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Precision Starts Before Birth: Reimagining Fetal Care Through FcRn Immune Modulation

Dr. Moise:

Today we're exploring how FCRN inhibitors are poised to change the management of antibody mediated fetal neonatal disease conditions like hemolytic disease of the fetus and newborn and fetal neonatal alloimmune thrombocytopenia, and the pivotal trials every maternal fetal medicine clinician should know about. This is CE on ReachMD. And I'm Dr. Kenneth Moise.

Dr. Markham:

And I'm Dr. Kara Markham.

Dr. Moise:

So before we jump into the therapeutic side, let's pause on an important clinical question. Dr. Markham, could you help us identify which pregnancies are at risk for immunization?

Dr. Markham:

Uh, well, all women are technically at risk for alloimmunization. Um, there is always some of the fetal blood that gets into the maternal circulation during pregnancy or during delivery. Um, and that can potentially cause an immune reaction that results in antibodies being formed that can cause fetal anemia. So all women are screened for this early in pregnancy via what we commonly refer to as the prenatal battery. Um, we can then use different things to kind of stratify that patient's risk of disease, including things such as her history of having a baby with fetal anemia, um, or what antibodies she has. Uh, which antibodies, um, sorry, I'm gonna stop that.

Dr. Moise:

Before we jump into the therapeutic side, let's pause on an important clinical question. Dr. Markham. How do we identify which pregnancies are at risk for immunization?

Dr. Markham:

Isation, all women are screened for potential red blood cell alloimmunization. Uh, routine blood work in early pregnancy includes a type in screen, a test that will identify the presence of red blood cell antibodies that can potentially cross the placenta to cause fetal anemia. We can then stratify the patient's risk of the baby becoming anemic in a number of different ways, including identifying what type of antibody she has, uh, how much of the antibody is in her system commonly caused, called a titer, um, and or if the father of the baby and more importantly, the fetus have the corresponding red blood cell antigen. Um, if, for example, the fetus is negative for the antigen, there's no risk of hemolytic disease. But further monitoring is certainly warranted if a fetus is positive for this antigen. Um, this can involve serial antibody titers if the patient has no history of hemolytic disease and the antibody titer is below a critical level. Otherwise, we start monitoring via ultrasound with middle cerebral artery Doppler monitoring. We start that weekly as early as 16 weeks to screen the fetus for anemia. And if anemia is suspected, we either will have to recommend delivery if the patient is 35 ish weeks pregnant or beyond, or intervention by a fetal transfusion. If the patient is earlier in gestation.

A similar condition is one called fetal neonatal alloimmune thrombocytopenia or fate. Um, this is a baby that has low platelets at birth

and can have associated bleeding, including most critically bleeding within the brain, having such a history. Maybe the only indicator that a, a patient is at risk for this disease. Um, we don't routinely test moms for antiplatelet antibodies. Now that can be done, um, if the patient has a history of a baby with low platelets or, uh, intracranial bleeding. Um, but the management differs quite a bit from HDFN in that there's no ultrasound screening that can tell us if a baby has low platelets. So management primarily involves trying to tamp down the immune system using something called intravenous immunoglobulin, um, and then proceeding with delivery often via a c-section to prevent bleeding in the brain at the time of delivery. In uncommon situations, we can monitor the platelet count and provide transfusions, but this has really largely fallen out of favor. Um, now importantly throughout all of this, to optimize these outcomes for HDFN and FA patients should be referred to a maternal fetal medicine specialist specialist with expertise in these diseases.

Dr. Moise:

No, thanks for those comments, Dr. Markham. And I think you make a, an important, uh, comment about determine if the fetus is at risk. We know that free DNA is now available at 10 to 12 weeks of gestation, particularly for different red cell antigens and it's commercially available. And more recently, I believe you can actually determine the fetal platelet antigen status through, uh, genotyping by free DNA. I think that's an important change.

Dr. Markham:

Yes, definitely. That has really revolutionized our management of these diseases and simplified them for some women, for sure. Um, Dr. Moise, can you walk us through how the neonatal FC receptor, also known as the FCRN, contributes to the pathology of auto, of alloimmune conditions like HDFN and FA?

Dr. Moise:

Uh, sure. So, uh, FCRN is an important, uh, structure, uh, found in two different places. First, it's found on the epithelial cells that line blood vessels, and we can think of it as sort of a recycler or salvager. So it actually, uh, grabs maternal IgG from the serum, uh, when it, uh, and then incorporates it into the cell, into the endothelial cell, and then it recycles it and protects it and returns it back to the serum. So it is very, uh, important in its role in maintaining the half-life of the circulating pool of IgG. The other thing we all know is that ffc, RN is the major transport mechanism to have maternal antibodies cross through the placenta to the fetal side. Now obviously, all good antibodies can cross. That's how babies get immunity at birth from their mothers. But in alloimmune conditions, pathogenic antibodies like anti D or anti cal or antiplatelet platelet antibodies are cross the placenta. When these antibodies that are pathogenic cross, they can attach to fetal red cells or to the fetal platelets in the case of FA and cause either fetal anemia or fetal thrombocytopenia with the risk for intracranial hemorrhage. So

Dr. Markham:

The management that we have already kind of discussed can be lifesaving, but it's entirely reactive, not preventative. These disease processes can greatly impact the health of the pregnancy revi requiring very close monitoring, possibly even invasive treatment with risks of complications and even death of the fetus or newborn. It would be far preferable to avoid anemia due to HDFN or thrombo thrombocytopenia due to h um, I'm gonna start that again. 1, 2, 3. It would be far preferable to avoid anemia due to HDFN or thrombocytopenia due to FNA entirely. So if FCN is the gatekeeper here for IgG antibody transfer across the placenta, what happens when we block it? Let's kind of explore that therapeutic rationale a little bit further. Dr. Moise, how does FFC RN inhibition work and what makes it especially promising for alloimmune disorders during pregnancy?

Dr. Moise:

Well, as I mentioned earlier about the mechanism of ffc RN blockade, these monoclonal antibodies, uh, actually attach to the FFC RN and block it, block it from working and doing its salvage operation, uh, along the epithelial cells. So that lowers the circulating level of pathogenic antibody, but more importantly, they block the placental passage of these antibodies across the placenta and so that we don't see pathogenic antibodies getting to the fetal side at all. What's important about these is that it doesn't affect T-cell function and it doesn't affect other subclasses of antibodies like IGA or IgE, and therefore it's only the IgG that's affected by this particular blockade. Uh, IVIG probably works in a similar fashion in blocking the ffc RN, but it's probably about a thousand fold less, uh, potent, if you would, than a nippo cide, which is one of the antibodies we're gonna be talking about today.

Now, the proof of concept for this idea came in the Unity trial, which was a phase two open-label trial when nivolumab was given to 13 patients that were at very high risk for having recurrent HDFN. Many of these patients had had previous losses or multiple transfusions in previous pregnancies. They were enrolled in the trial, received weekly doses, nippo umab. And what we found is that it decreased the rate of intrauterine transfusion by 32 weeks by almost half. So less than half of the patients needed any transfusions, uh, before 32 weeks. And the gestational agent deliberately was markedly increased. The live birth rate was almost tripled. And so it seemed in this

phase two trial to be very effective. And when we looked at the babies, although their IgG levels were slightly lower because of the blockade at the placenta, the babies did not develop any overt unusual infections during their pediatric life. And they seem to respond to vaccines. So the good news is that this blockade is short acting and reversible, and that's especially important in pregnancy because we don't want this to stay around a long time, but just be there for the pregnancy itself.

Dr. Markham:

So that was certainly a very promising, I would even say landmark study. Um, that's the science behind it. And let's talk a little bit more about how we're poised to bring this more into clinical practice. The Azalea trial is an ongoing multinational trial that aims to do just this. Dr. Moise, what's the focus of this phase three trial and how could it potentially change the treatment landscape for HDFN?

Dr. Moise:

Yeah, thank you for that question, Dr. Markham. So after a phase two trial, which does two things, it's basically a safety trial and it's also a trial where you determine the correct dose that you need for effectiveness. So as I said, the original trial was the phase two trial, and now we move to the AZALEA trial, which is ongoing, which is the phase three trial. Now, a phase three trial by FDA requirements is a randomized trial with a placebo arm. And so in this trial, we're gonna pick patients who've had HDFN, but anybody who had a previous transfusion or fetal hydrops would qualify, or if patients had a loss or even a neonatal loss with an antigen positive baby. And they have titers like anti D, anti cal, et cetera, including some other antibodies like c little C and E, and they have significant titers, which we'll define as more than 16 for most antibodies and more than four for Cal, they would be, uh, qualify for this trial.

As I mentioned, it's placebo controlled. It's a two to one placebo controlled trial, so you're twice as likely to get the drug as being in the placebo arm. It's also blinded. So the investigator and the patient doesn't know whether they're in the placebo arm or they're in the treatment arm. All patients are followed very carefully with, uh, weekly ultrasounds and managed the same way they would be managed as if they get the drug or the placebo. The goal is to prevent anemia and reduce or even eliminate the need for transfusions. So we move from a reactive type of treatment in pregnancy to a true prevention of fetal disease. And obviously this will have major implications in the future for the timing of how these patients are treated and the availability of treatments in a more widespread basis, particularly in centers that may lack clinical expertise in interuterine transfusion.

Dr. Markham:

Um, and you know, that's certainly fascinating and con revolutionize our management of HDFN, but um, I think we can also imagine how this therapeutic agent could play a role for any antibody mediated drug, uh, I'm sorry, start that again. That's certainly very promising and can revolutionize our care of patients with HDFN, but I think we can imagine how it could potentially impact our management of any antibody disease. Uh, ah, sorry, I'm having trouble with this one. Um, so yeah, so this, this trial certainly has the potential to revolutionize our management of women with alloimmunization to red blood cell antibodies and potential HDFN, but I think we can also imagine how it could affect any antibody mediated disease process in pregnancy.

Dr. Moise:

Well, that's an excellent point, Dr. Markman for that reason. Um, there's been an extension based on the data from the phase two trial on HDFN to take on the next disease that's related to maternal alloantibodies, which we mentioned earlier, which is FNA or fetal neonatal, all immune thrombocytopenia. So the Freesia one study expands on the use of NPO used in the phase two HDFN trial to women with a history of of FA. So Dr. Markham, could you tell us a little bit about the FREEZA one trial?

Dr. Markham:

Yes. So as you remember, FA is different from HDFN in that we don't routinely screen for it. Women usually have to have a bad outcome with a baby, with low platelets, even intracranial bleeding in order to know that they're at risk for it, and we can't non-invasively screen for the baby's platelet count. Um, so the FREESIA one trial is a trial that aims to use nivolumab for hopeful prevention of FNA. It's a double-blinded, randomized placebo controlled trial evaluating the safety and efficacy of nivolumab in reducing the risk of severe FA in at-risk pregnancies. So women are potential candidates for enrollment if they have a history of at least one pregnancy complicated by FA based upon either platelet count or a history of intracranial hemorrhage. Um, they also have to have certain anti HPA antibodies, um, and the fetus has to be positive for this antigen.

Um, according to cell-free DNA, um, they're randomized to receive either nivolumab or placebo at a two to one ratio,um, starting, um, at, uh, between 13 and 28 weeks of gestation. And the primary endpoint, um, is primarily looking at things like fetal death, um, severe in utero or neo neonatal bleeding, or a platelet count of less than 30,000. Of course, there are a number of different secondary endpoints as well as, um, the fact that the trial will collect data related to both maternal and fetal safety. So in brief, it's the first trial to evaluate the use of nivolumab for prevention of FNA in its sequelae. Um, and patients are actively being enrolled in several

international locations.

Dr. Moise:

No, I think that point you make about it being an international trial is key. As you know, in our countries we'll talk about in a moment, IVIG seems to have called it taken hold as a clinical way to prevent thrombocytopenia in these pregnancies. And so doing a placebo arm trial is much more difficult. However, that being said, in many of the European countries, IVIG is not routinely used in some of these pregnancies. And so doing a placebo based trial is possible. So I think it's gonna be interesting to watch this trial, uh, used and decide maybe what the role of IVG, uh, whether this is superior to IVIG, uh, in these particular patients. So let's move on and talk about Freesia three, which is another trial using nmid in these FNA patients. So Dr. Markham, can you tell us what the key aim is and how does this FREESIA three trial differ from Freesia one?

Dr. Markham:

You already kind of outlined that to some degree, Dr. Moise. Um, as you mentioned, pH freesia one is placebo controlled and women are excluded from enrollment if they've received or plan to receive intravenous immunoglobulin or IVIG during pregnancy. And that's feasible in many countries where IVIG is not standard of care in prevention of FNA. But practitioners in other countries like the US have routinely adopted this, and their, uh, simply is not the clinical echo poise right now to permit a trial that withholds standard therapy. Um, so the Freesia three trial is, uh, designed to address this potential issue. It's an open label randomized trial comparing nippo to what we consider standard management, which there are very well out, uh, outlined protocols involving use of IVIG, um, plus or minus prednisone with the altering dosing of all of that, depending upon gestational age and severity of disease.

Um, clinical inclusion inclusion criteria are very similar to Freesia one. Um, enrolled women are randomized to either receive nivolumab or IVIG at a four to one ratio. Um, and again, patients randomized to receive IVIG will be further stratified as either having a history of what we call standard risk FA or high risk FA. And the dosing of IVIG initiation of IVIG varies depending upon which of those categories they are sorted into. Um, the endpoints are very similar to that, a Freesia one. Um, and again, there are several locations in the US and internationally that are actively enrolling patients, allowing us to offer participation, participation in research involving nivolumab for prevention of FNA to a larger cohort of patients worldwide.

Dr. Moise:

No, Dr. Markham, I think you make an excellent point that in this study there's no placebo arm, right in freezer three, it's either randomized to Nippo or to IVIG. So there is no placebo arm. So patients are getting treatment, uh, with standard of care versus this monoclonal antibody. I think this is an exciting trial to help us decide, does Nippo cate, is it a better drug to treat these patients than IVIG since we hope it's more effective, and at least in the lab appears to be a better FCRN blocker than IVIG.

Dr. Markham:

Yeah, that's all absolutely true. And with all of this in motion, let's talk a bit about the role of clinician awareness and why this matters now more than ever.

Dr. Moise:

So I believe it's very important, obviously, to see these patients early in pregnancy. Uh, most of these patients are aware that they've had a previously affected pregnancy, whether it's with HDFN or fna, uh, and so they would come in, we hope to see their obstetrician or their maternal fetal specialist fairly early. Now, many obstetricians don't see this disease very often, and so we would hope that they are referred to a specialist who could timely refer them to a specialty center research site. In the case of HDFN, it's the azalea trial again, for fna, it's freezer one or freezer three. These, uh, there are, there is information on clinical trials.gov. Uh, both of these trials. Azalea has its own website, uh, specifically about the trial that list all the different centers throughout the United States and internationally. I think there's about 60 centers worldwide doing the Azalea trial. And so by getting these patients early, because these patients have to be randomized early in gestation before the antibody begins to cross, typically before even 18 weeks of gestation, getting them early for screening visits to determine their baby's antigen positive and then getting them enrolled in the trial and getting the placebo or drugs started would be important. So it's important to get these people there early to see if they're candidates and then get them enrolled in the trial if they choose to participate in the trial.

Well, this has certainly been a fascinating conversation, but before we wrap up, Markham, can you share with us sort of a take home message for your audience?

Dr. Markham:

Um, sure. Dr. Muis, I agree this is such an exciting topic and my take home message is that there's hope on the horizon for women with a history of these antibody mediated diseases, women who have potentially lost babies, had babies die in utero or, um, pre due to prematurity or had, uh, babies with intracranial bleeding and significant neurologic issues related to that. We strongly encourage our MFM colleagues to familiarize themselves with the current literature and the available opportunities for their patients so that their patients can potentially enroll in these trials and help us determine how nivolumab can best play a role in our management of these, uh, these disease conditions.

Dr. Moise:

Well, in my final take home message is that I'm most excited about these trials because I think they provide an opportunity to treat patients who don't have to move to specialty centers. We know that doing uterine transfusions take special surgical expertise. If we could treat these pregnancies medically, imagine the fact that the patient wouldn't have to travel great distances to get expertise. They could be treated by their local maternal fetal medicine with an infusion, and in a very effective way that would not put the patient to the psychological risk of multiple surgical procedures. We know that we do multiple transfusions in these pregnancies when we do treat them. So I'm excited about the future and the fact that we might be able to treat this disease medically. So I wanna thank you, Dr. Markham, for helping us today, uh, understand how we, uh, could use these drugs and how we can, um, let me go back on that. I wanna thank you today Dr. Markham for, uh, explaining to us about these clinical trials. And, uh, I appreciate your time today, and again, it's been great talking to you.

Dr. Markham:

Um, yes, and, uh, thank you Dr. Moe Moise. I agree this has been a great conversation and I I hope that the audience has enjoyed what we've shared.

Dr. Moise:

Okay. Can I ask a question? I don't know what the management of MUC is. What is MUC for our mid tag? For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Kenneth Moise, and I'm here today with Dr. Kara Markham. We're discussing recent advantages in the management of FCRN in the Alloimmunized pregnancy. For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Kenneth Moise, and I'm here today with Dr. Kara Markham. We're discussing recent advances in the management of Ffc RN blockade in the Allo pregnancy. Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Markham, can you share with our audience your one take home message?