Moving Closer to Cell Therapies for PD

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Current treatment for Parkinson's disease (PD) using dopamine agents to replace the loss of dopaminergic neurons has helped to ameliorate some of the motor features of the disease in its early stages. This significant response to dopamine agents has provided the rationale for testing cell-based therapies for replacement of lost dopamine neurons in the hope of altering the natural history of PD by slowing the progression of signs and symptoms.

A panel of experts reflected on lessons learned from the current research on cell transplantation as therapy for PD and discussed the prospects for using stem-cell therapy for clinical transplantation.

OPEN-LABEL CELL TRANSPLANTATION STUDIES

Roger Barker, MD, University of Cambridge, Cambridge, United Kingdom, discussed lessons learned from the open-label cell transplantation studies to replace the lost dopamine cells found in PD. The standard process by which cell-based therapies are moved forward to patients is to identify a cell source that produces dopamine, test it in an animal model of PD, trial it in a small open-label study, optimize procedures in open-label studies, and, finally, conduct a double-blind sham surgery trial. Dr. Barker presented data on a number of cell sources that have been investigated, including adrenal medulla, porcine fetal ventral mesencephalic tissue, Spheramine®, and human fetal ventral mesencephalic tissue.

Lessons learned from these trials include the following:

- Each cell therapy is different from the others.
- A critical look at the preclinical data is required because those data will accurately predict clinical response.
- It takes time to optimize how to best use a cell therapy; open-label studies rarely get it right the first time and so require learning along the way as well as cooperation among participants.
- All trials should include long-term follow-up, which is necessary to obtain data regarding true efficacy.
- Double-blind placebo/sham surgery trials should be considered only after knowing how to use the cell therapy optimally.

Prof. Barker then described a study currently underway—the Transeuro Open Label Transplant Study in Parkinson's Disease [Transeuro; NCT01898390]—which has been designed to incorporate the preceding lessons from prior studies. This open-label study is designed to optimize the characteristics of patients who are anticipated to respond best to fetal ventral mesencephalic tissue transplantation—that is, younger patients with earlier disease. The study is about to transplant its first patient and will run until 2018.

SHAM-CONTROLLED CLINICAL TRIALS

Stanley Fahn, MD, Columbia University Medical School, New York, New York, USA, reflected on the results of the 2 sham-controlled clinical trials using fetal cells [Olanow CW et al. *Ann Neurol* 2003; Freed CR et al. *N Engl J Med* 2001].

Dr. Fahn began with an overview of the historical perspective, including a discussion of doubts regarding the ethics of doing sham-controlled clinical trials. Dr. Fahn also noted that one lesson gleaned from this work is that sham-controlled surgical trials are possible and that blinding can be obtained and maintained throughout the study.

Major findings of the studies include the following:

- Subjective self-ratings after 1 year are unreliable. After 1 year, people tend not to recall the severity of their illness. A more accurate self-assessment can be made by having patients review a video of themselves.
- It is more difficult to achieve improvement in global self-rating than improvement in Unified Parkinson's Disease Rating Scale score.
- Fetal dopaminergic tissue implants can survive and provide long-lasting dopaminergic effect.

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- Patients with persistent dyskinesias had the greatest significant improvement, with both the presence of dyskinesias and their subsequent improvement reflecting dopaminergic activity.
- Currently, immunosuppression is not thought to be essential, although Dr. Fahn thinks that it may still be critical in the majority of patients, as it may help with better survival and a better result.
- Symptom relief is not guaranteed by image-detected survival of dopaminergic neurons.
- Future research studies on transplantation should be considered for young patients with early PD, before they develop levodopa dyskinesias.

Dr. Fahn ended by emphasizing that sham-controlled trials are essential to truly test the effectiveness of cell therapies for PD.

PROSPECTS: LOOKING AHEAD

The session ended with a discussion by Prof. Barker on the issues that need to be addressed to move cell therapy for PD forward, highlighting four main questions:

1. Do dopamine cell therapies work for PD?
2. Can stem cells safely be made into authentic nigral dopaminergic neurons?
3. How can such therapies be tested in patients?
4. Are these therapies competitive?

Referring back to his talk at the start of the session, Prof. Barker said that the studies have shown that dopamine cell therapies do work for PD but that a lot will rest on the findings of the Transeuro trial. Studies also need to show that the stem cells are able to yield authentic nigral dopaminergic neurons, which can be made using good manufacturing practices and regulation and are safe with good fiber outgrowth.

As for testing cell therapy in patients, the Transeuro study is helping to shape the type of trial needed. A number of strategic grants have been given to investigators in several countries worldwide, and the close collaboration among these investigators will help answer the critical questions that will move cell therapy into the clinic. A stem cell source will be ready for clinical trial in the next 5 years, but there are still unresolved issues on how to translate the emerging preclinical data into a clinical trial (eg, which patients to include, trial design). How to regulate stem cell therapy trials has been and will continue to be a major concern.

The final issue will be to determine whether a cell-based therapy is better than any other therapies for PD in terms of efficacy, cost, and effect on natural history of the disease. Prof. Barker emphasized the inevitable changes once commercial investment enters the picture, which may affect the timeline of these therapies as well as outcomes.

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