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A Successful and Safe Stem Cell Therapy for Progressive MS

Dr. Turck:
An international collaborative study has shown that the injection of a specific form of stem cells into the brains of patients with progressive multiple sclerosis, or MS, is safe and effective in preventing further brain damage. Is this the future for MS?

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Charles Turck, and I'm speaking with Dr. Stefano Pluchino, who's a Professor of Regenerative Neuroimmunology and Honorary Consultant in Neurology in the Department of Clinical Neurosciences at Cambridge University.

Dr. Pluchino, thanks for joining me today.

Dr. Pluchino:
Good morning, Charles. Thanks for hosting me.

Dr. Turck:
Well, let's start with some background, Dr. Pluchino. What did we already know about stem cells in relation to MS before you conducted your study?

Dr. Pluchino:
We knew quite a bit because, actually, I did my PhD on the very same topic using the very same technology means, but in animal models of MS-like disease, so the phase 1 study, which was published in December is the end or the beginning. Actually, it's the end of 20, 25 years of extensive pedantic systematic work in preclinical animal models of a MS, so we knew enough to be ready to jump onto a first-in-man proof of concept phase 1 clinical study in humans.

Dr. Turck:
And would you give us an overview of what happens in the brain during progressive MS?

Dr. Pluchino:
We don't know in full what happens. So we know that after a couple of decades, usually, in general, of acute active inflammation, which we characterized what we call relapsing remitting MS, very much of that inflammation progressively goes down, and it is replaced by alternative mechanism of tissue damage, which are characterized by diffuse activation of microglia and macrophages and astrocytes in the brain and continuous progressive loss of neurons, which is the major old mark of progressive MS. So in terms of interventions, we need to be smart and creative when identifying new interventions, which are able to penetrate the brain and which are able to interfere with major markers of disease progression, which characterize progressive MS.

Dr. Turck:

Now turning to your team's first-in-human study, would you explain what you hope to uncover, Dr. Pluchino, and who were the participants?

Dr. Pluchino:
Yeah. The phase 1 study was successful in showing that developing advanced cell therapies based on tissue-specific stem cells for people with active and nonactive progressive MS is doable. It was a success in terms of showing that the procedure is safe, and it was a success in showing the procedure is also very well tolerated by individuals with MS without evidence of adverse events or reactivation of disease or increase in the speed of progression.

I don't think we can claim that the procedure is also effective because in the absence of a control group and with the specific very biased characterization and the recruitment of people for a phase 1 study, I think it would be very ambitious to claim that some data out of the phase 1 study anticipate means of efficacy, so we need a different type of clinical trial to address rigorously whether an advanced cell therapy made of brain-specific stem cells is indeed leading to amelioration of disease features.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Stefano Pluchino about his recent study on stem cell therapy for patients with multiple sclerosis.

So let's dive a little further into your study, Dr. Pluchino. What happens to the brain's metabolism after treatment? And why is this significant in understanding the progression of MS?

Dr. Pluchino:
The metabolic side of the study is extremely exciting and extremely interesting. We don't have yet a final answer of what happens to brain metabolism and whether the understanding of metabolic responses of the brain are at all predictive of functional responses, but what happened in the phase 1 trial is that despite the very advanced stage of the disease of those participants to the trial, despite the very long duration, and despite a pretty long conversion from relapsing-remitting MS to progressive MS, we were able in a very elegant and completely unbiased way to measure and profile metabolic responses in major biological fluids that are usually conventionally analyzed for biomarker research.

The unique nature of the phase 1 study that we conducted allowed us sampling longitudinally, CSF, and serum for as much as between five and to seven times in 12 months of follow-up only from those participants to the study, so we ended up the study with five independent cerebrospinal fluid samples from individual, from the participants, and seven independent serum samples. These samples were appropriately processed for untargeted multiomic screening of proteins, metabolites, and lipids, which is the way we decided to approach the study of the metabolism of the brain. And what we found incredibly interesting is that while the output of the serum analysis were very, very messy without us being able to distinguish between individuals belonging to different treatment groups, what we found in the CSF-only was a time sustained and dose-dependent response of the CSF, and that response was characterized by increasing levels of carnitines and byproducts of fatty acid metabolism, which is something to discover, but which implies a reactive or a reaction of the brain of the participants to the study to the single that we applied 12 months before, which was the transplantation of allogeneic brain-specific stem cells. So now we have the curiosity but also the responsibility of putting together a follow-up study to investigate whether that specific response is maintained over time and whether it might be associated to effective responses to the treatment, which we can only do in a phase 2 clinical trial.

Dr. Turck:
And are there any other key findings from your study that you'd like to share with us?

Dr. Pluchino:
Yeah. The other key finding was the most important one is a lack of adverse events following not only the injection of the cells but also the surgery leading to the cellular delivery. It was a pretty much a stability of MRI findings, and it was a stability of the accepted biomarkers of neuroregeneration over a limited time period within which we followed up with our patients, which is 12 months post transplantation.

Again, this is all very promising. It is very rigorously analyzed, and we are already working very actively towards putting together phase 2 clinical trials, which will have the ambition to start addressing the preliminary efficacy means of these advanced therapies.

Dr. Turck:
Now you've started to touch on this already, but I thought I'd see what you envisioned next in this avenue of research, and what are the expectations in the scientific community that stem cell therapy might become a useful treatment before a patient gets to the progressive stage of MS.

Dr. Pluchino:
Well, the expectation is very high. Not only from the scientific community but also from the patient community, and I think it is very high because of the longstanding promise that stem cell therapeutics in general that we are here discussing of a nonhematopoietic stem cell therapy—so it is a tissue-specific stem cell therapy—because of the promise that stem cell therapies have been holding for quite a while already. We are still in the field missing convincing efficacy data out of clinical trials because there have been a number of unfortunate efficacy trials, which have failed, so the expectation is very high, and the interest is possibly even higher due to the intricate or complex biology of the stem cells. Stem cells by definition are cells which are able to jump between different phases of the cell cycle. They're able to proliferate, but they are also able to undergo quiescence. They are able to become multipotent, which implies in specific conditions to differentiate and to replace what is damaged or what is lost.

MS is a very complex disease, which is characterized by very complex pathobiology, including substantial myelin damage and demyelination with partial inability to remyelinate. There is also neuronal damage regardless of the intact status of myelin. So we need for MS very smart, new advanced therapies able to modulate different mode of actions at the same time, and I think what we've been studying as stem cells is extremely exciting because, over the last 20 years, which was your initial question, we have been able to demonstrate that they are indeed, stem cells, so they're able to differentiate and replace and integrate after transplantation, but they also have possessed remarkable abilities to reduce microgliosis, astrogliosis. They're able to inhibit antigen-specific, T cell responses. They're able to provide direct neuroprotection to nerve cells in the brain. So there are by definition natural-occurring DMTs, disease-modifying therapies, endowed with multiple abilities of action, which now we need to test in clinical trials.

Dr. Turck:
Well, this has been such an exciting advance in the development of multiple sclerosis treatment, and I want to thank my guest, Dr. Stefano Pluchino, for sharing his insights from his team's research. Dr. Pluchino, it was a pleasure speaking with you today.

Dr. Pluchino:
My pleasure. Thanks very much, Charles.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.