Rituximab Treatment Patient Education Webinar- April 19, 2023

Becky Strong: Welcome, everyone! This call is now being recorded. I'm Becky Strong and I will be your host for today's webinar. Thank you for joining us. I would like to thank you for being on the call with us and for the support provided by Sanofi and Regeneron, for making today's call possible. I would like to start off today with a quick poll. Let us know if you are considering taking Rituximab as part of your treatment regime or if you are currently using Rituximab for the treatment of your disease? And while you are answering the poll, I would like to introduce you to our speaker for today.

Dr. Donna Culton completed her medical degree at the University of North Carolina at Chapel Hill. While there she also earned her PhD in the Department of Microbiology and Immunology where she studied autoreactive B cell development and regulation. She continued her training at UNC and following her Dermatology residency she began applying her knowledge of autoreactive B cell pathophysiology to pemphigus and pemphigoid. In her current position as Associate Professor of Dermatology at the University of North Carolina at Chapel Hill, she serves as the Director of the Clinical Immunofluorescence Laboratory and the Associate Director of the Clinical Trials Unit at UNC. She sees pemphigus and pemphigoid patients from North Carolina and neighboring states in her specialty Autoimmune Blistering Disorder clinic. She has served as an investigator in clinical trials in mucocutaneous autoimmune diseases, has contributed to consensus statement publications as part of the International Blistering Disease Consensus Group, and supports outreach, education and advocacy through her involvement with the International Pemphigus and Pemphigoid Foundation.

Now I would like to go over a few housekeeping items. You will remain in listen-only mode through this webinar. For those of you who are on their computer for this webinar, you will see on your screen that you can access the audio either by using your telephone to call in or from your speakers on your computer. Click on the little carrot or up arrow next to "audio settings" in the bottom left hand side of your screen. As you see on my screen right now you have the option to select your computer speakers or to dial in by telephone. Please be sure to select the method that you will be using. If you would like to ask a question please click the Q&A button on the bottom of the screen and then type your question into the text box. We will try our best to answer as many questions as we can within the hour. Please feel free to type your questions into the text box throughout the presentations. Dr. Culton will be answering your questions at the end of the presentations. On the webinar today we will be discussing Rituximab. If you ask a question that does not pertain to the webinar subject I will have to ask you to email me after the webinar. For those of you on the call that aren't on the web, you will not be able to ask a question. So if you would like to ask a question, please click on the link that was provided to you in your confirmation email. Now, it is my pleasure to hand it over to Dr. Culton.

Dr. Culton:
Great. I'm really excited to be here with you today. This is such an important topic, and pretty complicated. So I'm going to share my screen. I do talk with my hands a lot, so I don't know if

you have the option to like. Leave my little, you know. Picture up top, but I may be doing some hand gesturing to help kind of explain what we're talking about here. So we're gonna talk about Rituximab. I think this is where you all start your journey with what you see on your skin. So blisters or open sores. Sometimes those are crusted over like you can see here on the skin and in the mouth, and I don't have any mouth pictures, but we know many, vast majority of patients have a pemphigus in their mouth as well. And so this is what we see on the skin. What we see under the microscope. This is all going to lead us to our talk on Rituximab so hang in there with me. What we see under the microscope and pemphigus is, we see, a split in the epidermis right? And then what we see in pemphigoid is a split from the epidermis away from the Dermis. So it's a little bit deeper in the tissue. And so those you know, those are the essentially under the microscope what your blisters look like, and the whole problem here is caused by antibodies, and it's antibodies that are attacking proteins that hold your skin cells together, whether that be skin cells in the mouth or skin cells on what we think of as the skin. And so those antibodies we can actually find in your skin, and we can also find them circulating in your blood. And so these pictures on the right here at the bottom, are the immunofluorescence to confirm the diagnosis. Vast majority of patients will have a biopsy for direct Immunofluorescence. And so you can see here in Pemphigus that we see the green kind of outlining every single skin cell that's antibodies all around every single skin cell. And then for Pemphigoid, the antibodies are right there, where the epidermis meets the dermis. So the 2 layer of skin cells attach, and so their antibodies attacking those proteins that are holding your skin cells together. So antibodies are the problem, and antibodies come from B lymphocytes. So I put this up here just to remind everybody when we say blood counts or blood cells. There's lots of different types of blood cells. So there's red blood cells that bring oxygen around to your tissues. There's platelets that help with clotting. And then there's the white blood cells, and the white blood cells come in all different varieties, and the one that we're going to be talking about today are the lymphocytes and the white blood cells fight against infection right? The lymphocytes come in 2 flavors B cells and T cells. And so here I have the B lymphocytes. And I put the little asterisk there because B cells are the ones we're going to be really focusing on today. So B cells come in a vast majority of what we call specificities like what they recognize out there in the world. I call them flavors or different colors M and M's. I use all kinds of analogies, but there's a bunch of different types of B cells with different specificities, and most of them are good guys that bind to the protein you get when you get vaccinated, or viruses, or bacteria, or all the bad things out there in the world that are trying to get us. The B cells recognize all those different things. But there's some bad guys, and those are B cells that react to self proteins. And so your body, you would think. Well, why would the body even let the bad ones exist, and it doesn't. As so in most healthy patients these bad B cells are identified and eliminated before they can get out and wreak havoc. But sometimes a few bad ones sneak out. And so these are all the different types of be like, just, you know. Again, it's just a picture to show there's all different kinds of flavors of B cells, and the one we're going to focus on is the red one we're going to say, that's the bad guy that somehow snuck out snuck past all these mechanisms to keep the bad guys in check like broke out of jail. Okay? And so again, the antibodies come from the B cells, and we just talked about how a few bad B cells get out. And so now I'm going to take you back to where you know where do B cells come from like, how does this even happen? And so these cells are born in the bone marrow that's where they're

first born, and then they leave the bone marrow, and they go out into the spleen, and the lymph nodes and kind of out into the the body, where they grow up and they become mature B cells. And then, once the B cell sees its protein target right? I told you they all have different ones and have different specificities. Once it sees its target protein, it goes into a germinal center that usually happens in spleen or lymph nodes, and the germinal center is where the B cell gets even better at recognizing its target. Out of the germinal center you get 2 different things. You get cells that secrete antibodies right? So, and then you get memory B cells so B cells that remember. Oh, I've seen this protein before, and the next time I see it I'm going to respond even more quickly. So there's 2 things that kind of come out of the germinal center. Antibody secreting cells or memory B cells. and the antibodies secreting cells come in 2 different varieties, long lived ones and short lived ones. Okay. And so then they, I call them like the factories, antibody factories, right. The antibody factories, the plasma cells. They secrete the antibodies. The antibodies get up in there next to your skin cells, causing the separation and the blisters. So if you could imagine the types of treatments that would, I've just explained to you rapid fire where these bad B cells, how they grow up, and then they make the antibodies and the antibodies are the problem. And if you could design any treatment you wanted, you would say, Well, what would I, what would I go after? And so sometimes I feel like I would go after the antibodies, because you just told me antibodies are the problem, and we do have some treatments that go after the antibodies. The tricky part is the antibodies are being made by the antibody factories, and so, if you never get rid of the factory. You're going to always get the antibodies back.There's not any really great treatments that target the antibody factories. And so, instead, what we end up doing with medications like Rituximab or other B cell depleting medications is we target everything that comes before the factories, and it's kind of like cutting off the supply. And so we can do that. You'll see the little hot pink kind of Omega sign. Here. We do that because all these other B cells have a little protein on their cell surface that we can use as a kind of a target for ourselves.

So what is Rituximab? Rituximab is a medication that recognizes CD20. Again, It's like the little pink thing on top of the B cell. It recognizes any cell that's expressing a CD 20, and so the good news is CD20 is only on B cells, and it's only on the B cells from the previe to the mature B cell stage. It's not on not on the factories. It's only on those kind of everything that's feeding in to make the factories. So what happens is all the B cells that have this CD20 on the surface will be eliminated, and the medication doesn't know the difference between the good B cells and the bad B cells. So all the B cells are eliminated, and what I explain it like it's like wiping the chalkboard clean. We like to erase all the B cells and then the good news is, your bone marrow can make new B cells. So it's like resetting everything with a new batch of B cells, and hopefully a bad one doesn't sneak out again this time. And so people wonder sometimes like how did anybody ever think of using this in Pemphigus and pemphigoid? And so it was. Actually first the medication was first developed to treat B cell cancers, which are called the B cell lymphoma. and a few patients that had B cell lymphoma, and happen to have Pemphigus we're treated in both the lymphoma and the Pemphigus got better. And so a lot of doctors started realizing. Hey, wait! This makes sense. If we knock out the B cells, we may eventually make the factory shut down, and then there's no more antibodies to cause trouble.

So we're back to our picture. We're going to come back to this a lot, because I think it's like a nice landing place to kind of remind us of what we're doing here. So again we're wiping out all these B cells that have the CD20 on the surface. The bone marrow still has these little pro B cells, because they don't have CD20, and so it can make a whole new batch of mature B cells to go out there and help us fight infection as we just talked about the factories here that make the antibodies. They don't have CD20 on the surface, so they're still there, which you might say. Well, then, you know that's a problem because they're still going to be making antibodies. Well what we think is happening is that most of the antibodies that cause these autoimmune blistering disorders are coming from the factories that don't live very long. So they have like a short little half-life. So when you cut off their supply they eventually die, and then the antibodies stop coming. So that's how we think Rituximab is working especially well in our diseases.
Okay, so now that you kind of understand that Rituximab is wiping out all of these B cells. How do you know what else it does? So when I think about what happens to the B cells after Rituximab. I just told you we eliminate them. So after the Rituximab infusions, the B cells that you can measure in the blood are completely gone. You can't even barely find them. They don't even register on the test to look for B cell counts in the blood. And so this is a graph of like how many B cells do you have? The average here with the little line is 300 times 10 to the 6 per Liter. Okay, you don't need to pay attention to the units so much, but 300 right after you get the infusions like you can't even detect it fairly right. You can't find B-cells, and then, just like I said, the bone marrow starts to make new B cells, and that starts to happen around 6 months. So here this is the 6 month mark. So you start to see like a little blip that it's they're coming back, but truthfully like this is a year, day 360 here and this is 2 years, and the B cells still are not even back to that kind of where we started from. So really your B cells are starting to come back, but they're not fully back for a few years. Okay, what happens to the antibodies? I told you antibodies caused the problem. So what happens to the antibodies following Rituximab? This is a graph of just antibodies desmoglein 3, but desmoglein 3 looks pretty similar to what you can see here is that the antibodies drop down in days. We're here at 60 days, so they start way up here. They drop down at about 2 months. and you might say, Well, why, if the B cells went away right away, why did the antibodies take longer to go away, and it's because you have to wait for the factory to shut down, and then you have to wait for the antibodies to live their life, which is about 3 to 4 weeks. So there is a lag time after you get the infusions before the antibodies go down, and if I told you the antibodies are the problem. So most patients don't start seeing improvement for about 6 to 8 weeks to about 2 months.

So, dosing protocols. This gets really confusing when people talk about well, there's all these different ways you can get it. And so there's 2 main dosing protocols. the Lymphoma protocol. Again. I told you this drug was developed for B cell lymphomas. The Lymphoma protocol is four weekly infusions, like every week for 4 weeks, and you can see it's kind of weird here. 375 milligrams per meter squared. So it's a little bit based on your size. Meter squared. The second dosing protocol is rheumatoid arthritis, or Pemphigus protocol. Now it's approved for Pemphigoid.. So this is the one that's FDA approved. It's 1,000 milligrams no matter your size, 1,000 milligrams at day 0, and 15 the other way to say that is two infusion spaced 2 weeks apart. So no matter whether you're getting the 4 times 4 weeks, or the 2 space 2 weeks apart. We call that a cycle. So the number of infusions starts to get really confusing. If I don't know

what protocol you're on, we call them a cycle, and you would do one complete cycle of either of these different protocols. There's been a lot of off label protocols used like some patients. Then, if they get it, they only get one infusion of 1,000. There's like, I mean right, like a lot of different protocols have been used. Oftentimes Rituximab is combined with other medications like prednisone or other immunosuppressive agents, or IVIG and a lot of that has to do with it, because it doesn't kick in as quickly as we would want. You know we can't leave someone suffering for 2 months, and so a lot of times we combine Rituximab with other medications that maybe work more quickly for patients, and then the cycle, whichever one you end up doing. The cycle can be repeated every 6 months, and I put it as needed. So there's been as we started using this medication and our diseases. Most of the doctors who treat the disease there has been a bit of a debate, or like we talk with each other like what should we be doing? Should we just do it every 6 months, and never look back, or can we somehow, like reassess before the 6 months is up like. Does this person need it again? And so we'll talk a little bit about that in the next few slides.

So, a lot of the data that people want to know. Well is it going to work for me? How well does it work? Most of the reports that had come out were like one doctor, saying I had 5 patients. I had 10 patients. I had, you know, a little case series right, but it was never a controlled study. And so these are the 2 controlled studies, and what I mean by controlled is that there was an active treatment arm with Rituximab and then a group of patients who did not get Rituximab and it was blinded. So the patients didn't know who was who, the doctors didn't know which patient was getting what and the group that did the study compared at the end, which group did better. And so we call that, you know, a randomized controlled trial. So the first study was the Rituximab versus prednisone alone. There were 91 patients. It's like a lot of pemphigus patients who went into this study, and then what happens is they would start the prednisone, and people will get better just like most of you have experienced, like when you're on prednisone things are good. When you come off of prednisone it gets bad again. So they had prednisone for everybody. So everybody was good, and then they tried to taper the prednisone down, half of the patients were getting rituximab and the other half was not. And what they found out was that 90% of the patients that got rituximab reached complete remission off of prednisone at 2 years. It's kind of a long time to wait, but most patients had no blisters, complete remission, no blisters, and no prednisone. Which is right. What everybody's going for versus only 34 of the prednisone. And there were more actually problems, side effects in the prednisone arm, because, of course, those patients were on prednisone for 2 years, and we all know prednisone is really great when you need it, but it's not ideal to be on it for 2 years, if you can help it. Okay. So the second study was rituximab versus mycophenolate. So some of you are familiar with mycophenolate. It's another, it's a pill that suppresses the immune system that before rituximab came around was one of our main medications we used. And so this study had Rituximab and prednisone or mycophenolate and prednisone in 135 patients, and it was half and half in this study 40% of the patients that got rituximab reached complete remission off prednisone. You had to be offering them for 4 months, and this was for a year. So now it's not the 2 year mark. That was the first study, but at a year 40% of patients were off prednisone for 4 months. That's great. Only 10% of patients in the mycophenolate arm reached complete remission off of prednisone for 4 months. There were more flares in the mycophenolate arm. So you can see here 6% in the rituximab

arm versus 44%, so we all know that it's terrible when you're doing great, and then you have a flare. Feels like it really sets you back mentally, emotionally, physically, and so there were more flares in the mycophenolate arm. There were more infections in the rituximab arm, but not by a ton. So 22% Rituximab arm versus 15% in the mycophenolate arm. So that's some heavy data. But that is the best data we have right now to really show us that Rituximab works. I had reviewed some of the questions that came in before the webinar and some people were asking well like, Why would I do rituximab over some of the other medications that are available like mycophenolate? And this is one of the reasons why, right? Because we now have data that side to side compared randomized control trials. Rutuximab actually works better. So that's why you know, a lot of patients are choosing rituximab these days. So there was a question of like, is it considered first line, and it is now considered one first line, which means you don't have to try other medicines. You can go straight to rituximab when you get your diagnosis and second, that it's the gold standard. So really it's setting the standard for how Pemphigus should be treated. So all of this data is in Pemphigus. I know many of you probably have pemphigoid, and we just don't have as much data. So lots still of those little case series or case reports. But no big trials like this so far in Pemphigoid.

Okay, so then you're like, Well, why would I not do it if it's so wonderful? And really it has to do with safety. So most dermatologists partner with an infusion center. So very few dermatologists are doing this in their office, so we usually partner with an infusion center that has nurses, and oftentimes physicians who are trained to kind of respond to any infusion reactions. So it depends, like most of the time, like your doctor would write the orders, and then the Infusion center team would carry out those orders. and again it's so that you can be monitored while you're getting your infusions in the immediate infusion period infusion reactions are what we worry about. So infusion reactions can be mild. A lot of people might get a little fever, or they feel a little chilly, or maybe they get some hives, and the infusion team centers are usually really good. We have orders in place that if this happens, then I want you to do this. And so a lot of times it is like slow down the infusion rate. Stop the infusion and give a little benadryl, and let's see how the patient does, and then maybe restart at a slower infusion rate. So there's things that can be done to to kind of mitigate a mild infusion reaction. Then there's what we really worry about, which are severe infusion reactions. Trouble like serious trouble breathing like a drop of your blood pressure. Again, for this reason is why the vast majority of my patients get their infusion in an infusion center. So if these things are happening, you want somebody who knows CPR. Who can really like Epinephrine there? They can give it to you like they can handle the situation. Severe infusion reactions are rare, but they can happen, and you just want to be at a place that they like. See it all the time, and they know exactly what to do. So infusion reactions, Really, people wonder. Well, what are they right? Does that mean I'm allergic to the medication? Not necessarily. An infusion reaction can happen to any drug that is getting infused in your veins. So IV so anytime you put something in through the vein your body can have, like a freak out moment where it's like. I don't like what's happening. I don't like this going in my veins. And so it starts to do all these things that I just talked about like fevers, chills like random stuff can start to happen. Your body is just kind of having a freak out moment, but it doesn't mean that you're necessarily allergic to the medication, and so we often do premedications which can help reduce the risk of an infusion reaction. and it's things like, Benadryl, Tylenol,

sometimes a little bit of IV steroids, just to kind of like settle the immune system down so like when you get your infusions, it doesn't freak out.Then some people ask like, is re challenge possible? So like you had a terrible infusion reaction, is it possible you could ever try again? And it is. And so we just adjust the premedications like maybe a little more potent premedications. Higher doses go real slow, so we don't like, crank up the infusion rate. So someone asks about like, how long does it take to get an infusion? It kind of depends. So if your body is handling it, and you're not having an infusion reaction. You know the nurses have their orders like started at however many milliliters per minute, and if you're doing great after 30 min you can crank it up a little faster, so it can go in a little faster. So if you're doing wonderful they kind of just increase the infusion rate per whatever the orders are, and you could get out of there pretty quickly. But if you're somebody who had an infusion reaction. We might just stay at a very low infusion rate, which again just means to get the whole volume in, you have to be there longer. So especially for first timers. I say, just plan on the whole day. Don't be in a hurry to go anywhere. It'll take however long it takes, and they'll make sure that you get the medication and get it safely.

So other side effects. So those are infusion reactions which I would say are pretty common. Actually, there are other side effects. The ones we really worry about are severe infections. So severe infections happen about 8% of patients getting Rituximab. Typically in that first 6 months where you don't have any B cells, not even the little ones coming back.
And then there's a 2% lifetime risk of fatal infection. So that's no joke. That's you know that's serious. It really suppresses your immune system pretty aggressively. You know 2% might seem that high, and it's not that high. We talk about these diseases a lot like they used to be fatal diseases until we had some of these medications. You know most of us that treat it would say rituximab is actually probably safer than prednisone, especially in the long run probably safer than some of our other medications. We even just saw that mycophenolate even has a pretty high rate of infection. So it's something to keep in mind. I put it there to say like, when you say, why wouldn't I do Rituximab. That's one of the reasons. And then I put here triple whammy, because I think the patients we have data that the ones who are at highest risk for a severe infection are people who are on all 3, Rituximab, another pill, I have ISA here which means immunosuppressive agents. So something like maybe you're on Rituximab and mycophenolate and prednisone. All 3. Those patients are at the highest risk. Those are the patients I worry about. You know that I can't go to bed at night because I'm like, I sure hope they're okay. So you know most of your physicians will be trying to get you off the other medications as best they can. So you're not on all 3 at the same time.

So monitoring, some questions came up about like. Well, how do I need to be monitored? So most of the monitoring in terms of blood work is done beforehand, and the biggest thing is hepatitis. So a lot of people are exposed to hepatitis like back in the day, and their immune system kept it under wraps. So they didn't even know they were exposed to it. They didn't even know it was like hanging out there in their body, because they didn't ever fully manifest as hepatitis. So most patients, we ask if you have hepatitis, I mean you kind of know if you have hepatitis, but most people say no. And so we still look to see. Have you ever been exposed to hepatitis? And so that's a blood work that we would do beforehand, and that's because hepatitis

can be latent and Rituximab can allow it to reactivate. So if you're someone who had been exposed to hepatitis, and your immune system was kind of keeping it under check. You oftentimes have to go on an antiviral treatment before you can get on your Rituximab and that's just to minimize the possibility that hepatitis would reactivate. Blood counts, so typically like in my order set for Rituximab I have blood counts on the day of the infusion, like I don't need to know 2 months in advance necessarily. But the day of, if you have some of your blood counts are really low, particularly neutrophils, we might not do the infusions. It might not be safe for you. If you have a little bit of low lymphocytes especially if you've already had some Rituximab. Well, probably we knocked out your B cells, and that's why your lymphocyte count is low, but so most of the blood counts are actually done the day of the infusions for most people. And then kidney function again, just to make sure your kidneys can handle the medication. So it's not so much that the Rituximab is going to affect your kidneys. But if your kidney function is kind of wimpy it might be a. And again that one's a minor one. I don't really worry so much about kidney function. Most patients can handle this amount of medication. And then really no other monitoring is recommended after the infusions are done, so we wouldn't, you know, repeat anything until you're due for your next set of infusions. The only thing we might look at are your circulating antibodies, right? Your disease antibodies in your blood. And I'll tell you why we would look at that after the infusions.

So what I mean I just told you, like all this stuff, the bad stuff that can happen. What are the good things that can happen for being on Rituximab besides your disease getting better. So there have been studies to improve quality of life on patients that get Rituximab, and this is a weird one that just kind of came out. Somebody had asked about Why, I just told you about liver and kidneys and stuff. What about the heart? Improvement actually and long term cardiovascular risk and metabolic outcomes as like patients with diabetes and stuff on rituximab. Improvement. And nobody really knows why they haven't explored it yet, but maybe it's because patients who are on rituximab have lower overall exposure to prednisone, and we know prednisone can cause trouble with especially diabetes, right? And heart attacks and stuff like that. Or maybe there's some B cells involved with atherosclerosis. We don't really know. But anyways, patients that got Rituximab actually did better than those that were on azathioprine or mycophenolate So just some cool data that we don't fully understand yet, but I think is another one of the benefits. So in summary of responses like when you take those 2 big studies, and then all the little case reports and case series, and you put them all together. This is the take home message about how it works.

So, 3 bullet points, complete remission. That means no blisters in 75 to 85% of patients. So that's wonderful, that's pretty great, but it also means that 15 to 25% don't get complete remission after their first cycle. And I think that's one of the things that people get really excited about, like, okay, I'm ready. I like psyched myself up. I'm going to do the Rituximab and then they're like, why do I still have blisters like the magical like 2 months have passed, and I still have blisters. It can be really frustrating, but not everybody gets complete remission. But most people do. If this came up in some of the questions. There's a lower rate of remission in patients who had an increased amount of time from when they got their diagnosis, or when they first started having Pemphigus to when they got their Rituximab. So if you can get it within the first

year or so, maybe 2 years of your diagnosis. That's better than if you've had pemphigus for 20 years, and you get your first Rituximab. You're just less likely to go into complete remission after that first cycle if it's been a really long time. And I can explain why in another slide I'm going to go back to that picture and tell you why we think that's true. The time to complete remission is so great that 75% to 85% of patients are going to complete remission. How long does it take? The medium amount of time is 2 to 3 months, and again that lag time, I mean the B cells are eliminated immediately. I told you that, but the lag time is due to the lifespan of the factories and the antibodies themselves. So, about 2 months. So I tell my patients 2 months we have to wait before we even hope that we're going to see any improvement from the Rituximab and then this is the downside: the relapse rate is 50% to 70% of patients will have a relapse. Meaning you went into complete remission. You were lucky enough to be in that 75 to 85% of patients about half of patients. And this old comes, so that's, not the people who got it like right away, and it was the first thing they ever tried. This includes everybody who's had it for either a short period of time or a long period of time, but it's usually at about a year and a half. And again in my mind that's kind of like when the B cells are really fully back is when you're at most risk of a relapse. So what happens if you relapse? What should you do? Does that mean Rituximab is just not for you? What if you're one of the 15% to 25%, that didn't get complete remission after the first cycle? Does that mean you're never going to respond. Well, there's 2 studies, and I kind of combined them here. 150 patients. and they had the Pemphigus protocol the 2 infusion space 2 weeks apart. So again, 75% of patients went into remission after the first cycle. If you just kept doing cycles every 6 months the remission rates were 90% after the third cycle. So again it just keeps going up. The more cycles you get. So this is the data that we use to say- Okay, if you didn't respond to the first doesn't mean, you won't respond to the second. Let's do it again. And so this is another thing that again I mentioned all the Pemphigus doctors talk about a lot when we get together is, how can we predict who is going to have a relapse? Is there anything we can do to predict? There's a lot of research going on into this question. We don't want to be giving people Rituximab every 6 months if they actually went into remission. And how would we know if we just keep giving them the medication?

Some of the data that's come out is like baseline characteristics. How do you first start with your disease? So again increase time until you get your Rituximab. If it’s been 20 years you've had Pemphigus and you finally get your Rituximab. You might be somebody who relapses. You're more likely to relapse if you get your Pemphigus at a young age. If you have a high body mass index. If you have any mucosal involvement, like significant mucosal involvement. If you had horrible disease when you first started, these are like our numbers that we use when we measure how much disease activity. But in my mind, if somebody is very severe and covered when they first start, that somebody who's more likely to relapse. Dosing factors. So some of those lower doses, lower dosing protocols. We don't use so much anymore because they have a higher risk of relapse. Then the Lymphoma protocol might work better, especially in larger patients. And you remember when I told you that's the one that's kind of based on how big you are. The 375 mg per meter squared. So that kind of makes sense is that the pemphigus protocol is one size fits all, but for some larger patients it might not be enough. So Lymphoma protocol has better efficacy in larger patients. Then the response if you knocked out our B cells, that's great. B Cells coming back are associated with the relapse, and so we don't tend to check B cell

counts in the blood, because if they're there and you don't have a flare, I'm not going to do anything. It's mostly I'm going to look at you and say, do you have blisters on your skin? That's what we're going to use, not your B cell counts, but most of the time B cell counts don't start coming back for 6 months, and it's after that when they start coming back that we're at risk for relapse. And so that makes sense. If I told you the antibodies are the whole problem and you don't have any in your blood, you're less likely to relapse than somebody who does have antibodies still in their blood. And so when I'm with my patients, and we have done the Rituximab and we're coming up on the six-month mark, and we're trying to decide should we do it again? These are all the things that we take into consideration. So if you still have any pemphigus on your body or in your mouth. If you're still needing prednisone or any other medication right? The whole point of doing this is so you don't have to be on all the other stuff if you still have Pemphigus antibodies in your blood. If you had a severe disease, let's say none of these things are true. You have no blisters. You're not any other medicines, and you have no pemphigus antibodies in your blood. Do we have to do it again? If, when I first met you, you were covered in blisters, we might just do it again, anyway. And then the other thing to consider really is immunosuppression. We are just still kind of coming out of this pandemic. But during the pandemic some patients were like, I do not have any blisters. I don't have anything. I don't want to do it again, because I don't want to stay immunosuppressed. I'm ready for my B cells to start coming back. The other reason to consider not doing it again just for kicks is cost. But there was a study that showed that over the long run it's actually cheaper. Rituximab is cheaper than being on all the pills and the blood work that you might need to monitor to be on those. So just again and keep that in mind.

And so why does Rituximab work better if you use it earlier? I told you about the 2 different types of factories. There's the factory that can keep going forever, even if you cut off its other supply of B cells. And then there's the little short lived factories that shut down really quickly after the B cells are eliminated. And so what we think is that early on in the disease it's mostly the short-lived ones that are making the pemphigus antibodies. Where as like, let's say, you have the disease for 20 years, maybe now you start making these long-lived factories that like you can cut off the supply going into them all day long. They don't even care. They just live forever. So again, that's why I think the earlier you use Rituximab is probably why it works better.

So why do relapses happen right? I just told you we like to erase the chalkboard. There's no more b-cells. The bone marrow is going to make a new healthy batch that doesn't have any bad guys in there. Why do relapses happen then? And so there was a study that looked at. We can tell it's kind of like sciencey and nerdy, but we can tell the exact flavor of the B cell, and it has to do with the sequence of amino acids like what the protein looks on this particular part of the antibody, but we can tell. And so they did studies where they looked at somebody who came in with pemphigus. They looked at the flavor of B cells or antibodies that they had. And then, after they got rituximab that patient went into remission. No B- cells. You couldn't even find them in the blood. But then, when the person flared they looked again it was the exact same flavor of B cell coming back. So it wasn't like a new bad guy got out of the bone marrow. It was the same B cells, and what we think is that. you know. Maybe they were just hiding. So those memory B

cells like maybe they persisted somewhere, and they came back. And so there's a lot of research now going into like, Where are those little B cells hiding between Rutuximab? So, like the disease goes away. But then it can come back, because you have a few little naughty b cells hiding out there. And so we think it's probably in the skin, actually, but a lot of data is going into that right now our research.

So I've been talking mostly about pemphigus just because that's again where we have the most data. But I would say the second disease is the most common disease that we use Rituximab in in Mucous Membrane Pemphigoid. And so we don't have a big randomized control trial, but we know it works really well in these patients. And so this was a big study that came out of France, whereas 109 patients all at the same center. So a single place in France saw 109 patients, and what they did is, they gave Rituximab again the 2 infusions 2 weeks apart. They gave it every 6 months until the patient went into complete remission, and what they found was that it took to get to complete remission. It took a year. You remember I was telling you about the pemphigus patients. It takes typically a couple of months for these patients itt took a year and 85% of patients had to get a second cycle. And so what it means to me is that for this disease it works, but it's just a little slower to respond than pemphigus. So I use a lot of Rituximab in mucous membrane pemphigoid patients. I will say like a lot of times, I'm looking at other medications that might be maybe safer, less immunosuppressive. But if someone has it in their eyes or in their esophagus not just mucous membrane pemphigoid in the mouth. If there's other high-risk places where they have the disease, a lot of times we'll move to Rituximab pretty early on. Again, just not as much data in the other diseases. And then, Covid. There were a few questions about Covid. What we found when we kind of looked at all of our autoimmune blistering patients is what the AIBD stands for. There were no real differences in the rate of positivity. So it wasn't that, like our immunosuppressed patients or blistering patients were getting Covid more between Rituximab and the other immunosuppressives. But the people who are on Rituximab had worse outcomes with Covid. So more likely to be hospitalized, or even pass away from Covid. And this was early on in Covid. We know it's rapidly changing, and maybe it's not as severe now as it was a year ago or two years ago. But again, the disease itself does not make you more likely to get it or have a bad outcome, but it's our treatments that do. And so Rituximab is especially immunosuppressive.

Then, vaccines. So a lot of patients ask about this. If I wiped out your B cells, you do not have any B cells to respond to a vaccine, so the vaccine is safe for you to get. But, like you don't have any B cells to come running and respond to it. So what we found was that most patients on Rituximab did not mount an antibody response to the Covid vaccines afterwards, and it wasn't just like If you had had Rituximab in the previous 6 months, it could be all the way to a year, a year and a half since you have Rituximab, you still might not make a response, an antibody response to the vaccine. You do make T cell responses. And so there's still studies going on to try to understand if the T cell responses people make can still protect them from Covid. Is that enough? Or do you need the B cell response to? So in general, we tell people that there's some data saying, if you hold your immunosuppressive treatments, and that's like the pills. You can't hold Rituximab. But if you hold the pills a week or 2 before and after it. Might it might have you respond better. and truthfully, the current recommendations are to get vaccinated and boosted,

and really time it as best you can. So there's never an ideal world when you're trying to balance like. What do I want my pemphigus to flare or. I want to build a vaccine. So it's a lot of moving parts, and you just time it as best you can. Ideally, a month before you getRituximab or 6 months after is the best time to get a vaccine. Okay. this came up a lot. Reasons not to do Rituximab. Ithink we covered a lot of these throughout, but it is long-standing immunosuppression. We say 6 months. But I already showed you. That's not true. Is usually a year and a half, maybe even longer, and there's no way to reverse it quickly. So there's no antidote to bring the B cells back more quickly. Once they're gone, they're gone. You have to wait for your bone marrow to make more. The cost, there are manufacturer assistance plans available. So a lot of paperwork, but it can be really worth it, even if you have insurance, and your copay is very high. The manufacturer assistance plan can work with you sometimes, and provide some assistance on your copay. But again I already said it might be cheaper in the long run. So even though Rituximab is a lot of money in the long run it might be cheaper than doing the other medications. Mild disease, so someone asked about this. Well, if I have a mild disease, why should I not get Rituximab? And really it's a personal decision between you, your family, your physician. Because it's all about risk and benefits. So I even think, if I had a really mild disease, would I go for Rituximab? I'm not sure I would if I could get away with something that is not as immunosuppressive. Someone asked, why should I not do it? What if it is not working. Maybe you have only long-lived factories, and Rituximab is just not working. You do it every 6 months. And you've done it for like how many times I think I have one patient that's done 10 cycles. At some point you just have to pause and say, like I just don't think it's working, and so does it really makes sense to be that immunosuppressed if it's not working.

Then, finally, the side effects. Again it is mostly about infusion reactions or the side effects of having an infection. Okay, I don't even know how many slides I have left. I think we're near the end. Biosimilar, What’s a biosimilar? We get a lot of questions about this. A biosimilar is a nearly identical medication that was just made in a different factory but it's nearly identical, and I think of it like a generic, and most of the time the insurance companies may have some deal with the different factories or companies. But they work almost identically to Rituximab and if your insurance says I'm not paying for Rituximab. I'm only paying for Truxima. I mean they're nearly identical. They have not gone through the whole big study with randomized control, because it's identical medications like you wouldn't put a generic through that same study. And so this is similar. And so in general, we go with what your insurance approves, and these are the ones that are out there. Truxima, Ruxience and Riabni which is the only one that's FDA approved. So the FDA is starting to approve these biosimilars as well. But somebody said, is there a cost savings? Not always unless you know it's only like which one does your insurance? It's not like they're always cheaper than we're talking about. But with your particular insurance it may well be cheaper to do the one that they approve versus Rituximab.

I know that was a whirlwind. I again covered as many questions as I could in the presentation itself, but still 41 questions. I'm going to go back to my little B cell slide. Just so we can have that up in case it's helpful.

Becky: There's a lot of great questions.I think you already answered this. About how long does Rutuximab work or last rather?

Dr. Culton: It really is patient to patient. When you say last. The effects on the B cells can last anywhere up to a year and a half, 2 years. And so you know it really just depends on it. Some people never even get better after the first cycle. But if you are one that gets better after that like that's an average that, So a year and a half on average, if somebody is going to flare when they relapse. But that's an average. So some people relapse later. I do have a handful of patients that got Rituximab early, and they just stay in remission. I see them every year for, like, their skin cancer check and we always look for any lurking signs of Pemphigus. But they're just not there. So that's a patient, I would say, is in remission right in clinical remission. No pemphigus antibodies in their blood, no Pemphigus on their skin, and it's been years since they had their Rituximab. Does it mean it won't come back? No, it could, but probably not.

Becky Strong: Why is it important not to have any infections before getting a Rituximab treatment?

Dr. Culton: I mean it's really just because it's knocking out your B cells right? So if your B cells are going to be helpful to fight that infection, you're fighting a fight, and we're going to now tie one arm behind your back if you don't have your b-cells. So, mild colds, or whatever I mean, there's things that I would say are fine. We can still give it. But if you have raging pneumonia, yeah, probably we shouldn't probably get rid of your B cells just yet. So again a lot of times, we say, let's treat your infection, and then we can do it.

Becky Strong: Great. One member of the community is asking, Can we rituximab if we're trying to get pregnant?

Dr. Culton: I mean it 's not ideal, but also I think it does cross over the placenta, and so we try not to. But there's no medication that's really safe during pregnancy that we have to use. And so, you know, there's times where I would say the medication itself. Okay, so something to think about. The medication itself is out of your system in about a month. right? And so I didn't really talk too much about this, because it gets confusing. Rituximab itself is an antibody.So it gets confusing. But antibodies already said, they only live about 3 to 4 weeks, so the Rituximab itself is out of your system in a month. Now the effects of it we already talked about lasting longer, having no B cells, having low antibodies. but that part wouldn't translate to the baby, and so in my mind you could probably get your rituximab and then wait a month until it's out of your system, and then try to start getting pregnant if that makes sense.

Becky Strong: Great. And then we had a question, a couple of questions that I'm trying to link them together. That was asking about the use of Rituximab in pediatric patients. The one question that I saw was specifically talking about a 2 and a half year old with PV. And if this medication can be used to treat past pediatric patients with pemphigus and pemphigoid and how effective is this?

Dr. Culton: The hardest part in kids. So I think my youngest and biggest patient that we used it in was maybe 7 at the time. Pemphigus and kids are rare, but it can happen. And really the tricky part for children is those vaccinations, right? So adults get vaccinated like, maybe once a year for the flu. If you do that, maybe pneumonia, shingles. Kids get vaccinated all the time. And so I think the harder part is managing their routine vaccinations. You know, and then kids get sick all the time, too. I think about it. But in general Yes, it can be used, and it's just really kind of making sure that you're coordinating with the pediatric team on how to make sure that we're getting the vaccinations in that we need to get in

Becky Strong: Great.There are some other questions about. After getting rituximab infusion, and knowing that you're B cell depleted. What are some precautions that you should take to keep yourself healthy? Or if you have family members who are getting rituximab. What's the best thing to do or activities to stay away from that sort of thing?

Dr. Culton: Yeah, I chuckle at this because I think before the pandemic we would always say like, oh, don't go around sick people don't let somebody be sneezing all over you all that stuff. But patients just live their life. I mean, maybe they stayed away from somebody who is really sick. But in general patients just live their life, and they mostly define. But now, with the pandemic, I think we all know how to lock it down if we need to, and so really it's kind of a spectrum. I tell patients like ideally you wouldn't be in a large crowd, or like now we all know how to wear masks. For better or worse. We know how to do it. And so those are easy things that you can do, but it really is becoming now more of a personal preference on how much you limit your activities, because you're immunosuppressed. And so I just again try to remind ourselves of what life looked like for patients on Rituximab before the pandemic and they were not going to crazy extremes, taking precautions to protect themselves from possible pneumonia, or what have you. I think it's a spectrum. It's a personal decision. What I tell my patients mostly is. You know you're feeling better. Your blisters are going away, your mouth is healing and then you get like a little chest cold, and you're like it's nothing. It's just a chest. I feel great. You just have to take your symptoms more seriously than you used to. So if there's a change, maybe it's not like precautions and avoiding things, but it's like listening to your body and taking things more seriously than you used to, because it's not like a pill you're taking every day, I'm immunosuppressed, I'm immunosuppressed. You know it's like you've got the infusions, and you're done, and you can kind of forget about it, and sometimes your primary care physician forgets about it. And then you start feeling really lousy and everybody forgets that you're immunosuppressed because it was 4 months since you had your infusion. So I would just say to take your symptoms seriously, do not ignore stuff if it's getting worse especially, or persisting, and to get worked up quickly and remind everybody. Hey, I'm immunosuppressed.

Becky Strong: I imagine it's a little bit independent as well. Lily is asking if I if she's had one Rituximab treatment 2 months ago. Is it safe for her to get on a plane and go on vacation at the 3 month point while being immunosuppressed?

Dr. Culton: Yeah, I would say it's a personal decision. I love vacation, and I love traveling. And so the same I think about patients, Say, can I go back to church, or can I go, like there's things

that people miss doing. And again, pre pandemic people would do these things all the time. So I will say, you know people are getting Covid when they travel. People who have locked it down for 3 years are finally traveling. They're getting Covid, so that's what I would be more worried about. But again you know how to wear a mask. You know how to keep yourself safe, but staying away from big crowds. But again, I think it's such a personal decision, and I would hate to tell somebody don't go travel if they've been saving up and waiting for this vacation. But just be smart about it.

Becky Strong: Yeah. And I think talking to your doctor right to to help you to weigh out the the risks and the benefits of going.

Dr. Culton: If you're going to the middle of nowhere and you get really sick or if you are also on mycophenolate and prednisone after the Rituximab. That's a different story. So I agree, probably talking with your physician about your personal risks of travel would be a good idea.

Becky Strong: Thank you. Sharron is asking. Does weight and length of time of having MMP change the outcome or success of using Rituximab like it does with Pemphigus?

Dr. Culton: Yeah, we just don't have that data right now. So I think it's hard to know. When I now talk to my MMP patients, I say you are probably going to need it every 6 months or a while, and I think someone in one of the pre questions had asked. Is there a problem with me getting it every 6 months from here to eternity? And truthfully we don't. I mean, besides being immunosuppressed for that long. We don't think so. We haven't seen any other like cancers coming after Rituximab we haven't seen like I would say rheumatoid arthritis patients which is also FDA approved, for they pretty much get it every 6 months like forever and ever, and and I and they they don't think about this like oh, should we dose and redose. Should we not redo those? They've just, I think, as a community and I could be wrong, but it seems like most of my RA patients are just getting it per from the rheumatologist every 6 months, and so that's kind of the thing to consider is that we're not so far seeing any other problems with being on it long term. And so for MMP patients just knowing that data takes longer to get complete remission. If, especially again, if you have high-risk areas of involvement I think ocular saphagile, you should probably just get yourself ready for a few cycles, but we just don't have the same data about early use versus late use.

Becky Strong: Great. Thank you. Corey is asking, how do you handle the use of Bactrim to prevent pneumonia and patients after getting Rituximab?

Dr. Culton: Yeah, that's pretty hotly debated at our nerdy pemphigus doctor meetings. We talk about a lot. So any time you're going to be on prednisone, So you don't 100% need it for just for Rituximab. But if you're going to be on prednisone for over 20 milligrams for over a couple of months. Many infectious disease doctors would say that you need to be on some antibiotics to prevent pneumonia. The risk of somebody getting pneumonia is pretty low. A lot of so it's we're a lot of doctors are on the fence of like. Do you just give everybody yet another medication right here we go. You just got told you have pemphigus you're reeling. You're like, what is this

disease nobody's ever heard of. And now I'm giving you prednisone, and then you're gonna have. You know we're getting you psyched up for Rituximab or whatever the other treatment is. And now I'm like, and you have to worry about your bone health, and you have to worry about your pneumonia. And here's this other pill, and so I think a lot of doctors do not, but some do, and so I would just speak with your physician again about your own personal risks and kind of where you are right. Some patients are like, I take my chances, and other people are like. No, if I want to do everything to prevent everything, and so they want to get on it. The bactrim specifically, rarely, very rarely can cause this other terrible skin condition that a lot of us see called T. N. or Stephen Johnson syndrome. And so I think we also are like not the bactrim because it could do this other thing, but again super rare, almost as rare as getting Pemphigus. But you know we see it in our hospitals, and so I think we worry about it a little bit. But yeah, it's a good question, and again, no clear consensus on it right now.

Becky Strong: Great, Thank you. There have been a couple of questions about the use of IvIG with Rituximab as well, and I was hoping you might speak to that as well.

Dr. Culton: Yeah. So a lot of protocols use Ivig, or say a lot of physicians. And again, when you think about that lag time that's going to happen from when you get your infusions and your B cells go away to when the antibodies finally start going down 2 months later. Some patients during that period of time. Maybe they can't handle prednisone, or maybe you know, the prednisone is not working for them, and so IVIG is a treatment that can be really helpful.It's another IV treatment. So you're like getting all the IV's. If you're getting Rituximab and IVIG. So you have to get it 3 days, either in a row or ideally within the same week and it only lasts about a month. So it kicks in pretty quickly, usually kicks in within a week or 2, but only lasts about a month, and so. It's temporary and it's hard to do because you have to go to the infusion center again 3 days out of the month and then once later you have to do it again. And so what it really is doing. It's targeting the antibodies, but again, not the factories. And so a lot of people use it in combination, because, like you're getting rid of the antibodies immediately, and then you're eventually going to cut off the supply to the factories with Rituximab and so it can be a nice treatment to use together. I think the tricky part that we all kind of struggle with is, I just told you that Rutuximab itself is an antibody. So if I'm giving you an IVIG that's going to target antibodies like, could it accidentally target the Rituximab as well and not make it work as well. And so a lot of times when I combine these two I try to space them apart a little bit. So you're not getting Rituximab and infusion one day, and then 2 days later, getting your IVIG. But that again is a little bit of personal preference on your position, but they absolutely can be used together, and beautifully. Just takes a little coordination and a lot of infusions.

Becky Strong: Great. We are getting questions about breastfeeding, both with Truxima and with Rituximab. Should you be breastfeeding when you've had these infusions?

Dr. Culton: Yeah, really tricky again, I think it goes back to antibodies that can cross over into breast milk. And so again, ideally, during that period of time where the antibodies could potentially still be that Rituximab or Truxima itself. They are antibodies that could be in your blood. Ideally, you wouldn't be breastfeeding during that month after because it could transfer to

the baby, and the baby then could not have the B cells or the antibodies that you want them to have. Ideally what happens if you also give your antibodies to the baby through breast milk. And so, if you have antibodies. I mean good and bad, really right, like. We talk about the good antibodies and bad antibodies. There are cases of pemphigus or pemphigoid that can go to the baby through the breastmilk is really really rare, but in general it's kind of a risk benefit thing. And most people would say, you probably should not have a recipe for that month afterwards. But yeah, I've talked to your doctors tricky. It's a you know. It's a horrible, horrible disease to have. And then these treatments, really, you know, navigating having a baby, getting pregnant, having a baby breastfeeding is complicated on top of that. So I think it will be an in-depth conversation. And then there, you know, you would potentially be, you know. Ask your obgyn and pediatricians, because really the whole team can kind of rally around you to figure out what's best for you and your baby.

Becky Strong: Great, thank you. We got another question about Pemphigoid and how do you know when it's time to take Rituximab if you only have it in the mouth. What's the percentage of it appearing in any other place? And how well does it have control of flare if they can't take something like prednisone or dapsone?

Donna Culton: Yeah. So for Pemphigoid. And the question was specifically about it being in the mouth. So I'm going to assume that's meaning mucous membrane pemphigoid, which is the form of pemphigoid that likes to be on the mucosal surfaces. So for most patients it's almost always in the mouth. But we worry about the eyes. We worry about the esophagus, we worry about the skin. You can get on the skin, and that form of pemphigoid too, and the timeframe, like most people who are going to develop other areas, do it within the first year or so. But it doesn't mean you won't. So it doesn't mean we quit thinking about your eyes like 2 years down the road if you start having eye troubles. Of course we want to know about it. There is no data just yet to say that Rutuximab would like. If you only have it in your mouth, can prevent it from going to your eyes like we just don't have that data right now to be able to say. But a lot of patients will have tried prednisone, dapsone, methotrexate. Say, you know these all medicines work really well for mucous membrane pemphigoid. Azathioprine, mycophenolate and so I would say, we're just at that period of time where we're starting again. Use it more if you just have it in your mouth like, should we do it. Should we try it? It doesn't really answer the question so much. We just don't have the data like it's not gonna ever. I worry that you'll almost always need Ivig or prednisone or something short acting if you're talking about a true flare where it's like out of control because Rituximab is just as I showed you the data like a year for most patients before they get complete remission. So it just takes a lot longer, and then even then still not every patient got better. So you probably still need something else. We're just waiting for more data. And I'd say mucous membrane pemphigoid is one of the hardest diseases to study, because it affects so many different parts of the body that the dermatologists can't always evaluate. So like. I have to send my mucous membrane pemphigoid patients to an ophthalmologist, and I'm relying on their report back to me of like, are the eyes good or not good today, you know, like the patient, and I can tell whether the eyes are painful, or you know I can see scarring, but scarring is too late. Right? We want to catch it when it is just inflammation before the scars come.

Becky Strong: So I'm going to combine a bunch of questions. Here we're getting questions on. How long does a Rituximab infusion take and what determines the length of time?

Dr. Culton: Yeah. So we hit on that a little bit right? Is that it really depends on how you're tolerating the infusion. And so most infusion protocols have it built in that if you're doing great, and your heart rate is stable and your blood pressure is stable, and you're not itchy, or having hives, or whatever that you can crank up the infusion rate, so you can like, pump it in a little faster. And then another half hour goes by. Then they're supposed to check on you, and if you're still doing great, they can pump it up a little bit faster. So if you're doing great. You might be able to get it done within several hours, but you wouldn't ever want to go into that, and they're even protocols now, for, like rapid infusion, just sounds terrifying. But some patients can really handle it. But you would never do that on the first infusion, right? You make sure that, like things went well the first time, and then the second time, they might be able to do a rapid infusion. But it's never going to be like an hour. It's almost because they have to get those pre labs and wait for them to come back. It is just always a good few hours to be in there. It's just hard to predict. It's probably the best way to say it.

Becky Strong: Okay, we're also getting a question, asking if you've had a recent pulmonary embolism and deep vein thrombosis. Does that affect your ability to be eligible to get Rituximab?

Dr. Culton: There's not as much data around, I say as much of a risk with rituximab as ivig. So ivig is pro-thrombotic, and make you more likely to have blood clots, and so we worry about it a little bit more in a patient that's had a recent pulmonary embolism or deep in thrombosis, whereas I don't worry so much about it in Rituximab. Now, that being said, if you have had those things, you probably have a doctor who's helping you manage them. And so you would just want to double check with that doctor to make sure where you get the okay that the Rituximab is going to be safe for you.

Becky Strong: Are there any complications or contraindications to having high blood pressure or arrhythmias with Rituximab?

Dr. Culton: That's a good question. Not any that come to mind right off the bat, right? I think. Yeah, we don't tend to see Rituximab making those things worse. Now high blood pressure at any time you've had an infusion like I've had patients get to the infusion center all ready for their Rituximab, and their blood pressure is out of control, like 200 over 100. Something crazy. The infusion centers like, yeah, no, we're not doing that today. So if you, if you run a little high. It's probably not a big deal, but if you're almost in what we would call like a hypertensive crisis, even if you look fine, they're going to take pause and be like I'm not sure we should infuse you today, and it's more about the fact that you could have an infusion reaction which could drive your blood pressure up or low. You know they just don't want to mess with you. You're unstable when your blood pressure is that high. But arrhythmias are not ideal, but probably getting all your doctors on board to talk about it and see exactly what type arrhythmia do you have. How often you go into it. All of that would be good.

Becky Strong: Great, and I'm gonna wrap up with this last question, and I apologize. We have so many questions, and we're just really over time, and I appreciate that you've stayed late. But how does Rituximab affect your B cell immunity from diseases or viruses that you've had previously?

Dr. Culton: That's a good question, and this slide is I'm glad we have it up, because what we think, and we have data. I didn't show it. That B cells or things that you've been exposed to in the past a lot of times you end up making the long-lived factories for those. And so the antibodies that protect you against those things. That you've been vaccinated against for years are coming from these long live factories. And so you probably still have those antibodies. Because again, Rituximab is going to knock out your B cells, and then the short-lived factories are going to shut down. But the long live factory can keep going and making the antibodies. And so it really what we don't know so much about is what tells a B cell response to go this way or that way And we don't totally understand why some some responses make long the factory some make shortlist factories, but in general we think that a lot of things you've been vaccinated against for years. You're still going to have antibodies coming from those long live factories, so probably won't impact it as much as new things that you're being immunized to are exposed to. But again. Lots of research going into that right now. That's a good, really good question.

Becky Strong: Well, thank you so much for all the information you provided. These are really complex and complicated ideas. I think you've broken it down into smaller bites still big bites.

Dr. Culton: But yeah, it's a lot of data. And Becky knows that we've talked about it, but a lot of these slides are the same ones I use when I give lectures to other doctors who are not experts on Pemphigus. And so really, you know, we've just presented very high level information. I know it can be overwhelming, but I think it presents a picture of like how all this comes together for your treatment, and and answer some of the questions so hopefully, you got most of your questions answered, and you know, Happy to answer any questions after Becky a lot of times we'll send me some of the so questions that haven't really been answered by email, we can do that.

Becky Strong: We'll do that again, and thank you it went by so quickly, and a lot of information, but very quick, and I appreciate the time that you spent with us Dr.Culton.

I would also like to give a huge thank you to for the support provided by Sanofi and Regeneron for helping to make today's call possible.

Our next Patient Education Webinar will be on May 3rd with Dr. David Fivenson, Board Certified Dermatologist from St. Joseph Mercy Health System in Michigan to discuss Anti-inflammatory treatments. Registration is now open and you can register online today using the QR code on the screen.
Now is your chance to participate in The World Skin Health Coalition to help plan their upcoming campaign to raise awareness about skin diseases and conditions and advocate to policymakers

around the world to take action. Take the 3-5 minute survey by the end of today to have your voice heard.

We also want to thank all of those who participated in the Externally Led Patient Focused Drug Development meeting that we hosted on January 25th. If you didn't get to speak and share your story we are still looking for people to submit written comments. Please submit your written comments to pfdd@pemphigus.org. Written comments should cover either Your disease and how it impacted your daily life or the treatments for your disease, the side effects of the treatments and how to improve them. Written comments should be no longer than 500 words. All writtens will be published in our Voice of the Patient Report and shared with the FDA and industry partners and will be used for future decision making when developing drugs for our diseases.

Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected.

Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! Visit www.pemphigus.iamrare.org and join today.

The IPPF needs your help! Your financial support is crucial to allow us to continue to provide free programs and services like today's webinar and our Peer Coaches. Your support also allows us to continue pushing forward research and educate doctors and dentists about pemphigus and pemphigoid. If you are interested in supporting these efforts you can become an IPPF Healing Hero. Healing Heroes make monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small and your monthly donation goes a long way. Scan the QR code or visit www.pemphigus.org/hero to support our community today.

The IPPF has a number of upcoming virtual support groups across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting. Also, we are always looking to expand our support network. If you are interested in starting a support group in your region please contact Becky Strong at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients.

This call recording will be sent out with the survey following this call. Thank you all for joining us.