effects in these surgeries because placebo effects simply do not occur in animals. Nor could anyone have anticipated the complications of “off-stage” dyskinesias because none of the preclinical studies included an evaluation of animals with long-standing levodopa-induced dyskinesias. This complication is now being addressed, but it would not have been given a high priority had not clinical experience demonstrated the problem.

When should clinical studies be initiated? Guidelines for this were developed by a group of basic scientists and research clinicians actively involved with CNS transplantation and published as the recommendation of the American Association of Neural Transplantation and Repair. First and foremost, animal research must be conducted to allow the possibility of success. Clearly, this is the case for LBS-Neurons. Stroke is a focal injury with neuronal loss. It might seem extremely unlikely that implanted cells could form appropriate connections to restore function in an adult brain. Nevertheless, behavioral improvements occurred in animals following grafting of LBS-Neurons (Layton Bioscience, Inc., Gilroy, CA) into stroke models. These cells survived, integrated, and formed synaptic contacts. These were not isolated findings. Stem cells from human bone marrow, umbilical blood, adipose tissue, and fetal tissue have been used to restore neurological function following ischemia or stroke. Thus, although there may be better cells to transplant, cells that have been chosen have shown promise.

Another aspect that is equally important in determining when to initiate clinical studies is the potential risk–benefit assessment. The severity of the disease and the potential for other forms of therapy will in part determine how much basic research is needed before entering the clinical sphere. Stroke is the leading cause of disability worldwide and it is the third leading cause of death and disability in the US. Although an improvement in stroke-related deficits occurs...
after acute stroke, there is a plateau after which the deficits appear fixed. Clearly chronic stroke is an area that needs active clinical investigation. The Phase I study conducted by Kondziolka and colleagues included 12 patients who received transplants of LBS-Neurons.\textsuperscript{12,22} Although designed to evaluate safety, some patients displayed improvements in ESS scores. Therefore, in the Phase II study the ESS score was the primary outcome measure. Metabolic activity demonstrated on positron emission tomography (PET) scans increased in the area of the graft at 6 and 12 months, from which we infer that 6 months was not too early to observe improvement.\textsuperscript{21} Finally, data obtained in one patient at autopsy 18 months after implantation documented the survival of transplanted LBS-Neurons.\textsuperscript{22}

The LBS-Neurons are derived from a human embryonic carcinoma cell line that can be transformed into pure postmitotic neuronal cells with a treatment of retinoic acid. The LBS-Neurons can function as CNS progenitor cells capable of developing into a multitude of mature neuronal phenotypes that are capable of extending neuronal processes, expressing multiple neural transmitters, forming functional synapses, and integrating into a host.\textsuperscript{17,28} A concern in this study is that the 6-week treatment was too long, resulting in terminal differentiation, and that a shorter treatment might have allowed a more “plastic” response to the stroke environment.

A Phase II study should demonstrate safety but, more importantly, provide evidence of efficacy so that investigators may plan a definitive study. In this regard, I believe that this study fails. To evaluate optimal patient criteria, a sufficient number of cases must be studied to make reasonable inferences. Separation of patients by age, stroke type, size, location, or any other criteria leaves questions as to who is the suitable patient candidate for the next study. An underpowered study is almost as useless as no data at all. With only seven patients per therapeutic group, the question of whether there is a statistical difference between 5 and 10 million cells cannot be answered. Although the authors find it difficult to “infer” that fewer cells yielded better results and, therefore, wish to consider that ischemic strokes lead to a better outcome than hemorrhagic ones, there is no rational basis on which to make this judgment.

In fact, fetal transplants with fewer cells and better distribution can result in greater improvements than larger grafts.\textsuperscript{23} Including too many cells in the graft may result in greater cell death due to inadequate nutrition. The use of cells with a 50% rate of viability is also a problem. The result is a large number of dead cells that increases cytotoxicity. Despite the potential for rejection from dead allograftic cells, an argument against the use of CsA can be made. There is little evidence for rejection of intracranial neural allografts in monkeys\textsuperscript{2,13} and humans.\textsuperscript{9} There is also no reason to control for the effect of CsA. Although CsA has been demonstrated to produce neurotrophic effects in some models, it has not been identified as a factor for improvement in this stroke model.\textsuperscript{20} The lack of efficacy in this trial also indicates that CsA is not a major factor.

The control for the placebo effect in transplantation is controversial because it requires a sham operation. Much of the debate revolves around the interpretation of the requirement that risks to patients must be minimized. Supporters claim this has been done.\textsuperscript{1,10,11} Some opponents argue that almost any risk is too great for a patient who is not going to receive benefit.\textsuperscript{14} If taken literally, this would be so restrictive that even performing PET scanning in a control patient may be unethical. Others argue that equipoise provides a less ambiguous standard than “risk” and would still condemn sham controls\textsuperscript{15} or that core assessments can substitute for a sham surgery.\textsuperscript{5} The key arguments focus on the individual good versus the good of the whole and whether the individual can through altruism volunteer for a sham procedure.

Opponents of sham operations dramatically underestimate the placebo effect in cases of PD. Much of their opinion is based on the analysis made by Hrobjartsson and Gotzsche\textsuperscript{16} of clinical trials in which placebo was compared with no treatment. In their metaanalysis, these authors found that the therapeutic placebo effect was not a general phenomenon. Nevertheless, in their review of studies involving subjective measures or certain types of conditions such as pain, Hrobjartsson and Gotzsche found that a placebo did have a weak effect. The specific review of the placebo in patients with PD by Shetty, et al.,\textsuperscript{27} gives a different perspective. Physiological changes can be documented in patients given a placebo for PD; these changes are related to quantitative dopamine release\textsuperscript{4} and electrophysiological activity.\textsuperscript{4} In blinded trials long-term clinical improvements (in the 20\% range) can occur from either a placebo pill\textsuperscript{12} or placebo surgery.\textsuperscript{29} The placebo effect is very real in patients with PD, and those patients who feel they have benefited from surgery, regardless of treatment group, demonstrate improved standardized assessments.\textsuperscript{20} Therefore, sham-treated patients are not without benefit, which negates part of the opponent’s argument. In this unique situation, placebo-controlled surgeries are clearly justified if appropriate safeguards are instituted. These safeguards are well described.\textsuperscript{13,14} That is not to say that sham surgery is necessary in all situations. The underlying disease and study design should dictate whether the sham surgery is justified. A placebo surgery in patients suffering from stroke may not be needed.

Thus, although it could be argued that in the present study Kondziolka and colleagues used the wrong design, wrong surgical technique, wrong cell preparation, and wrong cell type, the bottom line is that this is an important paper because it pushes forward the frontiers of surgical treatment for stroke. Lessons learned from this investigation should inspire basic science studies and help refine future clinical studies. Congratulations to Dr. Kondziolka and colleagues for taking a bold step. I wish him luck in future investigations.

ROY A. E. BAKAY, M.D.
Chicago, Illinois

References