Background: Recently a multi-center sham/placebo controlled trial of implanted fetal retinal pigmented epithelial cells failed to demonstrate superior UPDRS “off” motor scores compared to placebo at one year, largely due to a large placebo response. Measures of fluctuations were not assessed with diaries.

Methods: We evaluated 23 subjects (32% of the entire study population) at a single center. Prior to unblinding, the site PI evaluated clinical global impressions and fluctuations to assess the likelihood that subjects received drug.

Results: Twelve subjects received implants and 11 were shams. Prior to unblinding, the correct arm (placebo vs. sham) was correctly predicted 11 were shams. Just prior to the scheduled unblinding at our site, we reviewed our cases via source documents to determine if we felt they received drug or sham. 11 was an “academic” exercise (placebo vs. sham) was not part of the study protocol. No exact formula was used but the anecdotal change that was most emphasized in the global analysis was reduction of fluctuations (milder dyskinesia and especially reduced intensity of on/off transitions). After unblinding, results were compared.

Methods:

Our 23 subjects seen at the Baylor College of Medicine were part of a 71 subject, multi-center trial sham controlled Spheramine® transplant trial, randomized 1:1. The surgical details are previously described. 6 A complex paradigm was designed to avoid unblinding. Surgeries took place at a different site from the treating investigator, a separate rating investigator was used, and post-operative imaging results were reviewed at a central location rather than the local site. Randomization unblinding was allowed in case of emergency but this did not occur in our cases. Dyskinesia duration (UPDRS #32) and number of required daily L-dopa doses were similar. One year UPDRS “off” motor scores did not improve. Four sham and two implanted subjects have since received STN surgery. Two transplant patients have died of unrelated causes.

Discussion: Fluctuations seemed to improve in subjects receiving bilateral fetal retinal pigmented epithelial cell transplant compared to controls. UPDRS motor scores may not be the best efficacy point for implantation trials.

DISCUSSION

Despite lack of significant improvement on one year “off” UPDRS motor scores, we felt that striatal Spheramine® transplantation benefited fluctuations in our patients with advanced PD. This may have resulted from the ability of the transplanted RPE cells to uptake and buffer exogenously administrated L-dopa, thus smoothing out fluctuations. The lack of benefit in “off” motor scores may have resulted from the relatively low survival in humans, as is seen in all cell transplant studies. The cell survival may have been robust enough to buffer against dyskinesia but not enough to statistically improve “off” motor scores. That said, there is no empirical data regarding the amount of viable dopamine cells required to alter basal ganglia output. Since PD is notorious for the loss of dopamine and quality of life only modestly correlates with motor examinations, other primary efficacy points should be considered. More quantitated motor examinations, such as accelerometer gait analysis and finger tapping can easily be used. On/off diaries are often used and would be an appropriate addition to any advanced disease study. Dopaminergic imaging can be considered, although correlation with clinical outcomes is poor. Quality of life and global impressions are useful, but may be overly influenced by mood. We would argue for a composite scale equally weighing motor examination, cognitive outcomes, objective motor assessments, quality of life scales, fluctuations, and clinical impressions.

INTRODUCTION

Parkinson’s disease (PD) is a common neurodegenerative disease with both genetic and environmental origins. Although a number of different central and peripheral nervous cells degenerate in PD, loss of dopaminergic neurons most contribute to the cardinal signs. Accordingly, transplantation of viable dopamine producing neurons or localized nerve growth factors targeting dopamine deficiency have been attempted. These studies have generally employed the “off” medication motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS) but have all failed to demonstrate statistical superiority against sham surgery. 7

Spheramine® is a unique product derived from human fetal retinal pigmented epithelium (RPE) cells passively attached to crosslinked gelatin microcarriers of about 100 microm. These cells produce levodopa, the precursor to dopamine, and express G2 receptors. Unlike fetal nigral dopaminergic precursor cells, these are easily cultured, resulting in thousands of potential transplants from a single donor. In vivo and in vitro studies show greater cell survival when attached to the microcarriers compared to injected cells. 2 Dopamine imaging studies also show in vivo viability. 2

An open label study demonstrated marked motor benefit after Spheramine® transplantation 3 but a sham surgery controlled study, assessing “off” UPDRS motor scores at one year, did not show benefit over placebo, largely due to a robust placebo response. 4

REFERENCES

2. Investigator Brochure. Study of the safety, tolerability and efficacy of Spheramine implanted bilaterally into the putaminal/perinuclear putamen of patients with advanced Parkinson’s disease 2006.