Q Study Updates

Expanded Inclusion Criteria and What's Next

You can watch the video of this podcast at: youtu.be/zs6w6dtqr3U

[00:00:00] **Krissy Dilger:** Hello and welcome to the SRNA "Ask the Expert" podcast series, Research Edition. I'm Krissy Dilger with the Siegel Rare Neuroimmune Association. This episode is titled, Q Study Updates: Expanded Inclusion Criteria and What's Next."

[00:00:20] I am pleased to be joined by Dr. Benjamin Greenberg. Dr. Greenberg is a Professor in the Department of Neurology at UT Southwestern Medical Center in Dallas, Texas. He serves as Director of the Transverse Myelitis and Neuromyelitis Optica Program and the Pediatric Demyelinating Disease Program at Children's Medical Center. You can find his full bio in the podcast description.

[00:00:45] SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org. This episode is made possible in part by the generous support of Amgen, Alexion AstraZeneca Rare Disease, Genentech, and UCB.

[00:01:09] Thank you for joining me today, Dr. Greenberg. We're here to talk about the latest updates in the study to investigate the safety of the transplantation of human glial restricted progenitor cells into subjects with transverse myelitis, which is more commonly called the Q study. This topic is one that many in our community are interested to hear more about, so we are excited to have you here to provide an update. To start us off, can you provide an overview of what the Q study is and a background of how it came to be?

[00:01:43] **Dr. Benjamin Greenberg:** Absolutely. So, thanks for hosting today. Happy to be with you and the whole community. The study that we're talking about today actually goes back easily twenty years. Ever since I was first involved with what was the Transverse Myelitis Association, now the Siegel Rare Neuroimmune Association or SRNA, there were conversations about how we can use stem cells to repair the nervous system and bring back function to those who have lost it.

[00:02:14] And the work that was done for decades really focused on trying to show what type of cells could be introduced into a nervous system that could repair, and then jumping through the very appropriate regulatory hoops to make sure that they would be safe to transplant—as safe as we can know before actually doing a study.

[00:02:35] And so, through lots of work from a lot of folks, ultimately a cell line was developed that was felt to be safe and hopefully effective for individuals. But then we had to figure out a way to get them into a spinal cord. It turns out if you inject stem cells into a vein, they don't go into the spinal cord in a way to lead to repair.

[00:02:56] And in fact, even if you inject them into spinal fluid, we don't see a lot of invasion into the spinal cord for repair. I get questions all the time, and I know you do as well from the community, about traveling

to stem cell therapy programs around the world to get stem cell infusions. I hate to tell everybody, but when we infuse cells into your vein, ninety-nine percent of them get cleared out by the liver and the lungs, and they never make it to the spinal cord.

[00:03:24] And so a whole separate part of the effort was to figure out a way to actually get cells into the spinal cord, and it's not as easy as it sounds. If I were to put a needle—which we've done by hand—into a spinal cord, in this case of an animal, with every heartbeat, the spinal cord moves and the needle tip would move.

[00:03:46] And so a surgeon out of Emory, Nick Boulis, developed a device that could stay attached to the spine during the infusions and could actually move with those movements so that the needle stayed in exactly the right spot while we were slowly infusing cells in. So, there were a lot of efforts that went into getting this study off the ground.

[00:04:08] The moment we were ready to launch, COVID hit, and we all remember those days. We're behind where we want to be in terms of the advancement of stem cells relative to myelitis, but we're finally there. We're investigating these glial restricted precursor cells, meaning when they're introduced into the nervous system, they will only differentiate into one of two cells, and one of those cells is the one that's responsible for making new myelin—the new coating around axons—which will hopefully lead to improved function.

[00:04:43] **Krissy Dilger:** It's exciting research. I'm eager to learn more. Can you talk about the study setup?

[00:04:53] **Dr. Benjamin Greenberg:** So, this is a phase one study. So as a reminder to your audience, there are four phases of drug development: phase one, two, three, and four. Phase one is designed to prove the safety and feasibility of doing an intervention or a treatment.

[00:05:08] Phase two is to gather broader safety data and to start to get a sense around both efficacy and maybe different doses that we want to study. And then phase three is what's called a registrational trial, where you can actually prove in a large number of patients efficacy and safety, asking the FDA—or in Europe, the EMA—for regulatory approval to market the therapy for a given indication.

[00:05:33] And then phase four, which we often don't talk about, is after a treatment is on the market, how do we track it over time to show post-marketing that it is both safe and effective? So, this study is a phase one study. The setup is to prove the safety and feasibility of the cells, the surgery, and the immunosuppression regimen we use after the cells are transplanted.

[00:05:57] This is like an organ transplant. So instead of getting a new liver, people are getting new stem cells into the spinal cord, so there's an immunosuppression regimen to prevent rejection of those cells. And so, the study is designed and structured to assess the safety of each of those components individually. And of course, we're always watching for an efficacy signal, but the setup primarily is one to confirm that it is safe to do this procedure and then proceed with larger and larger populations.

[00:06:29] **Krissy Dilger:** Great. So how will the results for the Q study be measured?

[00:06:36] **Dr. Benjamin Greenberg:** So, we break it into two broad camps first, and that's safety and efficacy. And then the primary goal is safety. Within safety, the results are measured relative to the surgical procedure, the cells, and the immunosuppression. So, let's talk about each. When we're looking at the safety of a study, we record everything that happens to our patients—good, bad, or indifferent.

[00:06:59] And it actually doesn't matter if it's related directly to the study or not. Let me give you an example. Let's say somebody has signed the consent form for the study. They haven't even gone to surgery yet, and they have a car accident, and they come into my clinic and report back pain. I have to report back pain as part of the study, even though they haven't done anything.

[00:07:22] Now, I will note that it's unrelated to the study, but every adverse event—everything that happens to a patient—is recorded, and then we, with a safety monitoring board and the FDA, look for patterns or anything that should be a concern relative to the study. So, we are recording the adverse events and serious adverse events relative to the surgery.

[00:07:42] Did anything happen in the perioperative period that put our patients at risk? For the cells, we do serial MRIs to make sure that the cells are not turning into cysts or tumors, which has happened with stem cell transplants before, but thankfully, not so far with these cells. And then we're recording the adverse events or serious adverse events that are happening with the immunosuppression regimen.

[00:08:04] Do people have side effects? Do people get infections? Do people get liver issues? And we record all of those relative to that safety. Then there are results relative to efficacy. We're looking for changes relative to motor function, sensation, and bowel/bladder function, and we're also doing electrical studies to see if we have improved conduction of a signal through the spinal cord.

[00:08:29] **Krissy Dilger:** Great. So, you mentioned this stage of the study is currently in phase one. Where are you at in terms of participation? Who can participate in this study? How many people have already participated, and has this criterion changed since the study was first launched?

[00:08:51] **Dr. Benjamin Greenberg:** Yeah, great question. Because as you allude to, we have evolved the criteria over time. So, when we first sat down with our colleagues at the FDA when designing this phase one safety study, the priority was to ensure that the surgical procedure and the cells would not induce additional harm to patients. And there was a concern that either or both might cause harm.

[00:09:13] So the original inclusion/exclusion criteria for the study indicated that individuals had to be more than a year out from their event, less than 10 years from their event, and had to have been stable over the preceding several months so they weren't continuing to get better on their own—so they had to have plateaued in terms of their recovery—and they had to be unable to walk.

[00:09:35] And the idea was if the surgery or the cells were to induce harm, we would not be causing a loss of important function if people were already unable to walk. With the original safety data that came from the first few patients in the study—the first four patients in the study—the FDA agreed to open up the criteria now to individuals who can ambulate with assistance over restricted distances.

[00:10:04] If somebody with a walker can take steps, they're now able to enroll in the study, whereas in the past, they were not able to. We have a couple of different cohorts moving simultaneously: those who are not able to walk, and a few spots for those who are. And we are still recruiting into the original cohort of nine patients.

[00:10:30] We are looking for an additional four patients and welcome anyone who's interested in learning more. We partner with the SRNA in terms of making people aware of this, and also, like all clinical trials in the United States, we are listed on clinicaltrials.gov, where anybody can go and search for any open studies. It has our contact information, websites, and emails, so people can reach out to us and learn more about the study.

[00:11:07] **Krissy Dilger:** That's very exciting to hear about the new inclusion criteria and the expansion of that part of the research. As you mentioned, we at SRNA are able to point anyone who is interested in the right direction if you're interested in learning more and participating in the study.

[00:11:28] We will also include a link in the bio for anyone who wants to learn more and contact the folks who are conducting the study. So how are participants chosen? I know they go through a vetting system on your end. What does that entail?

[00:11:50] **Dr. Benjamin Greenberg:** Yeah, again, it's a great question because often people who haven't had experience with clinical trials may question what this process looks like. So, anybody can contact us for information about the study, and we are happy to provide a list of what are called inclusion/exclusion criteria. These are things like you have to be at least eighteen years of age. You have to be competent to sign a consent form.

[00:12:15] You have to have been diagnosed with myelitis more than a year ago and less than ten years ago. So, there's a list. And then there are exclusions. So, if you have certain active neurologic conditions, you can't enroll in this study. So, we provide that information to anyone who requests it, and if somebody indicates that they are interested and they believe they would be a fit for the study, we do what's called an informed consent, and that triggers formal screening.

[00:12:44] And in screening, we do a deep dive into an individual's medical records and their history. We do our own lab testing and imaging, and we make sure that a person does not have any preexisting conditions that would exclude them from the study. So, after a person undergoes those screening tests, we meet together to review the results and indicate whether or not they meet the criteria to move forward.

[00:13:10] And that's the process for being, quote, "chosen." It's really a matter of you expressing interest—or the individual expressing interest—and showing they meet the inclusion/exclusion criteria, and then they get to continue on with the intervention. One of the things that happens during screening is we do a lot of testing, and we've had individual potential participants come to us with an interest in the study only to discover something about their medical history that they were not aware of that excluded them from the trial.

[00:13:46] And so anyone who's interested, I always remind them at the beginning that we're thankful for the interest. We'll do everything we can if they want to pursue the study to help them pursue it. But there are times when we find something that makes the individual non-appropriate for the study.

[00:14:02] **Krissy Dilger:** Got it. Thank you. And is there any location constraint as to participation? Are you welcoming patients from only Texas, or across the country, or internationally?

[00:14:15] **Dr. Benjamin Greenberg:** Yeah, sometimes Texas considers itself an international site, but we'll leave that for another podcast. We welcome any individual. One of the inclusion criteria is that the individual has to be able to travel to our site on a specified timeline in order to have in-person visits, and the individual, around the time of the surgery, has to commit to and be able to be in town for at least a couple of weeks around the time of the surgery.

[00:14:46] So if somebody flies in from out of state, they have to have support. They have to have somebody who can function as a caretaker, particularly for after the surgical piece, and be willing to stay nearby, whether it's with friends or at a hotel in a safe environment where they can make it back and forth from our clinic for monitoring purposes. But we don't restrict to individuals who live within a certain distance of our center.

[00:15:13] **Krissy Dilger:** Great. Thank you. The million-dollar question: is there anything you can tell us about the results up to this point?

[00:15:24] **Dr. Benjamin Greenberg:** I'm sorry, you were breaking up there. I missed that question. We'll have to go to the next... No, I'm just kidding. We get asked that question all the time, and we are sharing some of the results so far, but not all because the study is not complete yet. So, what I can share is we have had to date no safety signals which would cause a pause, stop, or reconsideration of the trial protocol.

[00:15:51] And in fact, our safety signal in a small—albeit small—number of individuals has been consistently good, such that we were able to expand the inclusion/exclusion criteria now to individuals who had some ambulation abilities. And so, on the safety side, we have been sharing that information at national conferences and in real time. On the efficacy side, we're not yet sharing results.

[00:16:16] And the reason is it's early, and we do not want to over-advertise or overstate what we're seeing in terms of the efficacy. Obviously, what we all want—what I want for all of my patients who've had significant harm from myelitis—is to do a treatment and get them back to full, unrestricted activities, running up and down the street.

[00:16:40] That has not happened. So let me be very clear. Whatever efficacy signal we're seeing is not from a superhuman feats perspective. I will say that we are cautiously encouraged by some of the early signals we see, but that's the extent of what we're saying relative to the efficacy side.

[00:17:01] **Krissy Dilger:** Great. Thank you for that update, and I am looking forward to hearing the results as the study progresses. Hopefully, we can have some good news. What is the next step after this phase of the study is completed?

[00:17:19] **Dr. Benjamin Greenberg:** Yeah, so that's a really good question. There are actually several different ways this could go. Usually, what happens when you do a Phase 1 study that's successful is you move into Phase 2, and you do a larger number of patients looking for safety and efficacy. And that very well may be the next step here. But there are discussions around also expanded patient populations that we may consider.

[00:17:46] Currently, we're restricted to individuals who have had idiopathic myelitis, meaning those who don't have an underlying secondary condition like multiple sclerosis, neuromyelitis optica, or anti-MOG associated disorder. So, the people who are enrolled in this trial have not had any of those secondary conditions.

[00:18:06] Additionally, at this point, the cells are being injected into the spinal cord. I would love to start injecting the optic nerve to see if we could bring back vision. And once this study completes and we have the complete data set—and actually even before it completes—there are conversations going on around what should be the next step.

[00:18:29] Should there be a parallel Phase 1 in an expanded patient population, or should we go to a Phase 2 in idiopathic myelitis but be inclusive of individuals with broader diagnoses? That's going to be a discussion both with the community and with the FDA. Once they have the opportunity to look at the entire study data, they will help guide us in terms of next steps while we pursue proving both efficacy and safety for this therapy.

[00:18:59] **Krissy Dilger:** Great. Looking forward to it. We do have a few questions that were submitted to us by Julie Lafalar and our friends at The MOG Project. First—I think you got into this a little bit in our last question—but what are the future implications for the Q cell study outside of just transverse myelitis patients?

[00:19:22] Would people with MOG antibody disease, neuromyelitis optica, acute disseminated encephalomyelitis, or acute flaccid myelitis be eligible for this type of therapy if proven successful during the trial?

[00:19:36] **Dr. Benjamin Greenberg:** Yeah, spectacular question. So, let's put the protocol in context for everyone. When this protocol was written, we had no FDA-approved therapies for neuromyelitis optica. When this protocol was written, we were just sorting out what anti-MOG associated disorder was. And so, when this went for initial FDA consideration, individuals with underlying secondary autoimmune conditions were excluded for a very specific reason.

[00:20:04] And I want to take a moment to explain this so that people don't feel like we're being exclusionary just to have a certain patient population and not others. One of the major safety concerns relative to transplanting stem cells into the nervous system is that the cells could induce an immune response leading to inflammation.

[00:20:25] So let's say I put these cells into the spinal cord, and you get a new myelitis. That would be a problem. So, for individuals who have a secondary autoimmune condition like MOGAD or neuromyelitis optica, if I were to do the transplant and they had new inflammation, was it the cells eliciting the immune response, or was it just a relapse of their underlying disease?

[00:20:49] I wouldn't be able to tell the difference. Since we didn't have reliable ways of putting patients into deep remission with NMO or MOGAD, the decision was made to restrict the individuals where if there was new inflammation, we would know it's coming because the cells elicited it. We would be able to see a safety signal.

[00:21:11] The exclusion of individuals with NMO and MOGAD was done purely for research purposes to make sure we could interpret the safety. Now we live in a world where our ability to suppress relapses in NMO, for example, is so exceptionally good that we're going to be able to piece together the safety signal in a much better way.

[00:21:30] And so this is going to be an area of active conversation with the FDA in terms of what do those trials look like and who do we enroll, but my expectation is we will be designing trials for these cells to be inclusive of individuals with anti-MOG associated disorder, neuromyelitis optica, and the like.

[00:21:49] One of the patient groups you mentioned on that list, however, was individuals with acute flaccid myelitis, and I get this question quite a bit. And the answer is: it depends. So, in about fifty percent of acute flaccid myelitis patients—and that's a rough number—the damage is only to the lower motor neuron, the neuron that goes from the spinal cord to the muscle. And in those individuals, these cells will not help. They are not going to regrow those neurons from the spinal cord to the muscle.

[00:22:24] In about half of acute flaccid myelitis patients, there is damage to both the wires that are going from the spinal cord to the muscle and those descending myelinated fibers going from the brain down the spinal cord. Those individuals may garner partial benefit from these types of cells. It's going to be on a case-by-case basis.

[00:22:47] **Krissy Dilger:** I know that this is a topic, as I mentioned before, that our community is very excited about. It makes sense that it would hopefully be able to expand beyond transverse myelitis. We know that when an inflammatory attack takes place in transverse myelitis, there is usually damage caused to the spinal cord. Does this type of damage differ between the different demyelinating disorders like MOGAD and NMO?

[00:23:22] **Dr. Benjamin Greenberg:** It does. That's part of the challenge. These cells are meant to remake myelin. The ideal recipient would be somebody whose deficits are purely due to the lack of myelin, but the

axons—the actual portion of the neuron that's going from point A to point B—are still intact and haven't been transected in any way.

[00:23:50] It's 2026, we have Claude, we have ChatGPT, we have incredible technologies in the world, and yet I still, on an MRI, cannot tell the difference between a person who has cut axons or just a loss of myelin. We do not have that reliable technology. And so, when we look at individuals with MOGAD, neuromyelitis optica, or idiopathic myelitis, the mechanism of injury is different in each of those populations, and the relative amount of damage to the underlying axons likely differs.

[00:24:22] If I had to line everybody up from the least amount of axon damage to the most amount of axon damage, I would actually say individuals with anti-MOG associated disorder are more likely than others to have limited axonal damage. Whereas in neuromyelitis optica, there can be a lot of necrosis and a lot of damage to the cord.

[00:24:43] So I do think the type of damage is different, but there is enough variability in individual patients who are part of that larger community that we really have to take it down to the single patient. So just because a person's diagnosis is idiopathic myelitis, MOGAD, or NMO, it doesn't in and of itself determine whether or not they'll be a great recipient. Are there patterns? Yes. But we still have to take it down to the individual.

[00:25:13] **Krissy Dilger:** Very interesting, and that totally makes sense to me. So, thank you for explaining it in those terms. I know you already mentioned the optic nerve as a potential way to expand this therapy outside of just the spinal cord. Would that also be possible potentially for the brainstem?

[00:25:37] **Dr. Benjamin Greenberg:** Yes. One of the things that—if we go back to the beginning of our conversation—it's about getting the cells into the site. So, for the spinal cord, it wasn't just a matter of developing the cells. There had to be development of a surgical technique to get the cells into the cord.

[00:25:53] The optic nerve needs its own technique, and it's actually very tricky to access the optic nerve without doing a major cranial surgery. And so, one of the biggest barriers to that optic nerve study is the surgical approach, and there are people around the country working on that right now. Once we get to the brain and the brain stem, it's the same issue.

[00:26:13] Trying to find a surgical approach is tricky, particularly when we talk about the brain stem, which neurosurgeons are taught from a very young age to do their best to avoid the brain stem because it has such a critical function for all life and life functions that it tends to be unforgiving relative to damage. The stakes during the surgery for a brain stem infusion are going to be very different than even the spinal cord, frankly.

[00:26:40] And so I think if I had to guess the sequence of events—and I could be wrong here—I think we're going to see the optic nerve come before the brain stem for sure, and even before the brain. When we're talking about the brain, the issue is the area that we may have to cover. If somebody has a focal abnormality, one that's of a certain size, it might be quite amenable to these injections. If we have to do the entire brain, both sides, that's a much bigger surgical approach and a lot more cells. And so, I think it remains to be seen how much real estate we can cover relative to brain repair.

[00:27:15] **Krissy Dilger:** Very interesting. I look forward to the future when we can maybe explore these ideas and expand further. That seems like a lot is in the pipeline. Yeah. You touched on this previously, but I wanted to expand it beyond just the TM patients. If this study shows that Q cell therapy can be successful, what can patients expect as an outcome? How much functionality can patients potentially regain? And I guess in terms of the optic nerve, if that were to be the case, would that restore vision potentially?

[00:27:55] **Dr. Benjamin Greenberg:** Yeah, it's a great question that I don't know the answer to yet. I'll tell you what I think is the determinant. I think the determinant is going to be the timing of therapy, the number of cells transferred, and the type of damage the person has.

[00:28:12] Unlike the spinal cord, where I have no ability whatsoever to determine how much damage to axons versus myelin has occurred, for the optic nerve, we have tests that can be used to try and sort through those things. I'm actually, in many respects, more optimistic that we're going to be able to stratify patients relative to their optic nerve pattern of damage and predict responders versus non-responders than I am able to at the spinal cord level.

[00:28:38] I think in the most extreme situation in terms of seeing benefit, I think individuals with prior optic neuritis, for some who have significant vision loss, could get back very functional vision. At least that's my hope, and I think there are reasons to believe that to be true.

[00:28:56] **Krissy Dilger:** Very exciting. I have reached the end of the questions so far, but I did want to leave you with the floor in case you have any final thoughts you want to add before we wrap up.

[00:29:08] **Dr. Benjamin Greenberg:** No, just to express my thanks to you, the SRNA, and the greater patient community. This has been a collaborative journey. This is not something that was done in a vacuum here at UT Southwestern by myself or my team. This has been something that really has taken a village, not just to get it launched, but to really be thoughtful about how we do it and what we do.

[00:29:28] I'm grateful for all the support and collaboration. For anyone listening who is interested, please feel free to go to clinicaltrials.gov or the SRNA and reach out if you have questions. We're happy to answer them.

[00:29:45] **Krissy Dilger:** Great. Thank you so much, Dr. Greenberg.

[00:29:47] **Dr. Benjamin Greenberg:** Thank you. Appreciate it.

[00:29:52] **Krissy Dilger:** Thank you to our "Ask the Expert" sponsors: Amgen, Alexion, AstraZeneca Rare Disease, Genentech, and UCB. Amgen 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. Amgen believes science and compassion must work together to transform lives.

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