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Type 1 Diabetes & the Role of Anti-CD3 Targeted Therapy

Dr. Herold:
[Session Title, Faculty/Degrees/Affiliations] Hello. My name is Kevan Herold, and I'm a Professor of Immunobiology and Internal Medicine at Yale University. Thank you very much for joining us for this session, which is entitled Foundational Basis Review of Type 1 Diabetes, Epidemiology, Risk Factors, Stages and Pathophysiology. I am delighted to be joined by my colleague, Dr. Chantal Mathieu, who will be following me in her comments on this topic.

[Breakdown of Immune Tolerance] I'm going to begin by discussing how immune tolerance is disordered in type 1 diabetes, and how we believe this eventually leads to the development of the disease. [Loss of Immune Tolerance Underlies T1D] Type 1 diabetes is an autoimmune disease characterized by the progressive and insidious loss of self-tolerance to the insulin-producing pancreatic islet beta cells by antigen-specific T cells. The loss of self-tolerance results in the destruction of the insulin-producing beta cells, eventually in the development of overt hyperglycemia, which is how we make the diagnosis of the disease, and then afterwards dependence on exogenous insulin. The mechanisms that lead to the loss of immune tolerance in type 1 diabetes are multifactorial, and include genetic, epigenetic, molecular and cellular factors, as well as environmental factors such as viruses and the host microbiome.

[Autoimmune Process in T1D] The clinical onset of diabetes is preceded by an asymptomatic period lasting months to years during which autoimmunity causes progressive beta cell destruction. Now, I have to say that we know that this process is going on by the identification of biomarkers of the process. But, as we'll come to in the discussion, we don't have a very good handle on the actual rate of this progression in any particular individual. In genetically susceptible persons, pancreatic self-antigens are processed by resident antigen-presenting cells, and these include dendritic cells, macrophages, as well a B cells, B lymphocytes. These antigen-presenting cells migrate to the pancreatic lymph nodes, recruit CD4-positive T cells, and activate other cells that will ultimately be the effectors in causing beta cell destruction.

[Autoimmune Process in T1D, cont'd] So, basically, the concepts that lead to the destruction of insulin-producing beta cells are depicted on this slide. CD4-positive T cells become activated when they see antigens that may be beta cell-derived antigens that are presented by an antigen-presenting cell. [Immune-Mediated Beta-Cell Destruction in T1D] And, we've shown on this slide a cell that looks a lot like a dendritic cell, or tissue resin in macrophage, but I would point out that other cells are also capable of doing this, including B lymphocytes. So, the CD4 T cells become activated, they undergo clonal expansion, and they migrate to the pancreatic islets. CD3 is a molecular complex on the surface of T cells, and is responsible for antigen recognition and activation of T cells. It's the business end of a T cell that gives it its specificity for a particular antigen that's presented by the MHC complex, the major histocompatibility complex. In the pancreas, autoreactive T cells recognize beta cell antigens and recruit CD8-positive cytotoxic T cells, which are believed to actually be the cells that cause the destruction of beta cells. Now, most likely, this is occurring in the draining pancreatic lymph node, but the exact location of where it is happening, of course, still is not completely clear. Autoreactive CD4-positive T cells can also activate B cells, B lymphocytes. These cells are required for the disease mechanism, but they may function also as antigen presenting cells. The autoreactive B cells can become activated and differentiate into antibody-producing plasma blasts and plasma cells that produce the circulating islet autoantibodies that we use as a biomarker of the disease.

[Mechanisms of Immune Tolerance Loss] Now, why this happens, of course, is still the subject of intense investigations. Patients with

type 1 diabetes exhibit defects in peripheral tolerance, including impaired regulatory T cell function. These are cells that in normal individuals are responsible for suppressing autoimmune responses and other unwanted immune responses. But, there's evidence from studies of both patients and in mice that impairment of these regulatory T cells can lead to the development of autoimmunity. In addition, there may be effector resistance to the effects of the regulatory T cells and soluble immune regulatory. The pathologic hallmark of type 1 diabetes is insulitis, an inflammatory lesion in the islet of Langerhans that's associated with beta cell loss. The inflammatory cells are seen in the outside of the islet at first, so called peri-insulitis, but also importantly within the islet parenchyma itself, which is termed insulitis. Many of the type 1 diabetes genes predispose to impaired immune regulation. The importance of the genetics is that it gets an individual to the point where they are able to progress to autoimmunity. The genes themselves, however, are fairly common in the general population, and having the genes alone is not sufficient to cause the disease. Environmental exposures may promote the loss of tolerance.

[Role of Islet Autoantibodies] What about the islet autoantibodies that I've discussed already? So, the islet autoantibodies are the main markers that are used that indicate pancreatic autoimmunity in type 1 diabetes. [Islet Autoantibodies in T1D] The islet autoantibodies have been identified against four biochemically defined antigens that are found, actually, on or within the secretory granules in beta cells. Probably most of these are familiar to you. These include glutamic acid decarboxylase, or GAD65, insulin itself, islet antigen-2, or IA-2, or ICA 512, and the zinc transporter that's found in beta cells, or ZnT8. These are autoantibodies that can be measured even in clinical labs that identify the pathologic process of type 1 diabetes.

[Islet Autoantibodies as Markers of Autoimmunity] To reiterate this, islet autoantibodies are the main markers of pancreatic autoimmunity in type 1 diabetes. Islet autoantibodies measured by sensitive and specific assays are the key components of the autoimmune response, and are monitored for diagnostic testing in persons at high risk for type 1 diabetes. The rate of progression from islet autoantibodies to clinical type 1 diabetes is primarily dependent on the number of autoantibodies that are present.

[Risk of T1D Depends Mainly on Number of Islet Autoantibodies] Let me just expand on that a bit. The appearance of islet autoantibodies may differ by age. For example, young children frequently show islet autoantibodies to insulin, whereas older individuals more frequently show antibodies to GAD65. The risk of developing diabetes, as I said already, is based on the number of these specificities. Children who develop only a single autoantibody against beta cells in the first five years of life have about a 12.7 percent risk of having clinically evident type 1 diabetes during the next 15 years. However, when you have two or more autoantibodies, the risk increases greatly to 61.6 percent over the next 15 years, and if you have three autoantibodies, the risk increases even further to 79.1 percent, whereas if there are no autoantibodies present, the risk is 0.4 percent.

[Risk of Developing 1TD Based on Islet Autoantibody Number] This is shown diagrammatically here. In other words, what we're looking at is the risk of developing type 1 diabetes based on the age of the participant and the number of autoantibodies that are present. And, you can see that in all age categories that if you have more autoantibodies, the risk of developing diabetes over five years, ten years, 15 years or 20 years increases greatly. In fact, what we have done is we've termed individuals who have two or more autoantibodies as having stage one diabetes. This term now has gone into the vernacular about staging of type 1 diabetes. It does not mean that an individual with so-called stage one diabetes has overt diabetes. Instead, they are identified of being very high risk of progressing to diabetes. And, as you can see from the data shown on this slide, essentially, they will all go on to develop overt type 1 diabetes. But we call this stage one diabetes because we know the autoimmune process has been initiated and will continue until there is the development of overt hyperglycemia. I'll stop there and turn this over to Dr. Mathieu.

Dr. Mathieu:
Epidemiology] So, let us now turn to the epidemiology of type 1 diabetes. When we look at the demography of type 1 diabetes, [Demography] most of us think that type 1 diabetes is a disease of children and adolescents, and indeed it is the most frequent autoimmune disease in that age segment. But, when looking at the number of people living with type 1 diabetes, many of them are adults. And also, when looking at the onset of type 1 diabetes, we see that many people only get type 1 diabetes when they are above 18 years of age. Now currently, when looking at the US, an estimated 1.25 million people are living with type 1 diabetes, of whom 132,000 are children and adolescents. What is interesting is that the incidence of type 1 diabetes is increasing steadily. It seems that diabetes type 1 is becoming more frequent, but especially when looking at the age category of newly diagnosed individuals, these children become younger and younger.

I will come back later on to the genetics of type 1 diabetes, but we have to say that it is, until now, typically a disease of Caucasian individuals, but more and more, we do see that the incidence is increasing also in non-Caucasian populations.

[Time Trends in Incidence of T1D] Now, here you can see a study by Dr. Norris published in *Lancet Diabetes Endocrinology* in 2020 where she clearly indicates that in many of the cohorts studied, you see an increase in recent years in the incidence of type 1 diabetes, the leader being Finland. [Estimated Rates of Annual Rate of Increase….] Now, what is of interest, if you go here to a study reporting in

26 European countries on the incidence of type 1 diabetes, you see that there is an increased rate in most of the countries that have been reported. [Inverse Association Between Rate of Incidence Increase and Average Incidence] And, what is interesting is that there is an inverse association between the rate of incidence increase and the already existing average incidence, meaning that in those countries with already a very high incidence rate, like the Scandinavian countries, Sweden and Finland, there is a growth, but the growth is mainly happening in those countries in Europe where we used to have typically a quite low incidence, like Poland, Romania, the Czech Republic, typically the Eastern European countries. So, overall, there is a rise in the incidence in type 1 diabetes, mainly spreading to those populations that were genetically at a less increased risk until now.

[Incidence Trends of Type 1 and Type 2 Diabetes Among Youth] Now, this is also clear from this study by Dr. Mayer-Davis, where they looked at the increasing trends in type 1 and type 2 diabetes in young people in the US. What you can see is that there is a steep increase in type 2 diabetes in young individuals, but look at the curve on the left-hand side, where they're looking at the increased incidence of type 1 diabetes. And, what is interesting is that it is mainly the black triangles indicating non-Hispanic black populations, and also the little crosses here, indicating the Hispanic populations that are seeing a rise, whereas in the Caucasian populations, it is rather stable.

[Incidence of T1D in the US by Age] Here again, one of the studies that clearly indicates that our idea that type 1 diabetes is just a disease of children and adolescents is not correct. I already said that many people are living with type 1 diabetes as adults, but also looking at the incidence of type 1 diabetes, we agree that the peak incidence is happening in younger ages, around 10 to 14 years of age. But, look at individuals above 18 years of age, also many people are getting their type 1 diabetes in adulthood.

[Risk Factors] Now, what are the risk factors? Dr. Herold already indicated that there are genetic and non-genetic risk factors playing a role in the onset of type 1 diabetes. [Environmental and Other Non-Genetic Determinants] And here, we have a treasure trove of findings from the TEDDY studies, where a number of environmental factors that play a role as possible triggers of type 1 diabetes have been identified. As such, increased weight gain during infancy has been associated with a higher risk of type 1 diabetes. But also, for instance, introduction of gluten in first months of life, and also exposure to complex foreign proteins present in cow's milk may be contributing to an increased incidence of type 1 diabetes at lower ages. And of course, what has come up in recent years are also viruses, microbiota that may play a role.

Are there any protective mitigating factors? Well, one of my favorites are the maintenance of breast milk, and then a quite controversial one that is also a topic of my studies, namely vitamin D. I think the jury is still out, but there are some intriguing findings saying that being vitamin D deficient at early age, when you're also at higher genetic risk for type 1 diabetes, is not good for you. And so, having supplements of vitamin D may mitigate that. [Candidate Risk Factors] Here you see a complex figure showing that for sure, there is not one trigger; there may be many, many triggers that can cause the onset of type 1 diabetes, or at least bring forward the onset of type 1 diabetes to lower ages.

[Heritability] Now, what about genes? There is an increased risk of developing type 1 diabetes in close relatives of people living with type 1 diabetes – children, siblings, parents. And, there is a familiar aggregation that accounts for about 10 percent of cases, but there's not really a recognizable pattern of inheritance. And, we have to admit that the majority of people being diagnosed with type 1 diabetes do not have anybody with type 1 diabetes in the family. So, we believe yes, there is a genetic predisposition for autoimmunity, or interesting data, and I'll also show, perhaps for a weaker beta cell. But we believe that there are triggers in the environment that will bring the autoimmune trait, as you want, to the surface.

[Genetic Determinants] What are the genes? Well, it is a polygenic disease, but with a major role being played by the HLA, the major histocompatibility genes that are responsible for the translation into proteins that play a role in the communication in the immune system between antigen-presenting cells and T lymphocytes. And, it is mainly the class 2 genes that are being accused of playing a major role in the genetic risk. [Genetic Predisposition: Driven by HLA] So here, I show you an overview of a report already several years ago where it is clear that type 1 diabetes not a monogenic disease; there's many, many genes being correlated with type 1 diabetes, but the biggest risk asset is being carried by the HLA genes.

Now, Dr. Herold already alluded to the presence of autoantibodies. And indeed, we know that in people with an increased genetic risk, antibodies will be the first biomarkers that will be able to tell us whether a person is on their way to type 1 diabetes. And typically, we have been looking for these autoantibodies in family members of people with type 1 diabetes. [Role of Islet Autoantibodies] However, recent studies, for instance the work of Anette Ziegler in Bavaria showed that you can also use presence of autoantibodies in the general population as risk factors, as predictors for onset of type 1 diabetes. Indeed, Anette Ziegler reported on a study in more than 90,000 children where the detection of islet autoantibodies did identify people who were at increased risk of moving towards type 1 diabetes. [Autoantibodies Reflect Autoimmune Attack….] Here, you can see another study by Dr. Ziegler where she clearly indicates that presence of autoantibodies will predict the onset of type 1 diabetes, and as Dr. Herold already alluded to, the more antibodies you

have, the higher the risk of you progressing towards type 1 diabetes in the near future.

Now, we are looking, of course, for novel biomarkers, autoantibodies. [INNODIA] Genes are one set of biomarkers, but finding novel biomarkers is, for instance, what we are doing in our consortium in our EU project, INNODIA in Europe, but also other consortia, TrialNet, etc., are looking for novel biomarkers, trying to better predict who will progress to type 1 diabetes in order to be able to then do intervention studies.

[Stages] I will end by going back to, again, a concept that was already alluded to by Dr. Herold, namely the different stages of type 1 diabetes. Until quite recently, we as clinicians talked about type 1 diabetes at a stage where individuals had hyperglycemia and the symptoms of polyuria, polydipsia, etc. [Natural History of T1D] Now, we acknowledge that actually going back to this very old concept of Dr. Eisenbarth that actually your autoimmune disease that is type 1 diabetes is starting many, many months, many, many years earlier. And, this is an old cartoon by Dr. Eisenbarth showing the genetic risk, the trigger, and then the onslaught of the beta cell bringing out clinical diagnosis of hyperglycemia when only a minority of functional beta cells are still left. [Natural History of T1D, cont'd] But, we know first of all that this is just a cartoon and that probably the process going towards the whole destruction of the beta cells is a much more complex one. But we also acknowledge that we shouldn't wait to make the diagnosis of type 1 diabetes until we have hyperglycemia. We know by presence of the autoantibodies that if you are on the slope down to clinical diagnosis of type 1 diabetes, you have type 1 diabetes; you have the disease, and hence this proposal to not talk about type 1 diabetes only in people with hyperglycemia, but also to start with our diagnosis much earlier because we have now tools that will be able to delay the progression of this disease. [T1D Stages] And so here, the typical stages, already alluded to by Dr. Herold, stage one, just having the autoantibodies, stage two, having the autoantibodies and already dysglycemia, and then stage three is really where, until now, we made typically our diagnosis. [T1D Staging Criteria] And so here, you can see a summary. This staging system dates from 2015, also really pushed forward by JDRF, so now we're talking about stage one type 1 diabetes, stage two type 1 diabetes and stage three type 1 diabetes. [Progression to Clinical T1D] Here again, very elegantly depicted by TrialNet consortium, again with a big focus trying to arrest type 1 diabetes. You have the genetic risk, you have the risk factors coming on, you have the slope going down, and we know now that once you have the autoantibodies present, you have type 1 diabetes. Thank you

Dr. Herold:
Good. Let me ask you one question, because I know it's of interest to you, and that is the vitamin D story, and your thoughts about, the very peculiar relationship between latitude and the development of diabetes. Those in northern countries tend to have higher rates than those around the equator. Do you think there's a relationship there?

Dr. Mathieu:
There's observation that, indeed, the northern countries have the highest risk of type 1, for instance in Europe, whereas Italy and Spain have a lower incidence of type 1. It is intriguing because we also have not only that observation, but we have a lot of evidence from animal models, for instance, where we do know that our animal model that is most used, the NOD mouse, so, being a mouse at a huge genetic risk of getting a disease that is similar to type 1. We know that in these mice you increase their risk of moving their autoimmune disease to a clinical autoimmune diabetes by making them vitamin D deficient. Restoring the vitamin D deficiency makes them more resistant against type 1. So, there's observation, together with the fact that we know from animal models that if you are genetically at risk and you are vitamin D deficient, that you get more of a disease like type 1 is, I think, intriguing. However, Kevan, we have no studies to show that giving supplements of vitamin D to humans can prevent the onset of type 1 diabetes, or reduce their risk. In mice, we need huge doses of vitamin D to prevent the onset of type 1 diabetes. So, in humans, I think the story is wobbly. It is observational, but we have no data to show that high doses of vitamin D would prevent type 1. Honestly, my only advice to people with a genetic risk of type 1 diabetes, don't become vitamin D deficient. It's bad for your bones, and maybe your risk of type 1.

Dr. Herold:
Okay, thanks. And then one other thing I wanted to ask you about, the stage concept. [Progression to Clinical T1D] Maybe we should just dwell on that a little bit more because, as you pointed out, we think of this in a linear progression, and it doesn't always follow the rules. So, there are people who have so-called stage one diabetes who then may progress to overt diabetes and you never see the stage two. And then, of course, the issue here is that it doesn't tell us a rate. It tells us a risk, and so that's a problem. So, I wonderwhat your thoughts are about that. I mean, have we gone too far in terms of staging it? Should we just call it prediabetes and then, you know, the risk is there? Or, on the other hand, we do know those who already have glucose intolerance on an OGTT are extremely high risk. How do you view it in terms of identifying who might be appropriate candidates for clinical studies?

Dr. Mathieu:
Yeah, I mean even look at it from a different angle, Kevan. So, this whole stage concept and the fact that we would acknowledge that having is already a disease state, is of course important when you think of intervention trials because going with an agent that can do something in people who already have a disease, the bar for safety requirements and the ease with which regulators will look at your

intervention is very different when you consider an intervention in a disease rather than prevention of a disease. So, that is really the background of the whole stage discussion.

Now, again, going back to my animal models, I am not sure that intervening earlier will give you the same results as intervening in individuals who are on this acceleration phase because as you very rightly say when I showed this slope going down is all fine and well, but there's some intriguing data, Kevan, that showed that some people stay quite stable and then poof, they come down. And so, there may be a window of opportunity where some therapies may be more effective than if you would've given them in individuals who just have autoantibodies. So, I think your approach, for instance, with your intervention studies, intervening in individuals who are dysglycemic with multiple autoantibodies, I think that makes sense because honestly, as a clinician, you and me, I think we agree that whether you have the hyperglycemia and glucosuria, or the hyperglycemia when you have an OGTT or mixed meal tolerance test, this is the disease. I mean, these people are sick, and it's just a matter of weeks or months. It's different, to me, for those who just have autoantibodies and a perfectly normal glucose tolerance. And so, I'm not sure that interventions that work in the dysglycemic would also work in the normal glycemic.

Dr. Herold:
Yeah, I agree. That's an unknown area, for sure.

Dr. Herold:
Okay, well, I want to thank Dr. Mathieu for her comments and for the discussion, and we'll look forward to having you join us on the other sessions.