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ReachMD

www.reachmd.com
info@reachmd.com
(866) 423-7849

Taking a New Approach to Treat Type 1 Diabetes

Dr. Anderson:

As the prevalence of type 1 diabetes continues to climb steadily, there's been a growing push toward more intensive management, which has unfortunately been constrained due to rising costs and the constant demand this form of therapy places on its recipients. But could a new outlook focusing on prevention rather than reversing the disease course change all that?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and joining me to discuss a new outlook on therapies for type 1 diabetes is Dr. Raghu Mirmira, who's a Professor of Medicine at the University of Chicago and the Director of the Translational Research Center there. Dr. Mirmira, welcome to the program.

Dr. Mirmira:

Thank you very much for having me.

Dr. Anderson:

So to kick us off, Dr. Mirmira, can you give us a brief overview of the most common type 1 diabetes auto-antibodies that we see?

Dr. Mirmira:

Yes. So just as a little bit of background, as you point out, type 1 diabetes is really an auto-immune disease, and one of the key signatures of the disease is the development of autoantibodies. And there are several such autoantibodies that develop in the course of disease. In fact, they develop prior to the actual clinical onset of the disease. So people tend to develop autoantibodies against specific antigens like GAD, glutamic acid decarboxylase, zinc transporter 8. They can develop antibodies against insulin itself. Another one called IA2, which are all proteins that really emanate from the insulin-producing beta cell. So several different antibodies that can develop and typically patients who progress to developing type 1 diabetes usually have two or more of these antibodies.

Dr. Anderson:

Well recently, there were some new studies focused on finding ways to prevent or delay the onset of early-stage type 1 diabetes. Can you tell us a little bit about these studies?

Dr. Mirmira:

Yes. So probably in the last five to six years, there's been a sort of rethinking about how we stage type 1 diabetes to begin with, and the reason why is because when we do clinical studies, we wanna know what point in the course of disease are we enrolling patients in these clinical studies. So effectively, there are what is now defined as four different stages of disease. The appearance of autoantibodies is considered really stage 1 disease, the earliest stage of disease. Stage 2 is when the antibodies are there and you have evidence of elevated blood glucose, but not necessarily at the level that we typically consider diabetes. And then, of course, stage 3 is when you actually have full-blown disease or present with it at an early point in the disease course. And then stage 4 is somebody who might've had disease for many, many years. So we have these different stages of disease.

And for the most part, most of our therapies up until now have focused on really stage 3 disease; that's the stage at which individuals effectively present with type 1 diabetes. And almost all of the therapies that have been utilized in stage 3 if they weren't successful, success looked something like, well people continue to require insulin, but their insulin-producing cells continue to produce a bit of insulin on their own. That's considered some level of success, but never have we been able to reverse anybody from stage 3 to stage 2 or stage 1. So given that, now there's been a bigger push to move to the earlier stages, stages 1 and 2 to ask the question, can we begin enrolling patients at those stages, and does initiation of any of these therapies that we have used previously now actually prevent progression to stages that are more advanced, such as stage 3 or stage 4?

Dr. Anderson:

Can you tell us a little bit about how you're identifying these patients at risk? First degree relatives, that type of thing?

Dr. Mirmira:

Yeah. So this is a great point that you bring up. So who do you test autoantibodies in? Well, at least in the United States, we test autoantibodies on somebody who might be a first degree relative of somebody who has type 1 diabetes. So we don't routinely do that as part of routine care of healthy individuals in a clinic. So really the only way we enroll such patients is we know that they've got a first degree relative and then we go and we draw blood and look for autoantibodies in those individuals. So that's pretty much the way we do it.

Dr. Anderson:

What percentage of patients who develop type 1 diabetes can you actually identify first degree relatives that you can actually try to intervene on?

Dr. Mirmira:

Yeah. That's another great question. So it turns out that probably about 80% of patients who present with type 1 diabetes, let's say in an emergency room or in a clinic setting, 80% of those patients don't have a first degree relative, right? So that means the majority of people who develop type 1 diabetes don't have a first degree relative. Now, 20% on the other hand do have a first degree relative. And so the implication there is knowing that somebody has a first degree relative certainly increases the likelihood that you could develop type 1 diabetes, but the majority of people don't, which means that how do we better identify those individuals who are going to get type 1 diabetes even when they don't have a first degree relative? That's the challenge but that's really where therapy is going to need to be directed in years to come.

Dr. Anderson:

Right. Well, I mean, obviously you wanna identify those 20%, but that's a really new mindset in that we're trying to be more proactive rather than reactive. Can you expand on the idea of being proactive in those patients that we might think are at risk?

Dr. Mirmira:

Well, so one of the challenges in type 1 diabetes is that we don't have any kind of therapy right now that we know can delay or prevent the disease. This is different than type 2 diabetes 'cause we know in type 2 diabetes, diet, exercise actually does a remarkable effect on preventing progression to type 2 diabetes, but type 1, we don't really have that. And that's because up until now, we haven't really done any clinical studies on type 1 diabetes prevention. So you can imagine that if we did those studies like we did in type 2 diabetes, we might be able to offer patients a lot more; knowing you had a first degree relative, what can you do to reduce your chances of getting type 1 diabetes? Would it be something like a specific diet or a specific dietary intervention? Could it be taking a particular medication? Those are things in all honesty we just don't know. So right now because of the absence of that data, it's hard for us as clinicians to give any really good advice to our patients.

Dr. Anderson:

For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and I'm speaking with Dr. Raghu Mirmira about type 1 diabetes and a potential new direction for therapies.

So, Dr. Mirmira, let me just ask a question. As you identify patients at stage 1 all the way through stage 4 in the development of type 1 diabetes, is there a level of risk that you're willing to take with therapies? For example, if you're stage 3 or 4, are you willing to try to engage in a little bit of more therapies that have risk rather than stage 1 or 2, or is it all the same?

Dr. Mirmira:

Yeah. That's a great question. So imagine you're stage 1 or 2, you don't have disease or your blood sugars are maybe just a little bit elevated and you're asking yourself, 'Well, geez, what is the risk that I will go on and develop type 1 diabetes, it's not 100%, but nevertheless, there is a chance; would I be willing to take a medication that suppresses my immune system? And then potentially risk severe illnesses to prevent myself from getting type 1 diabetes? And how long should I be taking those medications?' So I think there is a substantial risk in those individuals in stages 1 and 2. But it's a relative risk, so that's something that we have to think a little bit about the downsides of doing it. But it's only a relative risk.

In stages 3 and 4, you sort of already have the disease and so the question there becomes how much risk are you willing to take in an experimental therapy that could have dangerous side effects but could potentially reverse your disease? I think if you asked a lot of people with type 1 diabetes, there's a fair amount of risk they would take if they thought a medication could reverse their disease. So this is different though than if you had cancer. If you had cancer, you'd be willing to take almost any kind of therapy because you know the alternative is death from your cancer. That is not true with type 1 diabetes; we have a pretty good treatment and that's insulin. As

inconvenient as it is, as difficult as it can be to take and control, it is accepted therapy. So there's certainly risk, no matter which stage you're at, but it's a relative risk and I think it's certainly worth pursuing because it's a lifelong disease.

Dr. Anderson:

Dr. Mirmira, if we continue to zero in on this push for focusing on therapies that prevent type 1 diabetes rather than just trying to reverse long-standing disease, what are some of the potential benefits of this type of approach? Both for the clinicians as well as for the patients?

Dr. Mirmira:

Well even though type 1 diabetes represents a small fraction of total diabetes in the world, it's not an insignificant fraction. It's somewhere between 5 and 10%. And you can imagine what that translates to in terms of lifelong costs of medical therapy, right? The psychological downsides of having type 1 diabetes, having your blood sugars uncontrolled, the risk of hypoglycemia, the risk of uncontrolled hyperglycemia, the consequences including kidney disease, eye disease, nerve disease. So the benefits of preventing diabetes altogether are obviously huge, not just economically, but also at a very personal level. Everything from psychology to health, right? Because if you don't get the disease, your risk of any of those complications goes down substantially. And we're talking about lifelong risks, right? There are huge benefits in identifying these individuals. Just like somebody who's obese, there are benefits to putting those individuals who are at risk for type 2 diabetes on a very proven diet, exercise, maybe even medication regimen to prevent the disease and I think it applies to type 1 as well.

Dr. Anderson:

Are there any drawbacks to this type of approach?

Dr. Mirmira:

Well obviously it depends on , the kind of approach you use, right? So if it's medication, there are downsides because medications have side effects, right? So in the case of type 1 diabetes, some of these medications may be immune suppression agents, right? So would you take an immune suppressive agent when you are feeling pretty good? You're healthy, you don't have disease because it could put you at risk for severe infections, for example. So there are medication downsides to it.

There are other downsides. There are lifestyle changes that people may have to make that they don't like making. And that can be a problem, as well in some cases with type 1 diabetes, more so than type 2, many of these interventions have to be done in children, right? And they're of all ages and so given that, there's complexity in whatever risk you might put these kids under by taking a medication or having them adhere to a specific lifestyle.

So I think there are downsides and given that not everybody who's at risk for a disease will develop the disease, the question is, 'How much of that downside is balanced by their risk for disease?'

Dr. Anderson:

Talk to us just a little bit as we come to a conclusion here about TrialNet and how those of us out in the primary care community might be able to target patients who are first degree relatives of those with type 1 diabetes and what might that do for helping research?

Dr. Mirmira:

Yeah, so as you point out, TrialNet is taking an approach that is largely going to be more prevention-based. There are a lot of studies that TrialNet has going for prevention, but the challenge has been to identify individuals who are eligible for these studies. So we're looking for people, basically stage 1 and 2 disease. So those are individuals who have first degree relatives and then are willing to have antibody levels measured and if they get those measured then, you know, what kind of study would they wanna enroll in?

And there's a lot of different studies out there from simply having you followed without any intervention to actual intervention with drugs. So given that, we don't have as many individuals who are first degree relatives; the more of these people we can enroll, the more likely we'll be able to identify potential therapies that can prevent disease as we enroll them in trials. So it's a tougher group to enroll just because the percentage in the population is smaller and that's why going back to one of the first comments you made to me about what are the percentage of people who present with diabetes who don't have a first degree relative, if we can then identify biomarkers that might identify those individuals, we can then open up our pool of patients that we might otherwise screen for autoantibodies.

Dr. Anderson:

Great. Well as we've come to the end of our discussion today, Dr. Mirmira, do you have any other thoughts you'd like to leave with the audience?

Dr. Mirmira:

I guess the thought that I wanna leave is first off, this is the year 2021 and it's been 100 years since the discovery of insulin. And we're

celebrating the discovery of insulin; it's changed the lives of everybody with not just type 1 diabetes, but type 2 diabetes as well. But I think as we look forward into the future, I think we should be excited about the different therapies that exist or could potentially exist. We have technologies such as smart pumps and closed-loop systems that could help manage diabetes with minimal intervention, we have potential STEM cell therapies using your own cells. We have new drugs that can prevent beta cells from dying. So there's a lot to look forward to and I hope it won't be another hundred years before we identify the cure for type 1 diabetes, but I think we can look back at this successful past hundred and look forward to the coming years where we can really begin to employ all the knowledge that we've learned and bear on type 1 diabetes.

Dr. Anderson:

Well, this has been an interesting look at what the future might hold for type 1 diabetes therapies, and I wanna thank my guest, Dr. Raghu Mirmira—for joining me to discuss this research. Dr. Mirmira, it was great having you on the program.

Dr. Mirmira:

Thank you so much for having me. Really appreciate it.

Dr. Anderson:

I'm Dr. John Anderson. To access this and other episodes in our series, visit ReachMD.com/DiabetesDiscourse, where you can Be Part of the Knowledge. Thanks for listening.