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Altering the Course of Type 1 Diabetes: Prevention Trials

Announcer:
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Dr. Atkinson:
All right. Continuing on in our series about autoantibody screening to identify risk for type 1 diabetes, one of the main questions is, is there really a need? What benefit would there be to performing screening for type 1 diabetes? For many years, people were resistant to this notion because we did not have a way or means to actually impact the clinical course of the disease in terms of individuals who were at risk for the disease, with respect to delaying it. “Times are a changing,” as the old phrase goes. And it's my pleasure today to introduce Dr. Stephen Gitelman, who is Professor of Pediatrics at the University of California, San Francisco, and an internationally known expert in terms of intervention trials to alter the course of type 1 diabetes development, either in prevention of the disease or preservation of those individuals diagnosed with the disease recently. Steve.

Dr. Gitelman:
Thank you for that introduction, Mark, and it's a pleasure to be part of this symposium. So, you've heard about this roadmap, this risk for progression to type 1 diabetes. And so with this paradigm in mind, we can start to think about how and where we might come in with interventions to alter the course of diabetes. And most of our focus, of course, in this discussion is, can we screen and predict and then prevent the progression to clinical diabetes or Stage 3? There's also a lot of other research going on in the world of type 1 diabetes now at Stage 3 to try and preserve the beta-cell mass that is present shortly after the time of diagnosis and extend the remission or honeymoon phase. And of course, for people with longer-standing diabetes, there's very interesting efforts in replacing the missing beta cells. But for today's discussion, we're going to talk about this notion of prevention.

As you step back and think about how we might select for such studies, there are a number of criteria that start to come to mind that we use in devising these things. One is we'd like to have an agent that has been shown to be beneficial in an animal model of type 1 diabetes. They're not too many of these to choose from. One that we do a lot of work in is a model called the non-obese diabetic mouse (NOD). It's also very helpful to have had prior studies in humans, either Stage 3 or in at-risk subjects in looking at drugs that might be effective in related autoimmune diseases or transplant. We'd also like the mechanism of action of a drug to be tested, to be plausible, in the type 1 setting.

And in the studies conducted over many prior years, we think that one arm of the immune system that's very important in the pathogenesis of type 1 diabetes are T cells. So that's one focus. There's certainly many other elements that we can consider targeting that are related to this autoimmune process. Of course, we wanted to have a reasonable safety feature and not put people at inordinate risk. And in the ideal world, we'd like to have what we call “tolerance.” And that's the notion that you could give a drug for a limited period of time, fundamentally reset the immune response, and then withdraw that therapy so that you wouldn't need chronic ongoing

therapy. So that's our wish list. One thing that you might also have imagined in looking at that roadmap to progression to diabetes is what stage we would come in and offer a therapy.

We could come in very early in the process, say someone who just has genetic risk but no evidence yet of autoimmunity. So that's really high up on that curve, and we're not sure if an individual up there will even progress to type 1 diabetes. If we're going to conduct a study in that population, we probably will have to do larger studies over a longer period of time to get our answer. But if we do intervene early, maybe we could come in with a less aggressive intervention, perhaps a dietary manipulation or an antigen-based therapy, and it would be more likely to be efficacious. We could come in later on that curve, say someone who has autoantibodies at Stage 1 or autoantibodies and abnormal glucose tolerance response to a glucose tolerance test, and we would know that they're higher risk and likely to progress to type 1 diabetes Stage 3.

So by virtue of coming in at that later stage, we may be able to conduct smaller studies over a shorter period of time. But if we're coming in later in the game, we have to use a more aggressive intervention and thus be willing to tolerate some potential toxicity from a drug used at that stage. So those are the tensions we have to measure as we start to think about devising trials in this at-risk population. Let me move on now and talk about what we call primary prevention. And this is for people who have an underlying genetic risk, but no evidence yet of autoimmunity. Can we block their progression to Stage 3 clinical type 1 diabetes? Autoimmunity can develop quite early in life against the beta cells, and there's been a lot of interest in the role that food exposure might play in modifying the risk for progression to type 1 diabetes. And, you know, one of the early exposures, of course, is milk. And so there's been a lot of study of the role of milk in type 1 diabetes risk. It could be that breastfeeding is a protective factor. It could be that early exposure to infant formulas that are cow's-milk based put one at risk for autoimmunity. And there's support in the preclinical studies and animal models. So I think a very natural question to have been asked is, can a nutritional intervention decrease the risk for type 1 diabetes? So let me walk you through one such primary prevention effort. This is a study with a nice acronym, TRIGR.

And again, it's a primary prevention before the development of autoimmunity. And here's the study design and the study question: can avoidance of early cow's-milk exposure prevent type 1 diabetes? And the hypothesis is a little complicated because we don't really know why exposure to whole cow's milk might put someone at risk. There's suggestions that perhaps the immature gut allows some leakiness and passage of antigenic proteins into circulation. And the immune response against those antigens could cross-react with some beta-cell antigens. It could be that the choice of milk affects the development of the gut microflora. It could be that exposure to these different products impacts how T cells develop. So even though the hypothesis is not fully clear, there was a study designed to try and address this question. And of course, the best designed studies are randomized, placebo-controlled, double-blind trials, which is what was done in this case.

As I mentioned, with these early intervention studies, they're typically larger, longer—so in this case, approximately 2,800 infants of first-degree relatives. So someone in the family had type 1 diabetes, and these infants had higher-risk HLA types. The study design was such that the mothers could breastfeed as long as they wanted these higher-risk infants. And when they started to phase in a supplemental milk source, the infant was randomized to either an elemental hydrolyzed formula or a standard infant cow's milk formula. And then these subjects were followed prospectively until at least age 10, to see about their risk for development of diabetes. This was recruited over five years, involved 78 clinical centers in 15 countries. So no small task. Now I'm going to show you the results. All this work boils down to one figure.

This is showing the risk for progression over time to diabetes. The Y-axis is the percent of people without diabetes, and the X-axis is time. And here you can see the placebo group or the control formula. The standard cow's milk formula is in green. The hydrolyzed elemental formula is in orange. And you don't have to be a sophisticated statistician to see that these completely overlap. So the study did not show a difference between the groups. And the conclusion of the study group was these findings do not support the need to revise early feeding practice for infants at risk for type 1 diabetes. The intervention didn't work. There's still, despite the failure of this particular trial, a lot of interest in what we might do to appropriately intervene for primary prevention.

And some of these interventions include the use of vitamin D, omega-3 fatty acids, the avoidance of gluten exposure, use of probiotics, autoantigens, and antivirals. So although these are large and long trials, there remains a great deal of interest in the diabetes community for trying to conduct further primary prevention efforts and stop progression to type 1 diabetes. Let's now think about what we could offer for someone who might have already developed some autoimmunity. And so these would be secondary prevention efforts, and there's been a lot of interest in using antigens. So you've heard about autoantibodies. And we now have a good sense of what the immune system is targeting in people at risk for type 1 diabetes. And so we might be able to use those antigen targets as therapies.

One question, of course, is which "self" antigen? Do we use the whole protein or peptides or parts of the protein? Do we use a DNA or RNA vaccine to introduce the antigen? Do we use the native protein or modify it in some way to enhance the immune response? Do we use just one of these antigens or combination? And then the other challenge with antigen-based therapies is there are lots of things you

can modify: the dose, the route of administration, the frequency of dosing, whether or not [to] use an adjuvant to try and boost the immune response. And at what stage should you offer it? Should it be Stage 1 or 2, or even as a primary prevention? So let me summarize one approach with insulin.

It seems a little paradoxical that you would use insulin as an antigen therapy. But this is one of the earliest antibodies that appears in someone at risk for type 1 diabetes. And there have been a series of prevention trials at Stage 1 introducing insulin in various ways, either by mouth or intranasal. And I'll just tell you the story now about the use orally. Again, this sounds a little bit crazy to give insulin by mouth. And clearly that's not going to have any metabolic impact. The insulin is going to be digested in the stomach and will have no metabolic impact whatsoever. But the interest here is that perhaps those peptide fragments are presented to T cells lining the gut, and they help induce a form of T cells called regulatory T cells that might alter the autoimmune response within the pancreas.

So that's the theory. Now we'll move on to that single figure to see how this works. And here is another one of those curves. You can see in this particular study, the percent without diabetes on the Y-axis and time on the X-axis. There's a higher percent of subjects moving on to diabetes in 5 to 6 years of observation. The treated group in the solid line and the dashed line, the placebo control group, progressed basically at the same rate again in this particular study. There was disappointment in this outcome, but in post hoc analysis, we noticed something very interesting, and that is, if you look at subjects who had a stronger insulin autoantibody response at the time they entered the trial, their rate of progression to diabetes in the treatment group was slower than those in the placebo group.

So it suggests that oral insulin may have an impact in this subgroup. And in fact, when you talk to our statisticians, the oral insulin delay here would be on the order of 4.5 years. This is really starting to seem quite intriguing because there's absolutely no safety issue associated with this particular therapy. With this post hoc observation of mind, we went back and repeated this trial—same dose, very similar study design. And we repeated this to see what we would find. And here is the follow-up trial. And I think it's a little clear in this particular study that there was no difference between rate of progression in the oral insulin versus the placebo group. However, in a pre-specified analysis, we did look again at a subgroup. And it's interesting in this analysis that there was a difference between the oral insulin-treated group and the placebo group.

When we looked at a group of subjects who entered this study who had worse beta-cell function—and low first-phase insulin release refers to how they responded to their oral glucose tolerance challenge—this again suggests that oral insulin may be doing something to the immune response and slows rate of progression to clinical diabetes, at least in a subgroup. So colleagues in Germany have taken up this case and gone back and revisited this whole question. I should tell you that in our studies, we evaluated a single dose of oral insulin. One thing they did was look at that dosing. And this is a complicated table here, but I'll walk you through it. So this is from Bonifacio and colleagues where they looked at a series of different doses, and they looked at the immune response associated with those insulin doses in a group of at-risk subjects.

And they looked at the antibody responses and the T-cell responses. So what's highlighted here in dark blue are the immune responses to people who got that 7.5 dose used in the prior studies. And there was just a small number of subjects that had antibody or T-cell responses. As they looked at higher doses, particularly about a tenfold-higher dose, there's a much higher percentage of people who had antibody and T-cell responses. These are small numbers; this was a pilot study. But it has prompted them to go back and rethink delivery of oral insulin. And so they're now pursuing studies in a cohort in Europe where they're looking at this higher dose and using it earlier, as a primary prevention type of measure. There are further studies looking at whether we use the whole insulin molecule or, again, peptides or even a precursor form of insulin, a proinsulin form. And there are also other means to deliver it, a clever approach modifying Lactococcus, a gut microbe, where it's secreted from this. And there's also a way to deliver this via plasmid. So more to come on the insulin front. And there's also now exploration of other antigens such as the GAD molecule, which is also a very common antibody in people at risk for type 1.

So let's move on now from antigen-based therapies and talk about potentially using immune modulators. And we have learned from the studies every year, the complexities of the autoimmune response in type 1 diabetes and have thought about various places where we could intervene in this pathway. And one approach is to come in with an autoantibody targeting a portion of the T-cell receptor. This is called the anti-CD 3 monoclonal antibody. The thought is that maybe this would impact this process and lower risk for type 1. And it turns out this has been evaluated in the non-obese diabetic mouse where it can actually reverse diabetes. It's been evaluated in Stage 3 diabetes in clinical trials where it can extend this remission or honeymoon phase. And so the question's been asked now, what about using it earlier in the disease course to try and prevent type 1 diabetes?

So this is a study conducted by TrialNet at Stage 2. And let me just walk you through the design. It's a fairly straightforward design: two arms, double-blinded, placebo-controlled. Both groups got a daily outpatient infusion of either the monoclonal antibody or a matching placebo infusion. And the simple question was, could this treatment delay the progression for people at Stage 2 to clinical diabetes at Stage 3? So again, our Kaplan Meier curve. Here on the Y-axis: percent of people diabetes free over time. And this black line is a

placebo group, and this you can see is an even higher risk group because by 72 months, about 90 percent of this cohort had developed type 1 diabetes. And the red arrow here is showing you that drug exposure just the first two weeks. And here's the drug-treated group, and this is really a more dramatic separation of the curves than I've shown you in any of the preceding graphs. And in fact, this translates into a median delay in type 1 diabetes onset of 32 months in the drug-treated group. So this is quite exciting to the field and has raised a number of questions.

The first thing I should point out is that regulatory agencies looking at this study decide[d] this should be the first approved therapy to delay or prevent the onset of type 1. So that's exciting in and of itself. We're going back through this analysis and trying to see if we can figure out which of the people treated are most likely to respond to this drug. We're thinking about whether additional courses of treatment might help prolong that response that we've seen. I didn't tell you the details of the study, but the study was only open to people ages 8 to 45. And we wonder if this might work well or even better in younger children. Could we couple it with another drug and get additive or synergistic effects with a drug that may work by a different mechanism? Can it work better if we use it even earlier in in the course of disease, say Stage 1, and do other drugs work as well or even better at Stage 2? And finally, I think there's interesting implications for our approach to thinking about whom we screen for risk for diabetes and knowing what the risk might be. But I think an approved therapy might really shift the calculus and have us think more broadly about screening the general population.

So let me summarize my talk. First of all, I think all of these studies have shown that we can use immunologic, metabolic, and genetic screening to identify people at future risk for type 1 diabetes. Based on the success of some of the trials we've conducted, we may have bonafide therapies to delay or block progression to type 1 diabetes. I think you're going to hear more about primary prevention with manipulations, such as dietary changes, and I think you'll hear more about secondary prevention, including antigen-based therapies which could be used at any of these stages, but particularly at Stage 1. Then further, developments related to the anti-CD3 mAB, with this promising study I showed you at Stage 2. And if we indeed have therapies that work, that are safe and effective, then I think we should certainly consider more widespread screening of the general population. So I will stop there and be happy to discuss this further.

Dr. Atkinson:
Thank you, Steve, for our very encouraging report about the impact of clinical trials on type 1 diabetes, both past and future. One of the things I want to make sure our audience knows is one of the main topics of this lecture series is on autoantibodies. Is it the same autoantibody tests that are being used in these Stage 1 trials, Stage 2 trials, and Stage 3 trials, or are there switches around in those tests?

Dr. Gitelman:
So that's a great question. I think to the extent that we can, we try and work across networks so that when we conduct these studies, we can compare and contrast. Regarding the autoantibody assessments themselves, there are a number of international workshops to see that these are fairly well harmonized across networks. So internationally we're basically using very similar assays and all the same antigens that we're assessing the autoantibody responses against.

Dr. Atkinson:
All right. So do you have concerns if a child is undergoing screening or participating in one of these trials, if they have a history of allergies or asthma, that they would have contraindications, if you would, in participating in these trials? Or would those disorders seem to interfere with the predictability of the autoantibodies?

Dr. Gitelman:
Yes. I think part of this depends on the nature of the intervention. As we get more and more aggressive with things, and particularly the last immunotherapy that I talked about, we'd want to make sure that you weren't taking any medication that suppressed the immune response. I think one of the more common ones would be steroids, glucocorticoids. So if someone had asthma and needed a heavier glucocorticoid therapy to manage their asthma, that might modify their response and it could put them at risk for the drug that we're using, and it might obscure our ability to interpret the results to a given intervention. So for most of these studies, we want people who are otherwise healthy and don't have other medical conditions. But I think as we learn more about the therapies and more about people's response to these therapies, then we can be more inclusive in the studies.

Dr. Atkinson:
So as I mentioned in my introduction, I've been at this 4 decades, and I've seen, like you showed examples, there have been some highs and lows in terms of intervention therapies in individuals at risk for type 1 diabetes. This said, I feel like we're on the cusp of a breakthrough, and that for the first time we're going to effectively answer the question of why should I be screened? We heard that prevention of DKA is important. A whole series of factors are improved here. But do you share that optimism? And if so, what do you think are going to be the actual benefits of trying to delay type 1 diabetes or see preservation of the insulin response in individuals with recent onset disease Stage 3?

Dr. Gitelman:
I appreciate the comment and complex series of questions there. I would say up until that last study we'd conducted, the type 1 diabetes research community had conducted a number of very well-reasoned prevention trials. They're based on animal observations, some pilot data, all the right rationale. And up until 2019, the larger studies were all negative, and it was very depressing. And so I think there is great renewed hope now based on that last study with the anti-CD3 mAb that we can alter the course of progression to type 1 diabetes. And to me, the end of the beginning, and those questions I showed about where can we go from here—that's a lot of different things to sort out.

But it's so exciting that we're now at this stage to start to do this. And we've really stood on the shoulders of many people before us to get to this point, this particular therapy and understanding the pathophysiology. But there's a build on from here. So I'm very excited. I think it just opens the door with that drug and many other drugs, many of which we test first at Stage 3, and they're safe and effective. We're trying earlier in the disease course. But it's also interesting to see the number of possible therapies that are emerging. So fortunately, the drug companies are busy, developing newer and clever approaches that may work in and of themselves just in prevention. So we have a lot of exciting work to do from here.

Dr. Atkinson:
I greatly appreciate what you just said about the beginning of the end versus the end of the beginning. I think we're about to see a transition here, an inflection point, if you would, in terms of type 1 diabetes, researching care. And I would just like to open it up to any of the other speakers. We've heard now 3 outstanding presentations that walk through the various notions of screening, from how it's done, why it's done, and then in terms of clinical trials, why it's important. And I would just like to give our panel one last chance having heard all 3 of these talks. Are there any issues that you believe we need to emphasize or that we have not discussed yet? And I'll start with Dr. Sims.

Dr. Sims:
Thanks. I just want to second Mark's comments about how amazing each of the talks has been. I've really enjoyed and felt very informed by each one of them. I think one major issue that we really need to think about in our field is our coverage and outreach to underrepresented populations. If you look back at the makeup of a lot of the trials looking at type 1 diabetes interventions, they've been mostly non-Hispanic Caucasian populations. And so I think we need to do a better job of engaging other populations of individuals who stand to benefit from these kinds of interventions. And also making sure that if the interventions become available, that we're reaching other people, other populations.

Dr. Atkinson:
That is an important point. And one of the things that we've learned about type 1 diabetes, thanks to the NIH SEARCH study, is that whereas the disease is increasing in Caucasian populations, it's actually increasing at an even faster rate in African American and Hispanic populations. So you're absolutely right; we need to be more diverse as we move forward in terms of who we screen and who do we intervene with. Linda, do you have any comments?

Dr. DiMeglio:
I also want to echo what Emily said, and I very much enjoyed listening to her presentation and Steve's presentation. So thank you for inviting an engaging panel. I think one of the things that will be really critical going forward as screening becomes more prevalent, as more therapies become available, will be making sure that we are doing things that are patient focused and that we find ways to message the estimation of risk to populations, that we do a lot of patient-centered outcomes work, and that we make sure that we're meeting people where they are. Because as somebody that for our career has enrolled participants into clinical trials, I'm always grateful for their participation. I think it's really important that people who sign up to do something, whether it's a therapy or a study, know as best they can what they're going getting into and what the expected outcomes are, and that we have realistic expectations and good messaging.

I've been working with TrialNet for about 12 years, and I still struggle sometimes to explain to people the concept of risk and risk of diabetes and what does that mean and what is the likelihood. So I think making sure that those efforts are done in lockstep with the metabolic assessments and then also making sure that those are tailored to diverse populations will be critical.

Dr. Atkinson:
That's a very important point, Linda, and that's the whole purpose in a way of today's seminar. We want to make sure that not only the healthcare providers, but the patients and family members, those individuals that might have type 1 diabetes and in situations of general population screening, that everybody has an increased understanding of this disease and population screening for diabetes autoantibodies. Steve, as they always say, you get the last word.

Dr. Gitelman:

I very much enjoyed the talks as well. I'd like to go back to Emily's talk. I think those who have to live with diabetes appreciate what a challenge it is. It's very hard to mimic the beta cell with the current tools we have, and we really suffer for that—the individuals affected, the families, the healthcare teams, society at large. And there's I still think this notion that insulin is a cure and what's the big deal? And it is, it's a huge deal. And so I would not take lightly the idea that we could screen and predict and are very close to this place where we can alter the natural progression of this disease. It's remarkable.

Here we are, the hundredth year of discovery of insulin. And this really is just such an exciting time. You know, when I showed that study where we could delay by approximately 3 years the onset of diabetes, that's not our final resting point. That's not the home run, that's the single. But I wouldn't underestimate [those] 3 years. If you have a toddler who's destined to develop diabetes and you can push that out 3 years or an adolescent who's having a stormy time making their way through puberty and they're a couple years later into this process, that delay could be a big benefit to that individual and that family. But we will do better. There's no question. And so I think the whole notion of whom to screen and when to screen, how to screen, what do you do with this information? There may be some really important actionable responses and a therapy available. So I think it really is going to be a very exciting time to shift our paradigm and think about how we best get the word out and encourage people to do this.

Dr. Atkinson:
So in closing, I will say I agree with your sentence just 30 seconds ago. We will do better as we move forward, and we're going to do better because of people like you that are dedicated. You represent 3 people here, but there's dozens into the hundreds of individuals worldwide that have dedicated their lives to trying to improve autoantibody screening and bring therapies forward. I look forward to seeing where over the next few years this field goes. So thank you very much. I think you've made a very convincing case, and I hope that our audience agrees. Thank you.

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