What is Tolerization in NMO and MOGAD?

You can view this presentation at: youtu.be/SUw_zh3HFPA

[00:00:00] **Krissy Dilger:** We are excited to have Dr. Michael Yeaman from UCLA join us to give this talk on tolerization in NMOSD and MOGAD. We have been anticipating this talk for a while now, and we get a lot of questions about this topic. Thank you so much, Dr. Yeaman, and over to you.

[00:00:27] **Dr. Michael Yeaman:** Krissy, thank you very much. I really appreciate all the great work you and the team at SRNA do. Let me just share my screen here, and we'll dive right into this topic, which is what is tolerization in NMOSD and MOGAD. As always, we like to include disclosures, and you can see here are my disclosures that you can consider. What I'd really like to do today is review several topics and hopefully help learn together about tolerization and how it might be something in the future that could help patients with these conditions.

[00:01:13] First, some of the pros and cons of immune modifying therapy as it is established today. A little bit about the miracle and the mystery of immune tolerance, and it's a fascinating area. We'll talk about that together. The overarching objective of tolerization is to restore immune tolerance when it has been broken.

[00:01:34] We'll talk a little bit about NMO and MOGAD science, but in a way that you probably already understand, and we can think about it in terms of tolerization models. Then I'll talk a little bit about the very exciting progress going on in the field right now regarding tolerization clinical trials.

[00:01:52] And then just a couple of words about the prospectus. What do we see in the crystal ball in the future? Let's start with pros and cons of autoimmune therapy. We know that over the last few years there has been an amazing advancement in going from zero approved therapies to four approved therapies in the United States and another one in Japan.

[00:02:17] So there are approved therapies, and they are great first steps to help prevent relapses in NMO and perhaps MOGAD as well. There are no approved therapies for MOGAD as yet, but there are a lot of clinical trials in progress. These are great first steps, and we like to think of them as stepping stones to what might even be improvements.

[00:02:42] So there's room for improvement. And when I say that, what I mean by “room for improvement” is most immune modifying therapies used in autoimmune disease come with some baggage. For example, infusion or injection reactions and allergies can occur, and sometimes those can be worrisome. There is an increased rate and/or severity of serious infections with many of these agents and some more than others.

[00:03:11] There can be, it’s a remote chance, but there can be increased risk of cancer due to impaired immune surveillance. When you tamp down the immune system with broad immune modifying therapies, one of the things that can pop up is certain types of cancers. Of course, there are logistics issues of when to administer a drug, the infusion or injection logistics and timing, et cetera, sometimes lab checkups and monitoring.

[00:03:44] And of course, cost burdens of therapies and insurance coverage, et cetera.
Those are all burdens that have to be dealt with. So great first steps that there are approved therapies, and there's room for improvement. One thing just to point out is what I call a vicious cycle of immune modifying therapy.

[00:04:04] Let's say that a person is diagnosed with an autoimmune disease, and they are treated for that autoimmune disease, which largely means immune suppression. It turns out that there are millions of infections, and I'm just using data from the US, that are due to pathogens that can be drug resistant, antibiotic resistant, and there can be a lot of deaths associated with that.

[00:04:32] I'm not trying to scare anybody because most of these infections are not going to be that serious, but immune modifying therapies increase the risk of infections. Infections in turn are interesting because roughly one in six cancers are due to a preventable infection. So now there's a little bit of a link between infection and cancer. Of course we go back to cancer.

[00:04:58] and some of the treatments for cancers, especially the most recent checkpoint inhibitors, actually cause autoimmune disease. So, you see there's this vicious cycle, and the whole idea of tolerization is to break this cycle so that we don't have this continuation of causes and issues that lead to worse outcomes.

[00:05:23] With that as a backdrop, let's think about immune tolerance and what we know and what we don't know about immune tolerance, because it is a fascinating area. What is immune tolerance? In a nutshell, it's how your immune system protects you against internal, meaning self, and external, meaning microbial or environmental, threats

[00:05:49] such as cancer or infection without harming any of your normal molecules, cells or tissues that make up your body. Put another way: it's the system of checks and balances that prevents the immune system from hurting you while it also defends you against things that might hurt you. Immune tolerance is a dynamic process.

[00:06:14] You can see here, for example, endogenous tolerance might mean protecting regarding what's within you and exogenous tolerance, meaning protecting from things that are in the environment: infective agents, antigens, chemicals, et cetera. And on this side is all about health. We need the immune system to do all of this while allowing normal growth and development, tissue repair and remodeling, wounds, growth, et cetera.

[00:06:48] We also want the immune system to allow a healthy microbiome. Most of your gut has organisms, bacteria and others, in it that are very good for you. We don't want the immune system to get rid of those.

Also, the immune system needs to be able to handle a pregnancy, for example, in women, because that's a pretty foreign object, if you will, and we want the immune system to be able to look the other way for nine months while the fetus develops and everybody's healthy. At the same time, we need the immune system to prevent, detect, and destroy neoplasias and cancers that could be very harmful.

[00:07:30] We also need the immune system to detect pathogens that could cause infection and other environmental hazards, if you will. And of course, we want the immune system to avoid causing miscarriage or rejecting grafts, et cetera. So, we want the immune system to do all these things in a way that is pretty amazing.

[00:07:50] It's got to act as a gyroscope to know which things to defend and which things to leave alone. One of the most interesting aspects of tolerance has to do with a type of cell called a T cell or a thymocyte. These are lymphocytes that are made in the bone marrow. Through the first stage of what is a very fascinating process,

[00:08:17] these cells find their way to the thymus, which is a gland that wraps around your airway just above your heart. It's one of two primary immune organs. One is the thymus, one is the spleen. The thymus is composed of different sections: the outermost capsule, the next layer in is the cortex, and the deepest part is the medulla.

[00:08:43] These three sections you might think of as three different classrooms because T cells must undergo three exams in order to pass and graduate and become helpful in the immune system. I'll just keep this part very high level because it is quite complex, but basically T cells in training, if you will, are exposed to antigens including autoantigens, self-antigens, by two different kinds of cells.

[00:09:19] The first are called antigen-presenting cells. These are professional antigen-presenting cells. They move around the body looking for things that might be foreign. They'll process those, display them, and then show them to these naïve or training T cells. Another type of antigen-presenting cell is a B cell.

[00:09:42] These are normally thought about as cells that make antibodies, but they can also present antigen to a T cell. These two cells can cooperate to present antigens to the naive or training T cells. The three exams that I mentioned really have to do with what does this T cell do on presentation of these antigens?

[00:10:04] If it recognizes these as self, that is, proteins that are normally supposed to be in the body, they are deleted and that happens in one of a few different ways. They can be deleted by energy, they can be de be deleted by programmed cell death, et cetera, but they are typically removed. We don't want autoreactive T cells in the body.

[00:10:30] We do want the good T cells to be able to move on to become what we call effector T cells to protect against microbial pathogens, to protect against cancers. And we also want a subset of graduate T cells to be able to put the brakes on the immune system, and those are called regulatory T cells. Once T cells graduate from the thymus, they move into lymph nodes.

[00:10:58] You can see lymph nodes are distributed all through the body and they're little headquarters, if you will. They look like little nodules, and that's where T cells go to reside largely. They can, of course, go to other tissues, but what they do in the lymph node is they wait for antigen-presenting cells to bring them pieces of antigens that the antigen-presenting cells have detected in the periphery of the body.

[00:11:25] It's here where the antigen-presenting cells present the antigen to the T cells that are now trained, if you will. Once activated, these T cells will leave and go to the source of infection or cancer or wound healing and do their job there to defend against harm. That's the central tolerance mechanisms.

[00:11:48] When the T cells get out into the periphery and they're exposed to antigens by either antigen-presenting cells or B cells; there's a separate type of checks and balances. The first are the immune checkpoints and the second is what is called lack-of-secondary signal. These are now T cells that can further be censored by programmed cell death or energy, which is the inability to respond. They're cleared from the immune system.

[00:12:21] Again, we don't want autoreactive T cells to be in the body and causing harm, but we do want cells that can act against microbes and cancers. If there are autoreactive T cells that do emerge, for example, there are regulatory T cells that can prevent them from acting. Those are two different types called Tregs or TR1s.

[00:12:47] These largely block any rare autoreactive T cells that get out, that escape the extensive process of checks and balances in the thymus. What causes loss of immune tolerance? There's a lot of uncertainty in this area, and it's an area of a lot of intensive research.

[00:13:13] One possibility is abnormal antigens due to genetic or epigenetic, or what is called ectopic expression. This is where an antigen is expressed in the wrong place or at the wrong time. So, this is an antigen or the epitope of an antigen problem. Another possible cause is when the antigens are presented inappropriately. That is, the antigen-presenting cell in something called the MHC complex

[00:13:46] presents the antigen to a T cell in a way that makes the T cell think it is foreign or abnormal. We also know that there can be dysfunctional T cell or B cell receptors and signaling that can lead to loss of immune tolerance. It's pretty clear that certain types of infectious disease and or environmental antigens can cause loss of tolerance through something called antigenic mimicry.

[00:14:16] That is a process that is being studied very actively now. Interestingly, pregnancy, cancer, graft transplantation can all introduce something called neoantigens, which are antigens that sort of look like normal antigens, but they're actually different.

[00:14:36] They're either new or they're slightly different. That can trigger a loss of immune tolerance. With that in mind, let's think about NMO and MOGAD and how they really can be excellent models for tolerization. I'm just going to go briefly over the science of NMO and MOGAD here, so that everybody's on the same page in terms of how we might restore immune tolerance.

[00:15:00] As mentioned, this is an antigen-presenting cell that has encountered an astrocyte or an oligodendrocyte. The astrocyte expresses aquaporin-4 antigen, the oligodendrocyte expresses MOG antigen, and the antigen-presenting cell has processed these antigens and is now displaying them on its surface.

[00:15:23] This is antigen presentation, and it presents the antigen to what in this case is an autoreactive T cell [ARTc]. And it does this in context of three different signals, two of which we call the molecular handshake. That is how the antigen is presented and the second is how the T cell responds to that presentation.

[00:15:48] And the third signal is a context of cytokines that kind of amplifies the first and second signal interpretations. The point is that the autoreactive T cell is now activated by this presentation. It undergoes something called polarization, which means it turns into a T cell that makes certain kinds of cytokines like IL-17 [Interleukin-17] as an autoreactive T cell.

[00:16:17] This autoreactive T cell, now fully activated, can further interact with B cells. If the B cell also is autoreactive to aquaporin-4 or MOG protein for instance, through a primary or secondary signal, several things can happen. First, this B cell can be activated by the T cell to make antibody, and antibody then moves through the blood-brain barrier into the central nervous system.

[00:16:48] It binds to aquaporin-4 on astrocytes or MOG protein on oligodendrocytes, and that causes something called classical complement fixation. A big component of complement fixation is the generation of C5a from C5 complement protein. C5a then leaves the blood-brain barrier and moves out into the periphery where it calls in cells that are activated by this autoreactive T cell.

[00:17:22] Using cytokines, the T cell recruits neutrophils and eosinophils and also macrophages, which then move into the central nervous system and move to the site of complement fixation. And they just cause inflammation and damage to further kill and demyelinate astrocytes and oligodendrocytes and even neurons. So that's the basic process of the disease of NMO or MOGAD.

[00:17:53] Let's talk about what we're trying to do about this. We call it Project Cureageous. You've heard us talk about this where we're really focused on tolerization cures. Over the last 10 or 11 years the Guthy Jackson Charitable Foundation has held three summits for NMO tolerization.

[00:18:17] A fourth summit is coming up in March of 2026. Here are some of the people that attended the third summit, and many of the faces you'll recognize as leaders in the field of NMO and MOGAD. Let's really come to the heart of the discussion today. What is immune tolerization? Immune tolerization is the restoration of immune tolerance after tolerance has been broken, like we've talked about earlier today.

[00:18:48] We want this to be specific to certain antigens in a way that it could arrest and even potentially reverse autoimmune pathogenesis. Immune tolerization is a targeted and dynamic process that reprograms tolerance to specific antigens, specific autoantigens in particular, while sparing host defense against infection and cancer. In theory, tolerization should not come with the risks of infection or cancer in the long run.

[00:19:25] We are interested in curative immune tolerization to reset the cellular and molecular mechanisms of immune tolerance in a way that encodes what we call tolerogenic immune memory. If successful, this would be tolerance that lasts for the rest of your life without needing lifelong therapy. It's a bold, ambitious goal.

[00:19:50] We're hopeful it can be achieved. Why NMO and MOGAD as models of tolerization? First of all, we know they're autoantigens, they're dominant autoantigens, aquaporin-4 in NMO, MOG protein in MOGAD. Much of the autoimmune immunology, pathogenesis, and targets in terms of cells and molecules are established.

[00:20:15] We know a lot about those. A lot of science has gone into this over the last nearly 20 years, and we feel pretty comfortable. We know what's happening in the disease. There are also defined clinical phenotypes. There's an emerging relapse harmonization so that different people around the world will diagnose relapses in the same way, so we'll know whether a relapse has occurred or not.

[00:20:45] We know that [individuals] without appropriate treatment and even some individuals on approved therapies will continue to relapse, and that will cause chronic inflammation, more demyelination, more disability. There's also an increasing prevalence. I'll mention this briefly, but over the last nearly 20 years there has been a 50-fold increase in what we understand to be the prevalence of NMO. For example 18 years ago, the prevalence was thought to be one in a million. Today it's five in 100,000. That is a 50-fold increase. Now, it's not that there's been a 50-fold increase in the number of people with NMO, for example. It's that we

recognize it at a 50-fold greater prevalence. The approved drugs are great, as I mentioned, [with] many lives improved and saved, and at the same time, room for improvement.

[00:21:47] Relapses can occur and there can be lifelong effects and what we call AEs or adverse events such as infections, cancers, infusion reactions, et cetera. And lastly, there is a strong clinical, industry and patient interest in synergy in a way that work together to tolerize for cures. Let's briefly talk about the difference between desensitization and tolerization.

[00:22:14] Desensitization has been around for a long time. Most of us think about this as allergy shots, for example. Desensitization is used when the issue is exogenous stimuli, usually allergy, pollens, et cetera. Whereas in tolerization, it's endogenous stimuli, usually internal self-antigens as occur in autoimmunity.

[00:22:43] How do we desensitize? Typically, by escalating dosing of the allergen stimuli, by actually giving people a little tiny bit of the thing that causes the allergy. Whereas in tolerization, we want a reprogramming of the contextual processing and response to the autoantigen, and that's the T cell and antigen-presenting cell method that I just went through a moment ago. The goal in desensitization is to increase the allergen reaction threshold, whereas in tolerization, it's to induce autoantigen-specific non-response. We want the immune system to ignore autoantigens. The bias is that desensitization skews

[00:23:38] T cells to a non-reactive profile and it skews B cells away from something called IgE [Immunoglobulin-E], which can cause histamine release and strong allergic responses, to an IgG [Immunoglobulin-G] profile. Whereas [in] tolerization, we want the skew to be to T regulatory and T exhausted cells rather than T effector cells. In desensitization we don't really see a big change in autoreactive T-cell or autoreactive B-cell profiles, but in tolerization, we want those autoreactive cells to be deleted, that is, censored, or undergo inactivation energy.

[00:24:25] One of the key differences between desensitization and tolerization is that desensitization is temporary. It only lasts as long as you administer the stimuli, whereas the theory for tolerization is that it is durable. If we can induce tolerogenic memory, it should last a very long time.

[00:24:49] How might tolerance be restored? If the mechanisms by which tolerance is lost are correct, we should be able to address those very directly, for instance, to correct gene mutations or epigenetic modifications that lead to altered antigens that are perceived as autoreactive. We can also potentially correct protein structures and production in a way that involves mRNA and certain types of refolding of proteins.

[00:25:23] We can program the immune system to undergo something called deviation, which is where it reprioritizes which responses are most important to make the harmful responses less of a priority. We can delete autoreactive antigen-presenting cells, T cells, or B cells. This is called censoring. Finally, we can actually achieve hopefully the highest of all of the goals in tolerization, and that is to reprogram the immune system cells, so they no longer see autoreactive antigens as being foreign or abnormal.

[00:26:04] It's a live-and-let-live peace treaty between immune cells and autoantigens. Let's think about the timing of tolerization, when that might be best. Of course, we would want to not allow the disease to go so far as causing disability. In fact, we might not even want to allow it to manifest at all.

[00:26:29] As we go back to a prodrome, we might say, "Hey, how far in advance can we predict a person might have a risk of NMO or MOGAD?" for example. And all of this relates to far upstream causes of tolerance loss. You can see there are stages of predisposing factors, factors that might sensitize to autoimmunity, the actual onset of pathogenesis itself, and then ultimately, the clinical impact.

[00:27:02] This can be caused by endogenous, that is within, or exogenous, without/from the environment, kinds of factors. The point that I really want to make here is at present, the current treatment targets are out here. They are used when a patient already typically has disease and most often some degree of disability.

[00:27:27] What we really want to do is turn that whole thing into a different paradigm where we tolerize before a large degree of pathogenesis has occurred and prevent any clinical disability. One way to think about this is exemplified in this model because one of the questions that often comes up is: "Do we need placebo controls?"

[00:27:52] or "Will patients who are in tolerization clinical trials undergo a period where they're untreated?" The answer to those questions is "no". Let's just think about it for a second because it makes a lot of sense. In fact, the approved therapies really enable the tolerization trials that might be very helpful going forward.

[00:28:13] You can imagine patients who enter a tolerization clinical trial are randomized into different groups. One group is standard of care. That means an approved therapy, a therapy that's standard of care. Meanwhile, the other group, for example, in this model might get standard of care plus an experimental tolerizing therapy.

[00:28:37] As the trial begins, both groups of patients move forward. Now, what we really are going to look for in the tolerization arm is biomarkers that indicate tolerogenesis is occurring. When we see that, what we can do is start tapering the standard of care, slowly removing the standard of care, but keeping the experimental tolerizing regimen on board so that at no time is a patient left untreated.

[00:29:11] The study continues. We look for various biomarkers. If there's a safety issue, if there's a relapse, of course there's a rapid response. But you can see this is very carefully done. It's done in a way that neither the patients nor the doctors know which regimen is being delivered. But a group of doctors who are very carefully trained and are called the board, the Safety Advisory Board, for a given trial are always looking over the data to make sure everything's going safely.

[00:29:52] Then we get to the end, and we analyze the data and see, did the experimental tolerization regimen work as well, not as well, or even better than standard of care? This is an example of the way a tolerization clinical trial might work.

[00:30:12] The key end points in a tolerization trial are shown here. First, safety. Safety is always first in a clinical trial. We want any acute responses like allergy or anaphylaxis or cytokine storm or infection, et cetera, to be acceptable. There's never going to be a perfect drug that has no side effects, but we want them to be acceptable and non-serious.

[00:30:39] We also want them to cause no new disease symptoms, no new relapses, and no new comorbidities. So, safety first. Of course, we want one of the endpoints to be efficacy. Did the therapy work as well, not as well, or better than the approved therapies, for example? Did they have additional benefits? Were there biomarkers that emerged that tell us how these tolerization regimens were working?

[00:31:08] Did they improve clinical symptoms? Did they reduce disabilities? Et cetera. We're also very interested in how long the tolerization effect might last. Is there a need to give a few small doses? Is there a possibility that a one-and-done mode might be possible? We don't know that yet.

[00:31:30] We need to test these things in clinical trials. I mentioned biomarkers, but these could be molecular, cellular, imaging, clinical, cognition, EDSS disability [Expanded Disability Status Scale], et cetera, that might

correlate with the mechanisms of tolerogenesis. Let's briefly wrap it up with some clinical trial updates. I'll just use this figure to give you a sense that there are many different categories of tolerizing therapies now in play in various stages of research and development.

[00:32:06] You've probably heard about CAR T [Chimeric Antigen Receptor T-Cell] therapies. I'll talk more about this in just a second. These are cells that come from the patient. They're engineered typically from the same patient to seek and destroy the autoreactive T cells. That's called autologous CAR T. There's also T cells that might come from people who are not the patient.

[00:32:31] That's called allogenic or non-autologous CAR T therapy. That's also being pursued for CAR T therapy. These are cells that actually might go in and kill the harmful autoreactive T cells or B cells. There are antigen-specific tolerogens. These are little pieces of peptides or synthetic molecules that are decoys for autoantigen epitopes, pieces of auto antigens that might instead of causing inflammatory response, turn down the inflammatory response, cause tolerogenesis.

[00:33:09] Likewise, antigen specific tolerizing nanoparticles. This is where pieces of the autoantigen are within these little nanoparticles, which have been composed of material that turns the immune system down to these specific pieces of protein.

[00:33:29] Dendritic cell vaccines, which are basically antigen-presenting cells that are fed autoantigens, but at the same time taught to learn that these autoantigens are friend, not foe, and then they return to the patient so that they can go in and help reeducate the immune system to those autoantigens. There are some interesting new types of therapies called checkpoint

[00:33:55] inducers. Remember, in cancer, treatments are checkpoint inhibitors. The opposite is true in autoimmune disease. We want to induce checkpoints, but only to very specific autoantigens so that we spare post-defense to infection and cancer. There's an interesting process called HLA-G tolerogenesis that uses the same immunologic method for tolerance to a fetus but turns it to a therapy that tolerates an autoimmune disease.

[00:34:30] Very interesting work going on there. Basically, inverse nucleic acid vaccines are ways to flip the script, if you will, on conventional vaccines. Conventional vaccines turn the immune system up to a specific antigen. Inverse vaccines turn the immune system down to a specific autoantigen.

[00:34:52] There's a lot of really interesting and promising work going on in that area. There are also vaccines that go into the body and activate something called programmed cell death by using DNA that reaches autoreactive T cells and B cells and makes them self-destruct. Very interesting technology. There's also what we call endogenous tolerogenesis, for example, that use tolerance mechanisms already in our body, for example, that is why red blood cells have a degree of tolerance, and we may be able to link that mechanism to autoantigens and have the immune system see those autoantigens as being necessary to tolerate.

[00:35:43] A most extreme version of tolerization would be autologous hematopoietic stem cell transplant or bone marrow transplant. Yes, that is a type of tolerance. It is the most extreme type, but you're basically replacing the person's immune system, and that's been shown to have promise at least in early types of clinical trials.

[00:36:07] Sometimes the long-term effects are not so good, but that's still being studied. Let's briefly review some of these methods and how they exactly work in patients who might have NMO or MOGAD. With CAR or CAAR T cell therapy, healthy T cells are removed from the patient.

[00:36:30] They are transfected in the laboratory, meaning a little virus is used to put DNA into those cells and that DNA encodes for a chimeric receptor to an abnormal T cell. Now this T cell is armed to go look for autoreactive T cells or autoreactive B cells and kill them. It's using the patient's own T cell that's been engineered now to go kill the bad T cells or B cells.

[00:37:09] Similarly one might take a dendritic cell from a patient, feed it autoantigens that are causative of a disease, for example, aquaporin-4 or MOG protein, in the presence of a steroid and an anti-inflammatory cytokine, for example, TGF-beta. Now this dendritic cell is tolerogenic. It induces tolerance to these autoantigens.

[00:37:38] When you put it back in the body, it causes T cells to become regulatory and B cells to become regulatory, that is, anti-inflammatory to these autoantigens in particular. There are also these lipid nanoparticles that I mentioned. They contain little pieces of the autoantigen.

[00:37:58] They're processed by the dendritic cell so now the dendritic cell is tolerizing and again, they go in and teach T cells and B cells to accept, to tolerate the autoantigens that might be otherwise causing disease. Inverse vaccines--I mentioned this--they take mRNA or DNA, so either type of nucleic acid.

[00:38:21] They have a special kind of program in them that causes the immune system, like a dendritic cell, rather than to become inflammatory as a result of exposure, they become anti-inflammatory. Now we have inside of the body here, these tolerizing dendritic cells that make T cells and B cells become regulatory, not effector, not inflammatory. Finally, an example of a programmed cell death, dendritic cell tolerizing vaccine, for example.

[00:38:59] The particle delivers the autoantigen target gene, but also genes that induce programmed cell death so that when the cells that recognize the autoantigen are detected by this particle, these cells are then programmed to undergo self-destruction. It's a way to get rid of or delete autoreactive dendritic cells or autoreactive T cells, ultimately, and B cells, and induce regulatory anti-inflammatory T cells to that specific antigen.

[00:39:40] Finally, a quick update on the many exciting things that are going on in tolerization clinical trials and preclinical discovery research. Just 10, 15 years ago, the question was, is tolerance even possible in NMOSD, so NMO and MOGAD? I'll just remind you that early studies in bone marrow transplant showed promise, although there were issues and maybe not long-term success.

[00:40:11] But there were examples of patients who benefited acutely. Many different types of tolerizing therapies have now been attempted. For example, a dendritic cell vaccine in patients anti-MOG mRNA vaccine in various experimental models in the laboratory. There's a type of nanoparticle used in a different autoimmune disease that involves a type of autoimmune reaction to gastrointestinal tissue called celiac disease that has shown promise. There have also been certain types of B cell tolerizing therapies in NMOSD, and most recently a tolerizing lipid nanoparticle mRNA in MOGAD in an experimental study, not in patients.

[00:41:16] At the same time, there are many different CAR T therapies that have been forwarding in patients. There was a very exciting study in 2022 showing that a CAR T cell therapy directed at a B cell antigen in lupus was quite efficacious. Similarly, there was an anti-B cell maturation antigen CAR-T cell therapy in NMOSD, which also demonstrated remarkable efficacy.

[00:41:50] It was performed in China. There have been recently FDA fast track approvals to bispecific CAR-T cell therapies in MS. Also, certain companies have had CAR-T cell therapies against CD19 B cell antigen that also have a checkpoint induction on them that is offering sort of a two-pronged approach to induce tolerization.

Most recently there are types of CAR-T cell therapies called universal, bispecific, or even trispecific CAR-T cell therapies that act on multiple targets to induce antigen-specific tolerance.

[00:42:34] Just a few years ago the question was, is it even possible to tolerize an NMOSD? And I would say today, not only possible, but very probable. I think the idea is it's coming and we just need to keep pushing forward. With that, I'll just leave you with a couple of take-home messages.

[00:42:56] Immune tolerance loss is caused by mechanisms that are not fully clear. They likely involve genetic, epigenetic, infectious, peri-neoplastic, meaning early transformative stages on the road to cancers, and probably other factors that we don't fully understand. Second, immune tolerance does not suppress the immune system overall, like many immune modifying therapies, rather it resets tolerance only to specific autoantigens.

[00:43:32] That's the whole key here. Of course, the goal of curative tolerization is to permanently restore immune tolerance via antigen-specific regulatory memory, meaning anti-inflammatory memory to the autoantigens that would otherwise cause disease.

[00:43:50] Finally, acceleration of tolerization technologies and clinical trials has been very remarkable in the last few years, with many showing promising early success in NMO and MOGAD. Let me stop here and I'll turn it back over to Krissy. Actually, Krissy, let me keep the screen up and maybe I could ask you to just offer some questions that you might think patients and families and others might be interested in learning more about.

[00:44:27] **Krissy Dilger:** Thank you so much for that amazing presentation. I learned so much, and I'm sure our community did as well. We do get a lot of questions and I'm sure you do as well. Here are a few from our community. To start off, what patients may be most suitable to consider tolerization?

[00:44:52] **Dr. Michael Yeaman:** This is a question we hear a lot and I'm sure you do too. Obviously, patients who are doing very well on an approved therapy, for example, might not be the first to consider tolerization.

[00:45:05] Of course, if those patients have a lot of infections or serious infections or have other reasons that approved therapies may not be working best for them, [they] might consider tolerization. And certainly, patients who are not well controlled by any therapy, that continue to have relapses, those would be primary candidates for tolerization clinical trials.

[00:45:34] **Krissy Dilger:** Great, thank you. Do tolerizing regimens have risks or require hospitalization?

[00:45:44] **Dr. Michael Yeaman:** Another great question. We like to say there's no such thing as a perfect drug, a perfect treatment. Whenever you're altering the immune system, that has inherent risks, most of which in tolerization are modest or moderate. I will say that CAR-T cell therapies do for the most part require patients to go to the hospital for about 10 days. That's purely out of caution to make sure that if any adverse event were to occur, it would be handled in that environment.

[00:46:26] Most CAR-T cell therapies require something called immune induction, which is a treatment that makes the immune system vulnerable to the new T cells that they're going to receive. That induction therapy does pretty significantly suppress the immune system for a very short time, about a week. There are typically infections that occur in that week's time. Sometimes there can be cytokine storms that can cause immune overreaction. All of that is well controlled in the hospital, but it does mean patients typically are hospitalized for CAR-T cell therapy. Most of the other therapies I've talked about don't have that type of risk.

[00:47:13] Most of them might be used as you would a normal vaccine or a normal type of infusion or injection type of therapy, but those are things that have to be tested in clinical trials.

[00:47:28] **Krissy Dilger:** Gotcha. Do tolerization clinical trials require placebo control groups?

[00:47:37] **Dr. Michael Yeaman:** This is a really important question. Remember, before there were approved therapies, there were placebo control groups as required by the FDA to ensure that a treatment was actually working and it wasn't just the placebo effect. Now that there are approved therapies, it is hard to imagine that there would be placebo groups in a tolerization trial.

[00:48:05] As I mentioned, one of the sort of attractive models for clinical trials of tolerization therapies is that every patient is on standard of care to begin the trial, that is, every patient is on treatment. It might be an approved therapy for NMO. It might be a therapy that's emerging for MOGAD, but one arm on top of the standard of care gets the tolerization therapy, and it's only when the tolerization therapy shows evidence of inducing tolerance that the standard of care is tapered. So, a patient is never not receiving therapy. It's a really important point, Krissy. Good question.

[00:48:51] **Krissy Dilger:** I'm sure that eases a lot of people's fears as well. Is tolerization ongoing treatments or a permanent cure?

[00:49:02] **Dr. Michael Yeaman:** This is a fascinating point. We would like to think that a tolerization therapy will be so effective that it will induce lifelong tolerance to that autoantigen. In that case, it could be a permanent cure. You know how sometimes we can cause the immune system to remember for the rest of our live, sometimes we have vaccines that we only need once, and they last the rest of our lives.

[00:49:34] This is the same thing, but opposite. The perfect, if you will, tolerization therapy would induce tolerance to an autoantigen without the need for any further action. It's probably more likely, at least in the near term, that tolerization therapies might need an occasional boost, let's say every couple of years, just another dose of something that's not CAR-T which is more of a B cell or T cell depletion strategy, but rather some kind of a reminder, an additional dose of a nanoparticle or an additional dose of an inverse vaccine that just reminds the immune system to ignore aquaporin-4, ignore MOG protein, it's all going to be fine.

[00:50:32] **Krissy Dilger:** Finally, how can patients and families learn more about tolerization?

[00:50:39] **Dr. Michael Yeaman:** I think the fact that SRNA is producing this talk, I think the other excellent patient organizations, Guthy Jackson and many of the others are really the sources for the kind of information to keep up with the rapidly changing field of tolerization. I really appreciate SRNA being one of the leaders in educating patients, in getting the word out. I would keep the word going, stay tuned and really learn as much as you can about tolerization from organizations. There's more and more information in the published literature as well. I think there's just a lot to see that's coming very quickly, and I think there's going to be some pretty big breakthroughs in the near future.

[00:51:38] **Krissy Dilger:** Thank you so much, Dr. Yeaman, and I really hope that in a year or two or very soon, we can have you back again and you can share all the amazing updates that have come on tolerization. It does seem like a lot is happening, and hopefully it only leads to more good things. We appreciate your time.

[00:52:00] **Dr. Michael Yeaman:** Thanks so much. I really appreciate it. Thanks again for SRNA and all the good work you're doing.