

Cell therapy for Parkinson's disease: have the glory days gone?

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Over the past 25 years, cell therapy has been assessed in patients with Parkinson's disease (PD), with the aim of restoring lost dopaminergic function. Fetal ventral midbrain cells have been successfully grafted into the neostriatum of rodents with experimental PD and have yielded promising results in open-label trials in human beings.¹ The use of sham surgery as a control has been deemed unethical and unnecessary by many researchers;² however, despite this scepticism, results of randomised, sham-surgery-controlled trials have enabled balanced analysis of the safety and efficacy of this treatment. Such studies have revealed the occurrence of graft-induced dyskinesias,³ and reassessment of the patients described in an open-label trial showed that dyskinesias had arisen even though they had not previously been noticed.⁴ Inconsistencies in outcomes between open-label and sham-controlled trials have been noted for other surgical approaches in patients with PD, such as intraputamenal delivery of trophic factors⁵ and porcine fetal midbrain cell grafts.^{6,7} These differences suggest that surgical procedures should not be introduced into neurological practice unless they have been rigorously tested in controlled trials.

In this issue of *The Lancet Neurology*, Gross and colleagues⁸ describe the negative results of a controlled trial of intraputamenal implantation of human retinal pigment epithelial (RPE) cells bound to a porcine gelatin microcarrier in 71 patients with advanced PD. As for other types of cell therapy, the results of animal experiments and an open-label trial in human beings had been encouraging⁹ but did not carry through to the controlled trial. Whereas the aim with grafts is to repopulate the host striatum with viable and functional dopaminergic neurons, the melanin-containing human RPE cells were expected to provide constant local production of levodopa, the oral form of which is the gold standard treatment for PD. Locally produced levodopa would be decarboxylated to dopamine in the surrounding glial or neuronal cells, which would consequently provide continuous stimulation of striatal dopaminergic receptors.¹⁰ Unfortunately, although the activity of fetal grafts can be documented by functional imaging,¹¹ the activity of human RPE cells cannot be assessed after implantation. Poor graft survival and inflammatory responses could

have contributed to the negative outcome; indeed, in a study by Farag and colleagues,¹² post-mortem results showed that only 0.036% of human RPE cells had survived 6 months after implantation. Remarkably, patients in the study by Gross and colleagues⁸ were not given immunosuppressive agents. With hindsight, the negative outcome in the controlled trial was perhaps not unexpected, in light of the phase 1 pilot trial in six patients with PD;⁹ this showed a negligible improvement in time off medication and no increase in dyskinesias, which would be expected after intrastriatal levodopa release by RPE cells.

This trial adds another piece to the mosaic of cell-based treatments for PD. The research completed so far calls for reflection on how to invest time and money in future. Most cell-based approaches to PD treatment centre on dopaminergic neurons, although degeneration of dopamine-producing cells is not the first or the only pathological feature of this disorder. Symptoms not related to dopamine predominate in patients with complicated PD who receive cell therapy, and whether restorative approaches would work better at earlier stages of PD is a matter of debate. Comparison of different trials is difficult, because of variability in surgical techniques, selection of treatment targets, quality and quantity of implanted tissue, and management after implantation. In light of expertise accumulated from transplantation of fetal tissue grafts, a €12 million European research grant for investigation of neural transplantation in PD has been started,¹³ but whether this initiative is unwary or farsighted remains to be seen.

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I am a consultant for Teva Pharmaceutical Industries and have received honoraria from Lundbeck, Medtronic, and Novartis.

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Transforming multiple sclerosis trials into practical reality



Multiple sclerosis is an inflammatory demyelinating disorder of the CNS and one of the most common causes of sustained neurological disability in young adults. In the 1990s, the first immunomodulatory drugs were introduced for the treatment of relapsing-remitting forms of multiple sclerosis and since then interferon beta and glatiramer acetate have been the main treatments. However, these treatments are only partly effective and their subcutaneous or intramuscular routes of administration can be bothersome given the known potential side-effects of these injections and the difficulty of self-administration. Intravenous drugs such as the monoclonal antibody natalizumab and the cytostatic agent mitoxantrone are both effective but associated with certain risks. Thus, challenges with regard to acceptance, tolerance, and adherence affect the long-term response to such treatments, exemplifying the unmet needs in multiple sclerosis.¹

Fingolimod is an oral drug that binds to sphingosine 1-phosphate (S1P) receptors. It causes downregulation of these receptors and subsequent reversible sequestration of lymphocytes in lymphoid tissues. The effects are gradual and do not affect all types of lymphocyte to the same extent—for example, effector memory T cells are not sequestered, so it seems that immune surveillance remains largely intact.² In two large phase 3 clinical trials, fingolimod was shown to have clinical and paraclinical efficacy in patients with relapsing-remitting multiple sclerosis. This prompted the approval of fingolimod by the US Food and Drug Administration in September, 2010, for the treatment of relapsing forms of multiple sclerosis. Fingolimod has now also been approved by the European Medicines Agency (EMA), but with a more restricted indication:

failure of treatment with interferon beta and highly active relapsing-remitting multiple sclerosis.

The FTY720 research evaluating effects of daily oral therapy in multiple sclerosis (FREEDOMS) trial,³ a 2-year placebo-controlled study, showed the efficacy of fingolimod on relapses, clinical disability progression, and various MRI outcome measures. The trial assessing injectable interferon versus FTY720 oral in relapsing-remitting multiple sclerosis (TRANSFORMS)⁴—a 12-month, multicentre, randomised, double-blind, double-dummy, parallel-group study, in which the safety and efficacy of fingolimod were compared with those of intramuscular interferon beta-1a—showed that fingolimod was better with regard to relapse rate and MRI outcomes. In this issue of *The Lancet Neurology*, Khatri and colleagues report the results of a preplanned extension of TRANSFORMS.⁵ In the core study, patients were randomly assigned to receive two doses of fingolimod (oral 0.5 mg or 1.25 mg per day) or interferon beta-1a (intramuscular 30 µg per week). Patients who completed the 12-month double-blind treatment phase were eligible to enter the optional extension phase in which patients treated with fingolimod were continued on that treatment and those treated with interferon beta-1a were randomly reassigned (1:1) to receive 0.5 mg or 1.25 mg fingolimod.

The extension study data are important and have direct relevance for clinical practice. Fingolimod was well tolerated in the extension study population,⁵ and the tolerability and safety profile closely resembled that known from previous trials.^{3,4,6} The extension study scenario mimics clinical practice since, at least in the countries in which fingolimod is approved as a second-line therapy, most patients switched to

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