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Targeting the Fc Receptor Pathway to Treat Red Blood Cell Alloimmunization

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Targeting the Fc Receptor Pathway to Treat Red Blood Cell Alloimmunization” is provided by Omnia Education.

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Dr. Shulman:
Despite advances in diagnosis and management, hemolytic disease of the fetus and newborn, or HDFN, remains a clinical conundrum. In this program, we'll build upon the basic pathophysiology of HDFN that we discussed in the first episode in this series.

In this episode, we're delving into further detail about the Fc receptor pathway to better understand how it's tied to current and future treatment strategies.

This is CME on ReachMD, and I'm Dr. Lee Shulman. And I'm again joined by Dr. Ken Moise, Director of the Comprehensive Fetal Care Center, a clinical partnership between Dell Children's Medical Center and UT Health, Austin.

Dr. Moise:
And hi, I'm Dr. Ken Moise. Glad to be here.

Dr. Shulman:
Dr. Moise, let's dive right in. What can you tell us about the basic biology and function of the FcRn receptor and how it relates to HDFN?

Dr. Moise:
Well, Dr. Shulman, the FcRn receptor, it really has 2 functions in the human body. One we all know about it, were taught in immunology classes in medical school, that it's associated with the transport of IgG across the placenta to the fetus. And so that's one of its main functions.

But another function, less known probably to the practicing obstetrician, is that it's also involved in maintaining the circulating pool of IgG throughout our bloodstream. Now, the FcRn basically can be considered a protector of IgG. IgG is brought into the endothelial cells that line the blood vessels. It binds to FcRn, which basically rescues it in acidified endosomes, and then it's returned to the surface of the endothelial cell and brought back into the circulation.

If it's not bound to FcRn, which happens with some IgG, it ends up being circulated to lysosomes. And there it's degraded into its various fragments. So clearly, IgG is maintained by the FcRn receptor in the circulating pool of IgG in the body.

Dr. Shulman:
You know, by its basic impact on IgG, I think we'll be discussing later on in this presentation about the potential of myriad of options for treatment modalities in a variety of conditions.

But before that, Dr. Moise, how can we apply this to our current practices? And so in other words, what's currently available for our

patients, and what do these medications actually do?

Dr. Moise:
So there's various clinical trials, both phase 2 and phase 3 clinical trials, ongoing with a variety of FcRn receptors. One has already been approved just recently, I believe it was the end of last year, for the use in myasthenia gravis. And that's in patients who have positive antibodies for anti-choline receptors. And in those particular types of myasthenia gravis, this particular FcRn receptor has been found to be clinically useful in decreasing the incidence and symptoms of those diseased in a dramatic fashion. So it's out there already being used.

There are, as I mentioned, trials ongoing. There's only one trial in pregnancy that I'm aware of. And it's for the use of a monoclonal antibody called nipocalimab. Again, an FcRn-blocking receptor, but in this situation it's being used in cases of severe HDFN to try to prevent the disease and the anemia we talked about earlier in the fetus. So that phase 2 trial has recently closed. The data is being analyzed by Johnson & Johnson, the company sponsoring that trial. And they plan to submit that data to the FDA. To my knowledge, although I don't know the results of the trial, I know there have been no safety issues. I know the trial has not been prematurely stopped.

So FcRn now has become an interesting therapeutic target for a variety of alloimmune, that would be what we're talking about here with red cell alloimmunization, but autoimmune diseases too. So, much like in myasthenia gravis, there's a whole series of autoimmune diseases that haunt us, and we don't have good treatments for those. Many of those patients are on steroids, or they're on various other immunosuppressive drugs. Maybe they get intravenous immune globulin. And all of those things are not that effective because they're sort of generalized immunosuppressive therapies.

But if we could block IgG specifically, we would have a treatment for a variety of diseases. And I know there are trials ongoing for things like immune thrombocytopenia purpura, a warm autoimmune hemolytic anemia, Graves' disease, and chronic inflammatory demyelinating polyneuropathy. So there's a variety of trials that are addressing these auto- and alloimmune diseases using FcRn receptors.

Dr. Shulman:
You know, Ken, even though I'm not an immunologist, this whole topic is incredibly fascinating to me. Because what you're essentially saying is that the potential for focused therapeutics for a variety of conditions for which, up until now, we've had suboptimal interventions, mostly involving steroid use, has the potential to completely change our approach to autoimmune and immunological conditions. And I think its role in HDFN highlights its potential use not just in pregnancy but elsewhere.

So in that regard, let's turn to safety. What are the side effects we need to consider when using FcRn blockade during pregnancy?

Dr. Moise:
Well, as we mentioned, one of the major mechanisms of FcRn is to protect the circulating pool of IgG. So once you administer these medications – and they're either given intravenously or subcutaneously; they're not available as an oral preparation yet – you drop the circulating total amount of IgG. And it can drop by as much as 70% to 85%. So that means you're left with a 15% pool of circulating IgG. And of course, in that situation, we're worried about the possibility of infection.

Now in the one human trial in pregnancy, and in all the other ongoing trials, there have been no real alerts, no safety alerts of inordinate infections. But of course, we have to be a little bit concerned about that, given that these patients are walking around with 15% of their IgG levels. And so that's one of the biggest issues with that.

Now we know, interestingly enough, the FcRn receptor is also tied to albumin circulation. And so it is also involved in maintaining the up-circulating albumin pool. So there's the potential, because it's closely related to IgG, that this FcRn receptor blockade can drop albumin levels. And of course, those drop in pregnancy in general. We know that women who are pregnant have lower albumin levels towards the end of pregnancy. So we'd have to be worried about the potential for edema formation in pregnant women who would be on FcRn receptors.

There is some possibility, because albumin and lipid are tied together, that in order to maintain oncotic pressure, we know in some diseases that when albumin drops, lipid levels go up. So we have to be cognizant of the fact that these patients may have higher lipid levels as a result of dropping albumin. But the beauty of using these drugs in pregnancy is we're using them for a short period of time. So unlike, say, a patient with myasthenia gravis, this would only be several months of therapy for particular diseases like alloimmune thrombocytopenia or red cell disease, and you would stop the drug. So any effects on lipid metabolism, albumin, or even IgG would go away as soon as you stop the drug. In fact, the studies show within 2 to 3 months, you're back to baseline levels.

Dr. Shulman:
You know, that's so interesting, primarily because we're looking at its use not just in the mother, but in its impact on the fetus. And I

think as these medications go through their ongoing evaluation, it will be very interesting to see not so much how it impacts the fetus, but how it impacts that neonate and as that neonate grows into childhood.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Ken Moise. We're just about to delve deeper into maternal fetal conditions, focusing on FcRn blockade.

Dr. Moise, can you break down the potential clinical applications of FcRn blockade in maternal-fetal conditions?

Dr. Moise:
So if we can think about the alloimmune diseases related to the transfer of, if you would, pathogenic IgG to the fetus, we can think of a whole series of diseases that might be a target for FcRn blockade.

The first one that comes to mind, of course, is red cell alloimmunization. We know the antigens involved, usually D or Kell, or little c, and we know the antibodies involved. Now, if we block those antibodies, and as we mentioned earlier, if we drop the circulating level of those antibodies, so in that situation the maternal titer would drop, we would have a twofold hit if we would, two different mechanisms that would help us prevent the transfer of IgG and to lessen the amount available for transfer so that we would hope the fetus would escape the effects of these antibodies.

We can, in an analogous situation, think about fetal and neonatal alloimmune thrombocytopenia, an analogous disease to red cell alloimmunization, where in fact, if we could block antibodies again and reduce the circulating level, that fetus may not develop a low platelet count.

There are other diseases like congenital heart block. We know that anti-Ro, anti-La antibodies from the mother can cross the placenta, attach to the conduction system of the fetus, and cause congenital heart block which can be lethal. And so again, if we could stop that transfer, we could prevent that disease from occurring.

There are lesser diseases like gestational alloimmune hepatitis; we don't see that very often. Again, we don't know the antigen involved, but we believe that alloantibodies from the mother cross the placenta, and cause permanent liver damage and even death in a newborn child from fulminant hepatitis.

And if we think about this, if we're already using it in adults with autoimmune diseases, then what about things like antiphospholipid syndrome? We know that's a terrible disease in pregnancy. We know that those autoantibodies in the pregnant woman can attack the placenta, if you would, causing thrombosis and intrauterine growth restriction and even fetal death. So there's the possibility of even dealing with some of these autoimmune diseases in pregnancy by using FcRn receptor blockade.

Dr. Shulman:
Ken, I must say that you've brought us to what I consider to be the threshold of an entirely new approach to these conditions that have, as I said earlier, not had great interventions up till now. And for me, it's exciting to see how this will unfold and how we will be able to improve both maternal and fetal outcomes going forward in those pregnancies affected by these conditions.

So in that regard, Ken, what are your main take-home messages for our audience today?

Dr. Moise:
Well, Dr. Shulman, as you point out, I think that this is an exciting time. We are looking at changing the paradigm of using older techniques, like intrauterine transfusion that was introduced in 1963, and thinking about medically treating these diseases. So we may end up putting needles away and treating these people medically both for FNAIT, where we don't have a great treatment other than IVIG, both for red cell disease, where we put needles into fetuses and give them blood, and for other diseases. And I think we're going to see medical therapy become the reality in the next few years for some of these diseases that where we really haven't made that many major advances in their treatment. But this is pretty exciting. We're looking at a new paradigm here.

Dr. Shulman:
You know, for me, I think the important thing for our audiences is getting back to something I said in our first episode, which is that everybody's on the hook here, everyone needs to be screened for antibodies regardless of their past obstetrical history, regardless of anything that happened in the past. Because we obviously now have the real need to identify these people early so that we can provide, potentially, these new interventions that are going to make such an enormous difference in the clinical outcomes, again, both for Mom as well as for the fetus and newborn.

Unfortunately, that's all the time we have today. So I want to first thank our audience for listening in and thank you, Ken Moise, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Moise:

Well, great speaking with you, Lee. I appreciate the opportunity.

Announcer:
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