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https://reachmd.com/programs/cme/changing-treatment-paradigms-in-type-1-diabetes-role-of-anti-cd3-targeted-therapy-screening-for-islet-autoantibodies-in-children-and-adolescents-to-preventdelay-t1d/12695/

Released: 07/09/2021
Valid until: 07/09/2022
Time needed to complete: 30 minutes

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Changing Treatment Paradigms in Type 1 Diabetes: Role of Anti-CD3 Targeted Therapy -

Screening for Islet Autoantibodies in Children and Adolescents to Prevent/Delay T1D

Announcer:
Welcome to CME on ReachMD. This activity entitle “Changing Treat Paradigms in Type 1 Diabetes: Role of Anti-CD3 Targeted Therapy, Screening for Islet Autoantibodies in Children and Adolescents to Prevent or Delay T1D”, is provided by the Postgraduate Institute for Medicine and is supported by an educational grant from Provention Bio. Prior to beginning the activity please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Herold:
Hello. **[Slide]** My name is Kevan Herold. I'm Professor of Immunobiology and Internal Medicine at Yale University. Thanks for joining us again for this third program. The topic for today is screening for islet autoantibodies in children and adolescents to prevent or delay type 1 diabetes.

[Slide] There's been a tremendous amount of progress in this field, and fortunately today, we have two of the leaders who are very well-known for their expertise in screening and in therapeutic trials in type 1 diabetes, Dr. Anette Ziegler and Dr. Andrea Steck. Dr. Ziegler is Professor of Diabetes and Gestational Diabetes at the Technical University of Munich, and Director of the Institute of Diabetes Research at the Helmholtz Center in Munich. Dr. Steck is Associate Professor of Pediatrics at the University of Colorado. **[Slide]** We'll first hear from Dr. Ziegler, and the topic of her talk will be screening for islet autoantibodies to delay and prevent type 1 diabetes. Anette, thanks very much for joining us.

Dr. Ziegler:
Thank you very much, Kevan, for your kind introduction.

Over the past hundred years, since the discovery of insulin, there have been enormous advances in the therapy of type 1 diabetes. **[Slide]** Still, type 1 diabetes, when diagnosed before the age of 10 years, means 16 years loss of life, as recently reported in *The Lancet* by a study of over 150,000 individuals. That underlines the importance of new therapeutic approaches such as prevention or delay of the onset of diabetes in children. And, we are very fortunate that we actually in fact have already one therapy. [**Slide**] This is a milestone study showing that type 1 diabetes can be delayed by immunotherapy through one single course of 14 days of treatment with a monoclonal antibody, teplizumab, by an average of three years with a risk reduction to the development of diabetes of over 50 percent.

[**Slide**] So, the challenge today is really how we can, on a population-based level, identify people that benefit from such an immunotherapy. And, this therapy is given at a state of pre-symptomatic disease where children do not have a classical form of type 1 diabetes. [**Slide**] So, what does it mean exactly, identifying people with pre-symptomatic disease? I think you are familiar with the classical onset of type 1 diabetes, which we today also call stage three type 1 diabetes, where a child or individual has symptoms and is hyperglycemic. But, type 1 diabetes in its clinical onset is preceded by an asymptomatic stage of autoimmunity. This stage you can diagnose by the detection of islet autoantibodies. And, this is actually the stage where we want to apply these immunotherapies.

[**Slide**] We have, in Germany and Bavaria, explored a screening for islet antibodies for these early stages of type 1 diabetes in a study

called Fr1da. The rationale for this population-based screening was twofold. One, by early detection of the disease, we can prevent diabetic ketoacidosis on a population-based level, reduce family burden, and eventually also reduce healthcare costs. But, the second objective was indeed to identify children who benefit from immune-based therapies to be able to prevent insulin dependence, or at least delay the classical onset of type 1 diabetes.

[**Slide**] So, in this study, what approach did we take? We introduced the screening for islet antibodies into the population by attaching it to regular well-child visits at the age of 2 to 6 years. All children were offered a one-time screening in capillary blood. The pediatricians or primary care physicians took the sample and sent it to a central laboratory that was in my institution. We screened the sample with a very high throughput test for three antibodies in one test. When this sample was positive, then in the same capillary blood, we tested four different islet antibodies, and when we found more than two islet antibodies, we informed the pediatrician and we asked for a second sample, this time a venous blood sample. We took a venous sample for the second time because we are a little bit more confident with our threshold values in venous blood than capillary blood. Capillary blood is more frequently also hemolytic and sometimes not so easy to clearly check for the final diagnosis. And, if this second venous blood sample was positive again, then diagnosis of early pre-symptomatic stage one type 1 diabetes was made. And, the family, the children were invited further for metabolic staging, an oral glucose tolerance test.

[**Slide**] We had over 600 pediatricians and physicians participating in this research program. And, it was also supported by our Health Ministry. [**Slide]** The Health Ministry with this poster helped us to advertise this model project screening in Bavaria. [**Slide**] The results of our screening were published last year in *JAMA*. At that time of publication, we had screened over 90,000 children and we found 280, which is 0.31 percent, to have this pre-symptomatic stage 1 diabetes, or you can also say have at least two islet autoantibodies. [**Slide**] So, we invited those children for further staging, for the oral glucose tolerance test, and when we performed this test, we found that around 80 percent of the children were still normoglycemic. But already, 20 percent had some form of abnormal glucose values, or had even without any symptoms, hyperglycemia.

[**Slide]** We also invited the families to an educational program at that time to inform them about type 1 diabetes, how they can test blood sugar levels, and how the follow up would look like. So, all the families were invited to do some follow up for control of glucose levels of HbA1c. During follow up of these children, we found that already within three years, a quota had progressed to insulin-dependence without any immunotherapy. And, only two developed ketoacidosis; that is less than 5 percent, which is markedly less than the average decay in newly diagnosed children, of about 30 to 50 percent in most populations, showing that by this early diagnosis, one can indeed prevent decay.

[**Slide**] So, what contributes to disease progression? The number of islet antibodies detected, and also the specificity of these islet antibodies. In particular, if you had two antibodies, your progression rate was faster than average. But what was really also important: we did not see any difference in progression rate between children coming from the general population. The majority of these 90,000 children, almost all had no family history, but a few had a family history of diabetes, but their progression was absolutely identical.

[**Slide**] You may ask the question why we had chosen the age range of 2 to 6 years? I think that's an important consideration, what is the optimal age for screening? So, you can see here from two natural history studies, BABYDIAB and the TEDDY study, that these antibodies – and this is shown here as incidence – occur very early in life. The majority of children who develop multiple islet antibodies do so before the age of 4 years. This was shown by both studies.

What is also important is that before the age of 4 years, about 11 percent, so one-tenth, has already progressed to clinical diabetes, showing that finding the right age of screening is a compromise between being sensitive and having developed these antibodies, but not yet progressed to clinical disease. [**Slide**] Also, a very important screening consideration is that we found that there is in fact an exponential age-related antibody risk decline. What does this mean? A child, for example, because it has many antibodies predisposing for type 1 diabetes has, at birth, a risk of almost 10 percent, which is also shown here. Then, this same child, if it's tested negative at 8 years, has a projected remaining risk for the next five years of only 0.2 percent. So, in the first years of life, the decision is somehow made whether a child will develop this disease or remains healthy. And therefore, it is very helpful in these years to do these tests, to also give advice for the families what happens in the future.

[**Slide**] In the TEDDY study, we actually modeled the test performance. If you can only do one screen, then the best age in terms of sensitivity, specificity and performance would be 3 to 4 years. But, if you can afford to do two screens, it is of course better in terms of sensitivity, then the first screening should be at the age of 2 to 3, and the second screen at the age of 5 to 7 years. And, we have actually, in the Fr1da study now, implemented this. This Fr1da study now continues as Fr1da plus with two possible screens in children aged 2 to 10 years.

[**Slide**] In summary, I have shown you that population-based screening for islet antibodies is feasible and is very well accepted by

pediatricians, and can also prevent diabetic ketoacidosis. The approach requires a strategy with high test specificity because you do not want to identify children that have no risk to progress. Population prevalence of early type 1 diabetes in Germany is around 0.3 percent with 80 percent still normoglycemic, 20 percent already having abnormal glucose values. Disease progression is very similar between close relatives and children without a family history of diabetes. Islet antibodies appear early in life, and the risk decline is exponential with age. And, the best screening performance, if you do one screen, age 3 to 4, two screens, age 2 to 3, and again, age 5 to 7 years.

I thank you very much for your attention and I would like to pass over now to my colleague Andrea for the second presentation.

Dr. Steck:
Thank you for your introduction.

Today I will discuss potential for type 1 diabetes prevention. [**Slide**] So, what is needed for type 1 diabetes prevention? First of all, we do need accurate prediction for type 1 diabetes, which we currently actually have. And then, we also need appropriate screening strategies for subjects at risk for type 1 diabetes, which was discussed in the previous talk by Dr. Ziegler. And then finally, we will need to have available prevention strategies.

[**Slide**] This slide shows progression to type 1 diabetes in children with multiple antibodies. On the left, overall risk of progression is about 70 percent by ten years of follow-up since seroconversion. And then on the right, you can see that this cumulative risk does not differ by country, nor by first-degree relatives. This was a study that combined data from DAISY, DIPP and BABYDIAB. DIPP is a general population prospective cohort in Finland. DAISY is a cohort of relative of type 1 diabetes patients and a general population newborn cohort in Colorado with about 50 percent first-degree relative and 50 percent general population. And, the BABYDIAB is a prospective cohort of offspring of type 1 diabetes patients in Germany. And so, in these three studies, the rate of progression seems to be relatively constant at approximately 11 percent per year over a ten-year timespan.

[**Slide**] In 2015, the ADA, JDRF and the Endocrine Society published a joint statement that described stages of type 1. In stage one, a person is euglycemic with no symptoms, but is positive for multiple islet autoantibodies. Stage two occurs when a person with multiple autoantibodies begins to have dysglycemia, but remains clinically asymptomatic. And then, in stage three, a patient has classical diabetes symptoms and the presence of significant dysglycemia, and meets the standard ADA diagnostic criteria for type 1. Also, the sequence of event has become predictable. The rate of progression to type 1 varies widely between individuals.

[**Slide**] Type 1 diabetes is an autoimmune disease, but is heterogenous in various aspects, including from a genetic, immunologic, metabolic and pathologic standpoint. Here, I'm showing one of the heterogenetic aspects from a metabolic standpoint. C-peptide data from subjects diagnosed with type 1 diabetes and enrolled in TrialNet intervention study is shown here with 407 subjects from five TrialNet intervention studies. The percentage of individuals with stimulated C-peptide, defined as above 0.2 nmol/L, continues to diminish over four years after onset, and is markedly influenced by age, with a faster decline in subjects below age 12 compared to adults.

[**Slide**] Screening for autoantibodies. Screening associated with monitoring has been shown to result in significant reduction of diabetes ketoacidosis at diagnosis. It is not yet the standard of care. It's currently done in the context of research studies such as TrialNet, which is an international study for relatives of type 1 diabetes patients, and type 1 diabetes antibody screening is done for subjects between the ages of 2 ½ and 45 years. TrialNet also offers prevention trials. Research is now looking at universal screening, and this has been done in Fr1da in Germany, as shown by Dr. Ziegler, as well as ASK, which is a general population type 1 diabetes and celiac antibody screening for children in Colorado, ages 1 through 17.

[**Slide**] Other screening opportunities are developing. One is the PrIMeD study. This is a Virginia project screening for type 1 diabetes genetic risk, followed by antibody testing in those found to be at increased genetic risk. And, more recently, there is the JDRF islet autoantibody screening initiative, or T1Detect, where individuals can sign up online and order a test kit to be delivered to their home. Subjects collect their capillary blood on dry blood spot and send the kit back. Participants then receive their autoantibody results through their online account. This is not a research project, and the cost of the kit is about $59. Families have the option to forward the results to a clinician when signing up.

[**Slide**] Prevention strategies are classified. Primary prevention involves subjects at high risk of type 1 diabetes from a genetics standpoint. These include different studies, such as the TRIGR study which compared breast milk versus hydrolyzed formula versus cows' milk, or antigen-based therapies such as insulin and GAD. Some of these studies are still ongoing, but the results have been primarily negative to date. Secondary prevention involves drugs or insulin, for example, or abatacept at stage one type 1 diabetes, or teplizumab at stage two T1D. And then tertiary prevention are done at stage three type 1 diabetes with the goal to prolong the honeymoon phase [**Slide**] Studies in recent-onset type 1 that have shown a positive, most often transient effect, include rituximab, abatacept, teplizumab, low-dose ATG, as well as golimumab. And then more recently, the teplizumab study in stage two T1D, actually

showed a two to three-year delay to stage three type 1 diabetes.

[**Slide**] I'm now going to be discussing a few studies that are currently ongoing, or have recently been published in type 1 diabetes, including hydroxychloroquine at stage one T1D, teplizumab at stage two T1D, which is now an ongoing study at stage three T1D, and then golimumab, which recently published results at stage three T1D, and is now moving towards a stage two trial.

[**Slide**] In TrialNet, about 20 percent of individuals at stage one type 1 diabetes will progress to stage two within four years. And overall, almost 50 percent of those at stage two will develop clinically overt type 1 diabetes within two years. And, more children than adults typically progress from stage one to stage two, as well as from stage two to stage three.

[**Slide**] Hydroxychloroquine is an FDA-approved agent for the treatment of malaria, rheumatoid arthritis, lupus and dermatological conditions. It's widely used in clinical practice, including in children for malaria and pediatric rheumatology. Hydroxychloroquine has been shown to slow the progression towards disease in subjects who had the pre-disease state in rheumatoid arthritis and lupus. That is the reason that TrialNet is doing a trial in stage one type 1 diabetes. [**Slide**] This is a two-arm, double-blinded, multicenter, 2:1 randomized, placebo-controlled clinical trial where subjects are receiving either hydroxychloroquine or placebo. The primary objective is to determine whether intervention with hydroxychloroquine will delay the progression from stage one to stage two or stage three type 1 diabetes. Secondary objectives include safety and tolerability, as well as metabolic, immunologic and mechanistic outcomes.

[**Slide**] The T1GER study has shown benefits of golimumab, which is an anti-TNF alpha agent, in newly diagnosed type 1 diabetes patients aged 6 to 21 years old. This was recently published in the *New England Journal of Medicine*. On the left, you can see that the mean four-hour C-peptide area, and there's a curve at week 52, was significantly different in the golimumab group compared to the placebo group. On the right, the mean hemoglobin A1C levels were not significantly different between these two well-controlled groups.

[**Slide**] Here, the mean change from baseline through week 52 in daily insulin use was lower with golimumab than with placebo. And, on the right, a partial remission response, which is defined as either an increase or a minimal decrease from the baseline C-peptide area on the curve, was observed in 43 percent of the participants in the golimumab group compared to only 7 percent in the participants in the placebo group.

[**Slide**] This is the first clinical trial, using one course of teplizumab, which showed a delay in the progression towards type 1 diabetes in subjects that were at stage two T1D, meaning relatives who had multiple antibodies and signs of dysglycemia. [**Slide 17: Phase 3 teplizumab**] And, this has led to a phase III study using teplizumab in children aged 8 to 17 years of age, the PROTECT study, where children are receiving teplizumab within six weeks of diagnosis. The goal is to provide outcome data that will support the FDA approval of teplizumab as the first disease-modifying therapy in type 1 diabetes. **[Slide]** The primary objective of the PROTECT study is to determine whether two courses of teplizumab administered six months apart will slow the loss of beta cells and preserve beta cell function in children and adolescents with new onset type 1. The primary endpoint is the area under the curve of AUC C-peptide after a four-hour mixed meal tolerance test, which is the standard measure of insulin production and beta cell function.

[**Slide**] In summary, once two antibodies are persistently present, progression to type 1 diabetes seems inevitable, but is variable in time. We now have our first positive trial with teplizumab delaying the onset of type 1 diabetes, and better understanding heterogeneity will help us tailor prevention strategies for subjects at high risk for type 1. TrialNet in the US and the INNODIA project in Europe are some of the consortiums with the goal of finding type 1 diabetes disease-modifying therapies and prevention. And, these efforts will facilitate personalized prediction, prevention and treatment for type 1. Thank you for your attention.

Dr. Herold:
Anette and Andrea, thank you very much for those terrific presentations.

As you think about screening the general population, it's one thing to do measurements of autoantibodies using a serum sample. It's another thing to do an oral glucose tolerance test, which is not acceptable for very young children to the same extent as getting a single blood draw might be. The question I want to ask you is what your feelings are about the necessity to do this, because the graphs, for the most part, show progression of double antibody individuals. In other words, stage one individuals, and the natural history data, particularly Andrea, the graph that you showed with the different studies, looks pretty compelling that this is going to happen. Is it really necessary to require that oral glucose tolerance tests are done?

Dr. Steck:
As you may know, we have, at the Barbara Davis Center, looked at some other metrics besides the oral glucose tolerance test, and we actually have been doing continuous glucose monitoring, or sensors, in subjects with multiple autoantibody positives in DAISY, which is the study I presented. We're doing that in ASK as well. And so, we have shown in DAISY that if you spend more than 18 percent time above 140, which is similar cutoff than what we can take from the OGTT, you're at higher risk of progression to type 1 diabetes. And, we are currently analyzing our ASK data, which is not yet published, but it seems to be showing similar results. There have been a few

other studies, also looking at CGM, including the TrialNet study, which is also still analyzing results. But, I do think that there are actually going to be other measures that might be easier for following a lot of children, especially those from the general population, such as continuous glucose monitoring.

Dr. Herold:
Anette, what do you think, because you have experience with the very young general population?

Dr. Ziegler:
I think the oral glucose tolerance is still the gold standard, and I think we need to have some idea where the children are in terms of developing hyperglycemia and eventually also DKA in order to also tell them how frequently they have to self-monitor, etc. But, I agree that in the future, that may not be necessarily the standard oral glucose tolerance test. It could be other means that have to be, of course, compared so that we know exactly the definitions of stage three diabetes, for example. But, I think that glucose is important because we know… your studies have shown that as well, that if you have stage two, the progression is much faster than if you are still completely normoglycemic, and that is important information. I think that maybe one oral glucose tolerance test at first staging is sufficient; one doesn't need to repeat that every six month, or three months. But, I think at the beginning, it would be helpful.

Dr. Herold:
Maybe age can be used in that analysis of the data. In other words, a young child with two positive autoantibodies is very likely to progress rapidly. An older individual, maybe then we need to have an oral glucose tolerance test to identify the most rapid progressors.

Dr. Steck:
I agree with Dr. Ziegler, that I think we do need some information on dysglycemia status. Because I think some of our prevention trials, like teplizumab, one of the entry criteria is that they're already at stage two, right? So, we'll probably have more aggressive strategies for someone at stage two than we would have for someone at stage one type 1 diabetes. But, I do think in the future, we'll have probably multiple agents that can help prevent type 1 diabetes. But for these, even just to put them into trials, you would need a way to assess what your dysglycemia status is. And, we have also shown, I think at the BDC, both in DAISY and actually in TrialNet, that you can also do modified oral glucose tolerance tests where basically instead of doing a two-hour test, you do a one-hour test, and you don't even necessarily need to have an IV because what we have been doing is just the fasting and a one-hour test, so it's two blood draws. You don't necessarily even need the IV, which sometimes is an issue in little kids. So, there might be other ways, as either a modified oral glucose tolerance test or, my preference would be probably continuous glucose monitoring, which we have done in the ASK study which, in very young children, and is very well-tolerated to where a CGM for a week or ten days.

Dr. Herold:
Anette, your data is so compelling about the changes in very young children that seem to predict this progression to diabetes. I guess I still have in my mind this idea that we're talking about something that occurs a few years before the onset of disease, and yet what you're saying is that's not really right; it's actually occurring way before that. In individuals who are in their late teens, is it the same story? If we think about the early peak in the onset of diabetes and the later peak, later in adolescence, are those who are developing it later still changing to positive autoantibodies between the ages of 1 and 5? In other words, on a practical basis, you know, I like to use autoantibody screening to be able to tell families the likelihood that your child will develop diabetes is very low. Can we still make those predictions if we screen within the first five years?

Dr. Ziegler:
I think we can. We must say that after a certain age, be it 5 years or 6 years, the risk plateaus. There is still a very small remaining risk over probably the rest of your life. It is never going down to zero, zero, but it is much lower than in the first five or six years. And, this is why I think the first five years are so immensely critical. And, if you have survived them without developing any autoimmunity, then your likelihood is very, very low. But, it is not a hundred percent guaranteed that you don't develop it.

Dr. Herold:
Anette and Andrea, thank you very much. It was very, very good.

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