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STEM CELL THEARAPY IN PARKINSON'S DISEASE --- OPINION AND REVIEW OF SOME OF THE CURRENT LITERATURE

Patients with Parkinson's disease, their families and others are interested and frequently asking questions to me in my office about the current understanding of using stem cells in the treatment of Parkinson's disease (PD). Rather than answering each inquirers question, I will write it down and use it as a handout. There are many different origins, formats and ways of engineering the stem cells. Many are being considered to be potentially of benefit in the treatment of PD. Few, other than those mentioned below, have had appropriate clinical trials. Some are being considered to be used in humans for what could be or is called a proof of concept (apply the suggested treatment to a few patients and monitor them for clinical benefit, safety and tolerability). I am going to discuss in a focused review what is generally known now about the rational of using stem cells in the treatment of PD in humans.

I always relate to the patient that there is no biomarker for the diagnosis of PD. Hence, no way to have a 100% accuracy in the diagnosis of PD patients that are in a trial, other than autopsy or pathological examination of the brain. So the PD patients in a trial will have great heterogeneity clinically and probably pathologically, and may not be a representative clinical picture of PD. That however is true of all trials used to show efficacy for any Parkinson treatment, i.e. even of medications. This however can be somewhat minimized by having large numbers (the sampling size). Large numbers of patients is easier for testing oral medications and not so easy when doing an intracranial operation with considerable risk. I usually start by telling patients that the research in the area of stem cells has been going on for many years and it was found that some stem cells could survive and could become dopamine neurons. Dopamine is one of the neurotransmitters that is reduced in PD and needs to be increased for clinical improvement. Tissue and animal studies were encouraging in that stems cells, some or most survived, formed dopamine and in animals often made neuronal connections. There are many different “formulations” of stem cells and that is too complex to cover here. There has been some questions about the number of cells that survived and if they all remained neuronal dopamine producing cells. There has always been a concern that stem cells could develop into other types of cells and even concern that a malignant cell could result.

However, most importantly, when two large stem cell trials or studies were carried out, benefit was not generally shown. One trial had 34 patients, in a double-blind placebo controlled trial, using fetal nigral cells, transplanted into PD patients, was evaluated, and there was no significant overall treatment effect. Hence little clinical benefit was found. Also in one study 56% of the patients that had stem cells transplanted developed severe dyskinesia’s that were refractory to therapy and were "off" dyskinesia’s that persisted when off medication. Some of these dyskinetic patients required surgery to control these impairing dyskinesias. Also, in these trials, symptoms and signs of gait abnormalities, falling, freezing, and dementia apparently were not benefited but would have to be studied more carefully. However, since many of these just mentioned symptoms are probably not purely due to lack of dopamine, and may well be related to a non dopaminergic abnormality, they probably will not be benefited by dopamine transplanted cells.

Another significant concern for stem cells inoculated in the PD brain is that many now consider that there is evidence, as probably the Braak classification shows, that the disease may well start in the vagus nerve, the olfactory nuclei or peripherally . Biopsies now show Lewy Bodies (aggregated alpha synuclein) in the PD patient's colon, salivary glands and maybe in the skin and had In fact in some colon biopsies been documented before the PD patient had clinical symptoms. There have been some single case patients (antidotal experience by a few centers) who had fetal stem cell graphs, who seemed to have some benefit and on pathological study showed that the grafts could survive, reinnervate the striatum and be associated with some clinical benefit. However this was not reproduced in two well-structured trials as noted above. In one article in the Annals of Neurology, Dr's Olanow, Kordwer, Lang, and Obeso stated that "cell-based therapies that involve transplantation into the striatum of dopaminergic cells have attracted considerable interest as possible treatments for Parkinson's disease. However, all double-blind, sham controlled, studies have failed to meet their primary endpoint, and, transplantation of dopamine cells derived from fetal mesencephalon is associated with potentially disabling forms of dyskinesia". These same concerns are being strongly expressed by many today about all considered stem cell therapies of any type or format in PD patients.

Probably more important was the finding that the stem cells, when studied on autopsies in PD patients that had died that had gotten the stem cells grafts, had the alpha synuclein pathology (Lewy Bodies), in the stem cells. Hence the disease had spread in some way or been transmitted to the transplanted stem cells. This was found in a number of PD patients at a variable number of years. This however needs to be studied in many more transplanted patients after death but obviously will be difficult to do in large numbers. This phenomenon may be able to be studied in animal models hopefully, but that is not human data.

Then came the hypothesis's that alpha synuclein in PD patients is an aggregated, self-propagating, transmissible protein, much like the prion (an infectious agent). In the meantime, there was and is mounting solid research evidence by Dr. Lee, Dr. Chen, Dr. Luk and others that has carefully documented the validity of studies in tissue cultures and animals, that show that alpha-synuclein, a protein when it is aggravated or is in a misfolded fibrillar form (Lewy Bodies in Parkinson's Disease), can and does propagates (make more of itself) and spreads between interconnected brain regions. And as this aggregated protein is transformed or becomes toxic, it can turn into an “infectious” agent like the Prion that has been documented to be present in mad cow disease or other prion diseases (Creutzfeldt-Jakob diseases). Dr. Lee and others have shown that this aggregated alpha-synuclein (fibrils of alpha synuclein) as an abnormal protein can go from one cell to another in tissue cultures and in animals. The concept is that this, an aggregated (fibril) protein (aggregated alpha synuclein, found in Parkinson patients brain, in Lewy Bodies, a pathological marker for PD, in cell bodies of the substantia nigra and in the distal axon where the presynaptic dopamine terminals are, which contain Neurities and aggregated alpha synuclein), can accumulate, self-propagate, and be transmittable by travelling from one cell to another in the PD patient's brain. The clinical disease of PD may progress in a temporal (time based journey over years) pattern. And in an anatomical pattern or geographic pattern, it moves upward through the brain, much like the Braak pattern and pathological classification that is seen in autopsy studies of many PD patients at various stages in their clinical journey.

Recently, Dr. Prusiner (winner of the Nobel prize for his work on prions) has shown that in taking human brain tissue from patients with multiple system atrophy (MSA, a disease with Parkinson clinical features and aggregated alpha synuclein), and after inoculating a specific type of mice, under certain conditions, there can be a Prion like transmission of this aggregated alpha-synuclein protein (often called a fibril or aggregated) from one cell to another. Hence from human brain tissue, from a patient with a disease somewhat clinically similar to PD and that has an abnormal, aggregated alpha synuclein protein, the MSA inoculated mice developed signs of neurological disease and showed pathological evidence of abnormal alpha synuclein in clinically appropriate brain

cells of the mice. Dr Prusiner considered " this transmissibility is reminiscent of the human prion disorders such as Creutzfeldt-Jakob disease and suggests that MSA is caused by the accumulation of toxic alpha synuclein prions in the brain" This obviously puts the survival of implanted stem cells and the efficacy clinically of implanted stem cells in question, if not doubt. And it may explain how the transplanted stem cells in the autopsied human's brain that had stem cells transplanted, resulted in aggregated alpha synuclein in those inoculated stem cells. All of these findings and questions will have to be studied and discussed carefully by all the experts. The articles are numerous on this subject and many at this time. Every month a new article appears on the concept of how the aggregated alpha synuclein gets into the cell. A recent concept is that it enters the presynaptic nerve terminal by being taken up there and enters to damage important structures and cellular activities that then renders the cell damaged.

The question is clearly this one. If stem cells of any type, condition, formulation or processing are placed in the human brain of PD patients, will this aggregated, transmissible, toxic alpha synuclein in some way get into the transplanted stem cell and render them dysfunctional or diseased in some way.

So at the present time I and many others feel that the stem cell therapeutic approach will not be of clinical benefit in the near future. It will take double blind placebo controlled, human (sham) trials, with large numbers, followed for at least 5 years, establishing multiple endpoints (measurements) to determine efficacy, tolerability(adverse side effects) and safety, using the experience of the prior stem cell trials and the gene therapy experience in Parkinson patients as a guide for setting up the trials. And if any patients die, the brains will need to be examined carefully for Lewy Bodies in the stem cells and if they survived and if so were connections developed. If Parkinson's disease could be pathologically halted by some other treatment, then stem cells could be given and not be subjected to the transmission of a prion like protein. Or if some therapy could robustly slow down the progression of the disease by many years, then stem cell therapy could possibly, if proven to have clinical efficacy, safety and few if any adverse side effects, be used as a stop gap adjunctive (add on) therapy.

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