Improved fluctuations following retinal fetal cell Spheramine® implantations: Considerations on the Appropriate Primary Efficacy Point in Transplantation Trials

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ABSTRACT

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 in 19/23 subjects ($p<0.01$). This was largely based on an improved global fluctuations score (2.0± 0.9 vs 1.0±0.7, $p<0.05$), which was not a study efficacy point. 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 DBS.

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.

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 dopaminergic cells 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 surgeries.[1]

Spheramine® is a unique product derived from human fetal retinal pigmented epithelia (RPE) cells passively attached to crosslinked gelatin microcarriers of about 100 microm. [2] These cells produce levodopa, the precursor to dopamine, and express D2 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 survivability 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]

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. [3] 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 at our site.

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. This was an "academic" exercise and 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.

RESULTS

The multi-center study failed to meet its primary efficacy point of improvement in one year "off" UPDRS motor scores, largely due to a robust placebo response. [4] Longer duration efficacy and secondary efficacy points are being evaluated.

Our patient demographics are summarized in Table 1. Overall, the correct allocation (drug/sham) was determined correctly in 19/23 cases ($p<0.01$, X^2). The 4 subjects in whom randomization was incorrectly predicted were followed for a mean of 2.0 years compared to 4.0 years in the 19 correctly assigned subjects. In no case were there any extraneous clues to unblind assessments. One patient did have slow dyskinesia while "off". Interestingly he had only mild "on" dyskinesia and remained "on" consistently so that these were not a subjective complaint, but only witnessed in the "off" medication evaluation. Subjects who received Spheramine® had lower global fluctuation scores ($p<0.05$, two tailed t-test) but only trended to have lower dyskinesia duration (UPDRS #32) scores, and required an identical number of daily L-dopa doses. (Table 1) One year "off" UPDRS scores did not significantly improve (data not shown). Four placebo subjects and two Spheramine® subjects have subsequently had deep brain stimulation. Two transplant patients have died of unrelated causes.

	Age	Sex	Duration of f/u s/p inplant (y)	Fluctuation (0-4)	Dyskinesia (0-4)	Daily Doses L-dopa	Blinded Assessment P=placebo S=Spheramine
PLACEBO	46	M	1.75	1	1	6	S
	52	M	4	2	3	8	P
	58	M	1.5	1	1	3	S
	53	F	2	1	1	4	S
	59	F	4	3	3	4	P
	68	M	3	3	2	4	P
	58	M	5	3	3	6	P
	53	M	5	2	2	5	P
	57	M	5	3	3	6	P
	57	M	5	2	2	4	P
	64	M	3	1	1	6	P
M	**56.8**		**3.6**	**2.0**	**2.0**	**5.1**	**8/11**
SPHERAMINE	56	M	5	2	1	4	S
	64	F	4	2	1	4	S
	65	M	5	1	0	3	S
	66	F	4	2	0	3	S
	44	M	3	2	2	8	P
	46	F	3	2	1	7	S
	57	F	1.5	1	1	4	S
	48	M	4	2	3	5	S
	52	M	4	2	1	5	S
	58	F	1.75	1	1	8	S
	58	M	5	0	0	4	S
	52	F	4	1	1	6	S
M	**55.5**		**3.7**	**1.0***	**1.5**	**5.1**	**11/12**

DISCUSSION

Despite lack of significant improvement on one year "off" UPDRS motor scores, we felt that striatal Spheramine® transplantation benefitted 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. [5] 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 empiric data regarding the amount of viable dopamine cells required to alter basal ganglia output.

Since PD is more than a motor disease and quality of life only modestly correlates with motor examinations [6], other primary efficacy points should be considered. More quantified motor examinations, such as accelerometric gait analysis and finger tapping can easily be used. [7] On/off diaries are often used and would be an appropriate addition to any advanced disease study. [8] Dopaminergic imaging can be considered, although correlation with clinical outcomes correlates poorly. [9] 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.

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