Update: Study to Investigate the Safety of the Transplantation of Human Glial Restricted Progenitor Cells into Patients with Transverse Myelitis

You can watch the video of this podcast at: youtu.be/8Caqb38P5fc

[00:00:01] **Dr. GG deFiebre:** Hi, everyone, and welcome to the "Ask the Expert" podcast series. This podcast is titled "Update: Study to Investigate the Safety of the Transplantation of Human Glial Restricted Progenitor Cells into Patients with Transverse Myelitis." My name is GG deFiebre and I moderated this podcast with Dr. Benjamin Greenberg. SRNA is a non-profit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our web site at wearesrna.org. Our 2023 "Ask the Expert" podcast series is sponsored in part by Horizon Therapeutics, Alexion, AstraZeneca Rare Disease, and Genentech.

[00:00:39] Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:01:01] Alexion, AstraZeneca Rare Disease is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development, and commercialization of life-transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they are committed to ensuring that patient perspective and community engagement is always at the forefront of their work.

[00:01:21] Founded more than 40 years ago, Genentech is a leading biotechnology company that discovers, develops, manufacturers, and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche Group has headquarters in South San Francisco, California. For additional information about the company, please visit gene.com.

[00:01:42] For this podcast, I was joined by Dr. Benjamin Greenberg. Dr. Greenberg is recognized internationally as an expert in rare autoimmune disorders of the central nervous system. He splits his clinical time between seeing both adult and pediatric patients. His research interests are in both the diagnosis and treatment of transverse myelitis, neuromyelitis optica spectrum disorder, anti-MOG associated disorder, ADEM, encephalitis, multiple sclerosis, and infections of the nervous system. He is actively involved in developing better ways to diagnose and prognosticate for patients with these disorders. He is an unpaid member of the SRNA Board of Directors.

[00:02:24] Thank you, Dr. Greenberg, for chatting with me today. Do you mind just talking about what the Q study is and background about what it's looking at?

[00:02:37] **Dr. Benjamin Greenberg:** Absolutely. So, for decades, there have been conversations about the potential use of stem cells to try and repair the damage in spinal cords affected by myelitis, inflammation in the spinal cord. And the Q-cell study is the first of its kind to look at remyelinating stem cells. So, stem cells that have been grown in a way such that when we put them into tissue, they form the cells that make myelin and then hopefully make myelin in the human. And in the Q-cell study, we're transplanting these cells into the spinal cords of individuals who have been paralyzed by transverse myelitis.

[00:03:17] **Dr. GG deFiebre:** And then do you mind just talking about what it took to get to this study, even beginning the study, all the steps that are taken to do a clinical trial like this?

[00:03:31] **Dr. Benjamin Greenberg:** Absolutely. So, where we are today has literally been 20 years in the making. And so, the steps to get to a clinical trial can be complicated, and for cell-based therapies, they're particularly complicated. So, first is all the pre-clinical development. So, this is developing the cells, making sure they work in the mechanism we think they work, and then putting them into animal models and showing that they have a benefit to animal models and then simultaneously doing studies to make sure there isn't a toxic effect of the cells. So, in the setting of cell-based therapies, one of the biggest concerns is whether or not cells when transplanted into a human will do something other than their intended purpose. Could they form a cyst? Could they form a tumor? Could they do damage to the organ we're transplanting them into?

[00:04:21] So, regulatory authorities placed a high priority on doing a lot of preclinical studies to show that those events didn't occur, that as best as we could tell the cells would be safe to put into a human. But even then, you have to sit with the FDA and their group of experts who are quite knowledgeable in clinical trials and design a trial that balances safety with the search for efficacy. And in the setting of myelitis and Q stem cell therapy, the discussion really focused around which patients should be first in a clinical trial of stem cells. And the priority, whenever we're doing a first-in-human trial is safety. And so, we design the trial to maximize safety and to maximize our ability to identify any danger signals during the course of the trial.

[00:05:15] So, then once you design the trial and you get the FDA to give you permission to move into studies, you actually have to do the work. And in the setting of this stem cell trial, it wasn't just the cells that needed FDA clearance but also the surgical procedure and the device used to implant the cells into the spinal cord. A brilliant surgeon at Emory, Nick Boulis developed a device to implant the cells into the spinal cord, but that device had to get FDA approval.

[00:05:44] So, in this trial, we needed both the device approved, the cells approved, then the FDA to give us permission to move forward into humans. And right when we got that permission, the pandemic began, and pretty much all the human clinical research ground to a halt, especially if the research hadn't started yet or was considered elected. So, we had a multiyear delay in our launch. And finally, at the point, we were ready to then relaunch after the pandemic settled enough to allow research to start back up, it was just time for required data around the stability of the cell lines that had been frozen in freezers. We had to show the FDA that they were so viable. So, that led to the next delay. So, finally, in December of 2022, literally after 20 years of work, the first patient enrolled in our Phase 1 study of Q-cells for individuals who've been paralyzed by transverse myelitis.

[00:06:45] **Dr. GG deFiebre:** Great. That's very exciting. And I know it's been a long time coming. So, in terms of -- you mentioned what it takes to get a trial like this going. Do you mind talking about what inclusion and exclusion criteria and why they're included in trials and what their purpose is?

[00:07:06] **Dr. Benjamin Greenberg:** Absolutely. One of the negotiations with the FDA when designing a trial is who's going to be eligible. And this is a conversation that is based on trying to create a population enrolled in the trial that will allow us to judge the safety and efficacy of whatever intervention we're doing. And also, we have to make sure depending on the relative risk of the intervention that we're enrolling a patient population where we're minimizing the risk.

[00:07:35] So, in the setting of a trial that is surgically implanting cells into the spinal cord, the conversation with the FDA focused on which population of patients would be the safest to enroll in the trial. And there are many inclusion/exclusion criteria that we go through in screening patients, but there are two in particular that are important for this trial. The first was, the FDA wanted us to focus on individuals where the damage was in the thoracic spinal cord and not the cervical spinal cord. And it has to do with the surgical procedure. There's concern as we do operations higher and higher in the spinal cord that if something were to go wrong, it would have a greater risk to the life and limb of a participant. So, they wanted us to start in the thoracic cord. So, any patient whose transverse myelitis affected them in the cervical cord where they have symptoms in their arms don't yet qualify for this intervention.

[00:08:33] But the second requirement that the FDA had for this trial was that we were going to take individuals who were not able to walk. So, folks who can stand and move with a walker at this point don't qualify for the trial, because bluntly the attitude was, if there was a complication from the surgery, the risk of somebody losing function they had would be minimized if we're starting with a group of individuals with very limited function.

[00:09:04] So, while folks can have a little bit of movement in their legs and still enroll in the trial, it can't be enough that gets them the ability to stand or walk. And so, when patients contact us and we discuss the trial with them, we go through inclusion/exclusion criteria to make sure we're getting individuals who meet each of those criteria and allow us to do this study safely. Now, the goal is if we prove the safety of the procedure and the cells in this first cohort, we will go back to the FDA with that data and ask for broader inclusion/exclusion criteria, so we can apply this therapy to more individuals.

[00:09:41] **Dr. GG deFiebre:** Thank you. And so, what has happened so far? I know you talked about the pre-clinical things that had to happen. But in terms of the surgery, I know you mentioned that there was one recently, what one of the steps that have happened recently in terms of the study and involving humans?

[00:10:01] **Dr. Benjamin Greenberg:** So, currently, we have completed surgery for patient 1 and they're in follow up and we have been actively screening for patients 2, 3, and beyond. We're approved to go up to nine patients. And so, we're accepting inquiries from anybody and everybody. It's important to note that this study is happening just at UT Southwestern in Dallas. So, individuals do have to have the ability to make it to Dallas to undergo study-related procedures. But we have been able to navigate that process with folks pretty successfully so far.

[00:10:39] So, we are still screening and enrolling as patients are interested. And between each patient, we have a gap, a delay to ensure that there isn't a concern for safety before we enroll the next. So, the enrollment is going to go on easily over the next year while we continue to screen patients and put them into the trial.

[00:10:59] **Dr. GG deFiebre:** So, I was going to ask what the next steps were. But is it -- I guess, do you mind just talking a little bit about what's involved in the screening process before someone is enrolled?

[00:11:09] **Dr. Benjamin Greenberg:** So, anybody who contacts us who's interested, we do go through consent, and we ask for permission to look at medical records. We want to save people a trip down here if we identify a reason that they wouldn't qualify. We do a records review, and we look at MRIs. And as long

as we agree with their diagnosis and we agree at a top level, they meet the criteria, individuals come to UT Southwestern to do a screening visit that involves things as simple as blood work and MRIs, and physical exams, and things that most people are used to doing at this point. And then we go through our checklist of inclusion/exclusion criteria. And if, after providing informed consent, a person passes all of those criteria, we then talk about scheduling a surgery date.

[00:11:57] Individuals come, and they're admitted to the hospital, and they have a very unique experience. This surgery is different than anything else in the world. And there's a lot of moving parts. We work with the group that handles the stem cells that have been frozen to thaw them and make sure they're viable and get them to the operating room as our surgeons are getting patients ready, and our anesthesiologists and then in the operating room, we transplant the cells and then it's like a hospital stay like any other procedure. So, if you had your gallbladder out, you might stay overnight, same thing if you have stem cells transplanted in the spinal cord, you're going to stay a couple of nights in the hospital.

[00:12:36] And then we move our follow-up to the outpatient clinic where over months we have regular visits to do tests, to check in, and to look for any signs that the cells could be doing harm. And if you notice I'm focusing on the harm side because of Phase 1 studies about safety, would I love to see efficacy? Sure. It's our wildest dream. But at a minimum, we're looking to make sure that the transplant of these cells doesn't lead to any untoward effects. And one of the things that I haven't mentioned yet is these cells when transplanted are treated as an organ transplant as if I was giving somebody a new kidney or a new liver. And in order to prevent rejection of that transplant, individuals are put on immunosuppression for a period of months to allow those cells to grow, and hopefully not elicit an immune response. And so, a lot of the safety checks we're doing are to make sure that that immunosuppression isn't causing any issues for our patients.

[00:12:36] **Dr. GG deFiebre:** And so, as you talked about is that typical for these types of this phase of studies to have it be primarily focused on safety and ensuring that there is no harm and then later looking at efficacy or how does that play in?

[00:13:49] **Dr. Benjamin Greenberg:** Yeah, that's the traditional avenue for all studies. We talk about Phase 1, Phase 2, Phase 3, and Phase 4 relative to studies. So, Phase 1, which is human-based studies is almost exclusively focused on safety. We're on the lookout for evidence of efficacy, but the goal is to identify any issues with dosing, or any toxic events related to dosing of whatever therapy we're given. Phase 2 is a little larger, often a little longer, and balances both a very specific look at safety. But starting to keep an eye on the efficacy side of things. Are we getting reassuring signals that whatever we're doing is worthy of continued study? And then you move to Phase 3, which is also looking at safety over larger numbers of individuals but is definitely looking to prove that there is a benefit to the therapy. Because one of the things the FDA is charged with doing is not just trying to ensure the safety of a therapy, but they're also charged with ensuring that we don't sell people therapies that don't work. There are moral, ethical, and other issues related to the notion of a snake oil just because it's safe, doesn't mean people should be taking it. We want to make sure they're as best as possible there's a benefit.

[00:15:12] Now, the FDA does a very good job of balancing those issues relative to the disease we're trying to treat or the issue we're trying to treat. So, the bar, if you will, for efficacy for a product for a non-life-threatening or a condition that doesn't dramatically impact quality of life is different than for life-threatening therapy. So, in the world of Lou Gehrig's disease or brain tumors, the amount of efficacy you have to show is different than if we're treating acne. And so, there is a very systematic approach from the FDA to making those judgments. And then once a drug is found to be safe and effective and is on the market, there's still a requirement to do the monitoring. This is called Phase 4 to show that there isn't a new safety signal when a broader number of people take this medication.

[00:16:05] Now, in the setting of rare diseases, the FDA and Congress years ago realized we shouldn't have to do all of those phases to get drugs available for individuals who've been affected by rare diseases. And in fact, there have been drugs approved after just Phase 1 or Phase 2 depending on the data for a rare disease, because there's a recognition that there may not be enough of a population or enough time to move through all those phases. So, in the setting of transverse myelitis, we fully expect to need a larger Phase 1 or even Phase 2 study, but the likelihood be if it works, we wouldn't be required to go on to those other phases before submitting to the FDA.

[00:16:44] **Dr. GG deFiebre:** And then do you have any final thoughts or anything else you'd like our community to know about?

[00:16:51] **Dr. Benjamin Greenberg:** So, first, I have to say a huge thanks to the community that has been supportive of the SRNA and of our work at UT Southwestern in so many different ways. And it's made a huge difference relative to the work we're doing. And I would just want to say to folks that we're moving ahead. It's been a long time coming. Everyone's been very patient, but we're hoping to share exciting, good news as we get further down the line with this study, primarily on the safety and make sure that we can design the study to be more inclusive of more patients and see what type of effect if any of these cells can have for the betterment of life for our patients.

[00:17:35] **Dr. GG deFiebre:** Thank you so much.