CAR-T in NMOSD

You can watch the video of this podcast at: youtu.be/HIAlJI97NQ0

[00:00:00] **Announcer:** "ABCs of NMOSD" is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder, or NMOSD, a rare neuroimmune disorder that preferentially causes inflammation in the optic nerves and spinal cord. "ABCs of NMOSD" is hosted by SRNA, the Siegel Rare Neuroimmune Association. 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.

[00:00:51] **Dr. GG deFiebre:** Hello and welcome. My name is GG deFiebre and I moderated this episode, "CAR-T in NMOSD." I was pleased to be joined by Dr. Michael Levy and Dr. Benjamin Greenberg.

[00:01:03] Dr. Michael Levy is the Research Director of the Division of Neuroimmunology and Neuroinfectious Disease at Mass General, and Dr. Benjamin Greenberg is a Professor and the Cain Denius Scholar in Mobility Disorders in the Department of Neurology at UT Southwestern Medical Center. You can view their full bios in the podcast description.

[00:01:23] This episode is made possible in part by the generous support of Amgen; Alexion, AstraZeneca Rare Disease; Genentech; and UCB.

[00:01:32] Thank you both so much for joining me today to talk about CAR-T for NMOSD. So, for people who have never heard of CAR-T, what is this treatment, in plain language? Dr. Greenberg, do you want to start?

[00:01:48] **Dr. Benjamin M. Greenberg:** Sure. If people have heard about CAR-T, it has probably been in the context of treatment for cancers, because that's where it was first studied and there are approved therapies, and it's actually the basis of a Nobel Prize.

[00:02:01] The concept is that we can take a person's own immune system and program it to target something specific in the body. So, in the setting of cancer, we could take out a person's own immune system, insert a gene to train that immune system to go find cancer cells, and get rid of the cancer in people's bodies.

[00:02:21] And for certain cancers, this has literally been lifesaving. There were patients who had failed multiple different chemotherapy regimens who got their immune system programmed. The immune system was given back to them, and they literally walked out of the hospital cancer-free. Truly miraculous results in some situations.

[00:02:38] The idea was, can these immune cells be trained genetically to go after the part of the immune system responsible for autoimmune disease? And the first major work on this was in the field of lupus, where patients who had refractory lupus had part of their immune system removed, genetically engineered to take out a different part of the immune system, B cells, and allow an immune system to regrow without the confusion.

[00:03:06] So it's an immune reset, if you will. And the early data out of lupus was very impressive. And so, it's now moved beyond lupus to a multitude of different autoimmune disorders to try and remodel or reset an immune system by using a person's own cells to go in and root out the confused cells.

[00:03:26] **Dr. GG deFiebre:** Would you say this is more like, you said, resetting the immune system? This isn't like calming the immune system down. It is more like a reset? How would you describe it in those terms?

[00:03:39] **Dr. Benjamin M. Greenberg:** Yeah. I mean, if we put it into context of some of the drugs we use currently, lots of patients are on drugs that kill B cells, and we leave them on them chronically to keep those cells away. And as long as they're on the drug, most people stay in remission. What we're doing with CAR-T is going a step beyond what those drugs can do. We're not just taking out 90% of the B cells. Matter of fact, we're getting to pretty close to 100%, because a person's immune cells can crawl throughout the body and get to places that our drugs don't get to as well.

[00:04:13] And then we let a bone marrow grow a new immune system that hopefully forgot the old. And so instead of just suppressing an immune system chronically, we try to reset or remodel, take it all the way down to the studs. You gut the infrastructure of the house all the way down to the foundation, and then you build up a new house, hopefully without the bad wiring that was plaguing the first house.

[00:04:37] **Dr. GG deFiebre:** And so, what role do aquaporin-4 antibodies play in NMOSD? And so why are researchers studying CAR-T for aquaporin-4 positive NMOSD specifically? Dr. Levy?

[00:04:51] **Dr. Michael Levy:** Yeah, I think a lot of our patients have been on rituximab or Uplizna [inebilizumab], and they're familiar with the role of B cells, and B cells that can produce plasmablasts that make aquaporin-4 antibodies. These are all, these immune components are all involved in the pathology of NMOSD. And removing them, removing B cells specifically, is helpful.

[00:05:17] We've been using rituximab since 2005 for NMOSD and inebilizumab since, I think, 2020. These treatments are remarkably helpful. What CAR-T offers is an even greater depletion, as Dr. Greenberg said. It doesn't just remove some of the B cells, but really what we're trying to do here is remove every single B cell in the body so that any B cell that had previously been tuned to attack aquaporin-4 is now going to be removed.

[00:05:44] And when the bone marrow repopulates those B cells later on, hopefully they won't even know what aquaporin-4 is, and there won't be any immunity to it. And we'll be able to track that over time, because if there's no signal back to the bone marrow to make aquaporin-4 antibodies, then the antibody levels should be dropping over time, and we'll see if that happens in these patients.

[00:06:05] **Dr. GG deFiebre:** And so, could this someday reduce the need for ongoing treatment, or is that still something that's unknown, Dr. Greenberg?

[00:06:14] **Dr. Benjamin M. Greenberg:** That's the whole goal. So, the idea here is can we develop a one-time profound intervention so that patients do not need to remain on lifelong therapy? Or even, I take it one step below that, could we offer somebody a therapy that would provide them many years of remission without being on a chronic therapy? Let's say somebody was interested in starting a family, and they wanted a five-year or eight-year window where they wouldn't have to be immunosuppressed chronically.

[00:06:45] Even if it's not lifelong, I could make the argument that prolonged durable remissions could be very beneficial to a large number of our patients without taking that chronic risk. The goal is to get that long-term remission from a single intervention.

[00:07:01] **Dr. GG deFiebre:** And so, you're both working on a study on CAR-T and NMOSD. To talk a little bit about that specific study, do you mind giving kind of like a brief overview of it, and then what a patient would actually go through if they received this therapy, Dr. Levy?

[00:07:20] **Dr. Michael Levy:** This is an autologous CAR-T study. It's a little bit complicated, but the way it works is a patient would come in, and we would screen them and make sure that they're eligible. They have to be either on ravulizumab or on Enspryng, because we want to protect them while the immune system resets. We don't want them relapsing in the middle of all of this.

[00:07:40] If they qualify, we would take out, through a plasma exchange procedure, a bunch of their T cells and send them to the Bristol Myers Squibb laboratory, where the T cells would get re-engineered to attack B cells. Then they would ship them back to us, and we would infuse those T cells into the patient.

[00:08:01] Before they get the T cells, they have to get a little bit of chemo to make room. It's like if the glass is already full and the immune system can't tolerate any more T cells, you kind of have to make a little room in the glass to pour in a little bit more T cells. So, we use a little low-dose chemotherapy to do that.

[00:08:19] Then we add the T cells into the patient, and then the T cells just go. And over the next 30 to 60 days or so, those T cells are going to wipe out every B cell in the body. That's really what we're intending to do. They'll be in the hospital for the first eight days or so, and then after that, they have to stay in the area for about 30 days, then they get to go home.

[00:08:41] But we'll be tracking their aquaporin-4 antibody levels. We'll do MRIs if they have symptoms. We'll be keeping a very, very close eye on them, at least for the next two years, and then even keeping track of them for the 13 years after that, for a total of 15 years. But again, what we're really trying to do is reset the immune response, and if, just if, their antibody levels go to zero, we might be able to take them off of their Enspryng or their Ultomiris.

[00:09:10] **Dr. GG deFiebre:** And so, you mentioned there are two drugs there that they have to be on. Is the study not available for people who are on the other FDA-approved medications or something like rituximab for their NMOSD, Dr. Levy?

[00:09:25] **Dr. Michael Levy:** They have to be on one of those two because if they're on rituximab or Uplizna, that's the same target as what the T cells are targeting. We don't want to try to overlap those. We want their B cells to be there, so they have to be off of rituximab or off of Uplizna for enough time. They could have been on it in the past; that's okay. But as long as their B cells are back, they're detectable in their bloodstream, and they're on one of the other two meds, then they're eligible.

[00:09:53] **Dr. Benjamin M. Greenberg:** And if I can add, one of the reasons, as Mike is alluding to, is the therapy actually... The CAR-T relies on B cells being present in order for the T cells to expand. So, there's data to show that if somebody's had their B cells wiped out, the therapy just isn't going to be effective because it needs that stimulus for the cells to multiply. So, it's not just that we're worried about overlapping therapies; it's that the CAR-T won't work if somebody doesn't have any B cells to stimulate the CAR-T.

[00:10:26] **Dr. GG deFiebre:** And this is also, I don't know if we mentioned, is this only for people who are aquaporin-4 positive, or is it also seronegative?

[00:10:34] **Dr. Michael Levy:** This one is for aquaporin-4 positive only. There are discussions for future trials and with other CAR-T products to include seronegative.

[00:10:44] **Dr. GG deFiebre:** Okay. And then, Dr. Levy, you also mentioned, so they come in and do kind of the plasma to take out the cells. What is the kind of timeframe between when that happens until when the T cells are ready to be infused back into the patient?

[00:11:01] **Dr. Michael Levy:** These companies are really trying to reduce the time that they need for engineering. I think for this study, it's somewhere between two and three weeks. Dr. Greenberg, you can correct me if I'm wrong. That's how long it takes after the plasma exchange to re-engineer the cells, and then they would come back in for their infusions.

[00:11:20] **Dr. GG deFiebre:** And so, the study also involves medications given before or around the CAR-T treatment, and so I'm assuming this is what's used to kind of even things out... So, like cyclophosphamide, for example. So why are these medications part of the process? What is their role?

[00:11:40] **Dr. Michael Levy:** These drugs have to be part of the process of preparing the immune system to receive the CAR-T cells. If there are too many immune cells around and then you give them CAR-Ts, your own immune system's going to destroy them and say, "We don't need all these extra T cells. We'll remove them all."

[00:11:58] But if you give them just a little bit of this low-dose chemo, it's not even at a dose intended to really... Most patients won't even feel it. They're not going to get nauseated, lose their hair, or anything like that. It's really just enough to make room in the immune system for the CAR-Ts to be accepted.

[00:12:14] **Dr. Benjamin M. Greenberg:** Yeah. And people can think about in the immune system there are, within your immune system, it's got a gas and brakes, and so that what's called conditioning regimen—those drugs that people get beforehand—gets rid of some of the brakes. And by killing off some of the cells in your body, whatever gas is left—and we call it cytokines—the recipient of that gas is going to be the CAR-T cells.

[00:12:39] So that space that Mike is talking about is both physical and biologic space to allow those cells to expand, because the more they expand, we think the better people will do, because they can go to more parts of the body and hunt and kill all the cells we're trying to get rid of.

[00:13:01] **Dr. GG deFiebre:** And so, because this is an early-stage trial, safety is obviously a major focus. What are the main risks patients should understand if they want to participate in this study or one that comes up in the future that's similar, Dr. Greenberg?

[00:13:18] **Dr. Benjamin M. Greenberg:** The risks are going to fall into a couple of categories. So first, there's just a background risk to the conditioning regimen we use, the immunosuppression we use, and it's occurring on top of whatever drug the patient's on, whether it's ravulizumab or satralizumab. And so, there's risk of infections and risks of adverse events due to that conditioning regimen.

[00:13:41] Then there are some unique risks to CAR-T therapy that are well known in the literature, and it has to do with that expansion of the cells and two syndromes that we have seen. One is what's called a cytokine release syndrome. That's the gas I was referring to. If you get an excessive amount of it, it can make people feel sick, and it can have impacts on how they function. It can give people fevers, muscle aches, can affect sometimes the kidneys, and if it's profound enough, it can affect brain function.

[00:14:14] There's something called ICANS where we can have people who get inflammation in the brain presenting as confusion or a seizure. This has been seen in individuals treated with CAR-T for cancer. We

are trying to understand, are patients with neuromyelitis optica at a higher, similar, or lower risk for those types of events? And so, we'll be watching for any issues prior to the actual CAR-T cells being administered because of the conditioning regimen, and then in that week and two weeks after the administration, do we see the expected rate or a higher or lower rate of those cytokine release syndromes and ICANS?

[00:14:57] The last set of risks has to do with success, and that sounds a little strange, but this is a conversation Mike and I now have had for years. The goal is to see can we get rid of the autoimmunity? So, I'm going to be thrilled if we start seeing patients who are antibody-positive who become antibody-negative on this therapy. That's what we consider a huge win, a huge success.

[00:15:23] And let's say patients come off their background drug, off their Ultomiris, off their satralizumab, because now they don't have the antibody. What we want to make sure of is we follow people closely, and if the immune system swings back a year or two years in the future and the antibody comes back, is there a risk of a relapse at that point? So even in success, part of our safety evaluation is can we adequately monitor patients for the durability of that success?

[00:15:53] **Dr. Michael Levy:** I'll just add one thing about the safety concerns that Dr. Greenberg brought up: the cytokine release syndrome and the brain inflammation. In the oncology world, these are fairly common side effects, but in autoimmune trials like lupus and in multiple sclerosis, the risk has been a lot lower. It's probably because these conditions don't have as many B cells to kill off as in the oncology world, where they may have a B-cell lymphoma. The overall rate is just a lot lower, but we're still going to be monitoring for those.

[00:16:29] **Dr. GG deFiebre:** And so obviously we talked about that this study is for adults with aquaporin-4-positive NMOSD who meet specific criteria, including those who are clinically stable on certain NMOSD medications. So, why are early trials like this usually so specific about who can participate, Dr. Levy?

[00:16:50] **Dr. Michael Levy:** There are many different autoimmune conditions that are being tested with CAR-T therapy. We thought NMO would be particularly amenable given its response to B-cell therapies with rituximab and Uplizna. Given how long our patients have to be on these medications, we thought NMO would be a really good choice.

[00:17:12] And when you apply for FDA approval, you have to apply with the disease in mind. A lot of other trials are doing what are called basket studies, so they're going to include NMO and multiple sclerosis and stiff person syndrome and other conditions in a big basket, and that's another way to do this. But I think this study will enroll the largest number of NMO patients and is really dedicated to NMO.

[00:17:37] **Dr. GG deFiebre:** And then, yeah, Dr. Greenberg, in terms of... Is there a reason why people have to be stable on medication? Or what goes into why that is required for the study?

[00:17:50] **Dr. Benjamin M. Greenberg:** So, when designing a study, there are a lot of goals that have to be balanced. A study is done to create new knowledge or understanding of a condition or a treatment, and a study as a priority has to protect the welfare of participants. But ethically, we also need the study's results to be interpretable for as much of the population as possible. And we have an obligation to design a study in such a way so that we avoid negative studies for the wrong reason.

[00:18:31] Let me give an example. So, let's say in the setting of a CAR-T therapy, we were enrolling people who had just been diagnosed and were having multiple relapses, were not in control, and six weeks after dosing

the CAR-T, one of the participants had a new optic neuritis. In a small study, we might blame the CAR-T for the optic neuritis, when in actuality, it was the underlying condition, and the CAR-T hadn't even kicked in yet.

[00:18:58] And so, some of the requirements we put into a study are there to protect the safety of the patient—and that's the majority of them. But some of the requirements are there to make sure that if a negative or positive event occurs, we can ascribe it appropriately to the intervention.

[00:19:16] So if somebody who's been stable for two years enters the trial and all of a sudden, eight weeks into CAR-T, has an optic neuritis, Dr. Levy and I are going to look at it and say, "Hmm, that's a little concerning." Whereas if we were in the first three months, I wouldn't know how to interpret that. Same thing relative to the antibody status. One of the things that we've known about patients with aquaporin-4 antibody-positive NMO is once they're positive, they tend to stay positive. It's unusual for someone to spontaneously revert to seronegative.

[00:19:52] And so likewise, if somebody's been positive for years and then all of a sudden, six months after this CAR-T they go to negative, it's going to be a safe assumption. Whereas again, if we enroll different types of patients, for example, anti-MOG antibody-positive patients who can revert to seronegative on their own, it's a different study design to interpret the results there.

[00:20:11] So that's why the inclusion and exclusion are so specific. Some of them are there for safety, and some of them are there to create a population where we can actually trust our interpretation of the results in a meaningful way.

[00:20:23] **Dr. GG deFiebre:** And so, the study is recruiting at UT Southwestern and Mass General. I don't know if it's anywhere else. So, if someone's interested in participating, what would the first steps be? Do they have to be patients with you all? Can they come from anywhere? And how many people are you recruiting for this study?

[00:20:43] **Dr. Benjamin M. Greenberg:** I think we're going to put Dr. Levy's home address at the bottom of any screen, and all you have to do is go knock on the door three times and say, "CAR-T, CAR-T, CAR-T." But if you can't do that, once... So, we are in the stages of getting launched. We have our IND from the FDA and are in various stages with the IRB. Luckily, through a website, clinicaltrials.gov, there'll be contact information both for Dr. Levy's team and for our team.

[00:21:12] So, depending on where somebody is geographically, if it's easier to make it to Boston—which I would personally prefer in July and August compared to Dallas, but in January and February, we're winning—you can reach out to either center. You do not have to be a current patient of either of ours. I think I speak for Dr. Levy as well.

[00:21:33] This is open to anyone who meets inclusion/exclusion criteria who can also make it to the follow-up. So, if you are not geographically close to one of the centers, we are going to look you in the eye and ask you, "Can you look at the schedule of events? Look at the follow-up. Can you make it here in order to do the follow-ups?" This is a small study.

[00:21:53] Ten individuals are going to receive the therapy, and this is a partnership. There's no other way to say it. This is voluntary; people can leave the study anytime they want, like any study. But with something like this, a Phase 1 in a rare disease, one of the criteria is that Dr. Levy or myself feel as though the individual can make it to the follow-up. So, if there is a barrier that cannot be overcome, that's a challenge. But if people can make it, we welcome everybody.

[00:22:27] **Dr. GG deFiebre:** And is it 10 patients total or 10 patients per site?

[00:22:31] **Dr. Benjamin M. Greenberg:** 10 total.

[00:22:33] **Dr. GG deFiebre:** Okay. Anything else, Dr. Levy, you want to add about the specifics of the study?

[00:22:37] **Dr. Michael Levy:** Yeah, patients are welcome to come to my house and knock on the door, but they're going to encounter my kids and if they want to stay with us, they'll have to sleep in a kid's room, which is not going to be comfortable.

[00:22:48] **Dr. GG deFiebre:** There you go. So, we definitely encourage people to go to clinicaltrials.gov. And we'll put a link as well if anyone wants to check out the potential options there. To kind of close out, I have a few questions just about the future. So, we talked about the potential for aquaporin-4 antibodies to become undetectable. Do we know if that automatically means that the person is protected from future relapses, or is that kind of the question? This is obviously a safety study, but ultimately is that the kind of question as well as we move forward?

[00:23:23] **Dr. Michael Levy:** This would be the first time that we're going to use aquaporin-4 antibody titer as an outcome measure. We have no idea, except that we've been following patients for 20-plus years, and as Dr. Greenberg was saying, most people do not serorevert to negative. I've had a few maybe starting off low.

[00:23:39] I've even had a patient start off really high and then come low, but it's rare to see them serorevert. So, if... There was a study in China where 7 out of 10 patients did serorevert, which was very interesting to us. If we see those kind of numbers in a study where we're not expecting anybody to serorevert, then that would be pretty impressive.

[00:24:03] **Dr. GG deFiebre:** And then people with NMOSD are more likely to have other autoimmune conditions. Do we think that this potentially might help those, or is that only for kind of B-cell related conditions? Or kind of any thoughts around that as well?

[00:24:19] **Dr. Michael Levy:** Yeah, I think we specifically excluded people with concurrent autoimmune diseases. We just don't want to be confused about what's causing what. This is a very early phase study. We're just trying to make things interpretable for this trial. And then in the future, as you're saying, if people do have lupus and it's clear that CAR-Ts also help lupus, then it could be considered like a twofer.

[00:24:43] **Dr. GG deFiebre:** Okay. And so obviously, SRNA supports people with other rare neuroimmune conditions other than NMOSD. So, why might this research interest the broader rare neuroimmune disorder community, even if it's right now being studied specifically in NMOSD? Dr. Greenberg?

[00:25:02] **Dr. Benjamin M. Greenberg:** Yeah, it's a great question, and it gets to the notion of anyone who has an autoimmune disorder that puts them at risk for recurrent events over time, who either are on or are considering long-term, lifelong immunotherapy. So, for some of our patients with anti-MOG associated disorder, for individuals with neuromyelitis optica, this would represent an option, if it works, for a targeted, durable, but one-time intervention.

[00:25:33] And so, the lessons we learn here, we are absolutely committed to applying to individuals with other rare neuroimmune disorders. There's a large interest in the community to do that. One of the reasons we thought starting with aquaporin-4 patients would be helpful as a starting point are the features we've discussed.

[00:25:56] They tend not to revert to negative on their own. There are highly effective therapies that are keeping people stable. If somebody does have an NMO event after the CAR-T, it'll be pretty easy to say, "Geez, there's something about CAR-T that might trigger an event." And so, as a population to be a beacon for other populations, our partners with neuromyelitis optica represent, in many ways, an ideal group to ask and then answer this question.

[00:26:28] **Dr. GG deFiebre:** Yeah. And are there any plans to potentially expand this to some of the conditions you had mentioned that have relapses, like MOG antibody disease? Are there kind of plans to potentially expand beyond NMOSD to MOGAD, Dr. Levy?

[00:26:43] **Dr. Michael Levy:** Yeah, there are other trials. And I know that MOG is among those, including myasthenia gravis and other autoimmune diseases. And I think, as sort of next steps, one of the exciting things is can we re-engineer T cells not just to attack B cells, but other cells—specifically the bad B cells or any other cell that we want to eradicate?

[00:27:10] And so that's coming in the future as well. It's just that right now, we have the engineering process down really well for B cells, so we could do those studies. But as you're saying, as we learn more, we'll be able to apply future knowledge to other diseases.

[00:27:26] **Dr. GG deFiebre:** And so, this wouldn't be something potentially that could be helpful for people with monophasic conditions during, for example, the acute phase when they're first diagnosed or anything like that? Or is it really only for these kind of antibody-mediated diseases that do have the relapsing disease course?

[00:27:47] **Dr. Michael Levy:** Yeah, that acute treatment, that's outside of the scope of this trial. Maybe in the future there... The nice thing, you know, when people invented rituximab, it was one of the first biologicals that used a protein to accomplish a task, which was to deplete B cells. This is one of the first times we're using immune cells to accomplish a task.

[00:28:08] So now there are a multitude of different antibodies being used in medicine, and I'm sure in the future we'll have a multitude of different cellular therapies for different indications. We're just at the beginning.

[00:28:20] **Dr. GG deFiebre:** Okay. Any other final thoughts before we close out today?

[00:28:26] **Dr. Benjamin M. Greenberg:** No, I think we covered a lot of ground here. Dr. Levy and I are very excited to get this trial off the ground. It's been more than a year in the making, and we look forward to being open for business for everyone, and the partnership with SRNA, and the partnership with patients who are willing to kind of navigate this uncharted territory with us.

[00:28:48] **Dr. GG deFiebre:** Great. All right. Thank you so much.

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