

August 28th PES Call

Becky: Welcome everyone this call is now being recorded. I would like to thank you for being on the call with us today. Our speaker is Dr. Donna Culton, Associate Professor of Dermatology at the University of North Carolina at Chapel Hill. Thank you for joining us today and a big thank you to Genentech and Celgene for making this call possible. The call today will be a question and answer session about pemphigus and pemphigoid, but first let me introduce you to our speaker. Dr. Donna Culton completed her medical degree at the University of North Carolina at Chapel Hill. While she was there, she also received 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 completed a postdoctoral fellowship applying her knowledge of autoreactive B cell pathophysiology to pemphigus by studying B cells and auto antibodies from patients. Her laboratory generated a novel murine model of pemphigus allowing for a better understanding of mucosal pemphigus vulgaris. 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 at UNC and sees pemphigus and pemphigoid patients from North Carolina and neighboring states in her specialty Autoimmune clinic. She has served as an investigator in clinical trials in pemphigus and has contributed to consensus statement publications as part of the International Pemphigus and Pemphigoid Committee. She currently lives in Chapel Hill with her husband and daughters. Now, it is my pleasure to introduce you to doctor Donna Culton to talk to you about pemphigus and pemphigoid. Welcome.

Dr. Culton: Thank you. I'm excited to be here. Thank you for having me.

Becky: Donna I should have asked you this before the call, but I don't know if you have any conflicts of interest you want to disclose before we get going? Or there aren't any and you would just like to jump right into questions?

Dr. Culton: Well, the only conflicts of interests that I would need to declare here or just that I'm a clinical investigator on trials that treat patients with pemphigus or testing new medications. I

don't think we'll get into anything about those clinical trials today, but I am an investigator on those studies.

Becky: Great. Thank you. Well, let's just jump right into our first question then. Jerry has bullous pemphigoid and he wants to know what does diseases other than pneumonia, are you susceptible to, given that your immune system may be incapacitated or neutral at prednisone is being used?

Dr. Culton: So really any infectious disease you may be a little bit more prone to and certainly pneumonia is the one that worry the most about. But I think other common things that I see in my clinic because the skin barrier is already broken in many patients with both pemphigus and pemphigoid, oftentimes the cold sore virus or the herpes virus can jump in to open wounds and take advantage of as you said, that the kind of suppressed immune system after being on prednisone or other immunosuppressive medication. So that's one that we are often looking out for if some areas of your skin aren't healing. But really my advice to patients about concern for infectious diseases is to take your body symptoms a little more seriously than maybe you would have. If you're the kind of person who's used to wait with your cold and not go see the doctor, you know, now just recognize that because your immune system is suppressed from the medication that you need to take your symptoms seriously and be evaluated a little more quickly than somebody with a healthy immune system.

Becky: Great. Does bullous pemphigoid attack a particular kind of person? Maybe somebody with a weak immune system or the elderly. Are there anything that pemphigus and pemphigoid characteristics of people who generally get this disease?

Dr. Culton: Yeah. So bullous pemphigoid in particular does tend to occur more frequently in older patients. And certainly, that's not a hard and fast rule. We see some younger patients that have it as well, but because of that, you know, there's a lot of research going into figuring out why that might be. And I do think as we all age, our immune system does get a little bit weaker. And it's possible that the mechanisms that keep autoimmune diseases in check in your body kind of wimp out a little bit. And so bullous pemphigoid may be one of the diseases that takes advantage of that. And so, we see it more in the older population. Now, pemphigus is more kind of equal opportunity it can affect patients of all ages and tends to be more of a disease of the middle aged

patients. So, in that regard, I wouldn't say it attacks certain patients differently, it's just which patients have the right genetic background and potentially environmental triggers to allow the disease to form.

Becky: Great. Thank you. I'm kind of following up on that question, is there any kind of research showing any promise towards the actual cause of the disease or any investigation to find a gene that triggers the immune system or remove or modify the genes using like a CRSPR or other means?

Dr. Culton: So, I'll start with the first in terms of why patients get these diseases. We do think it's multifactorial, so some bit of genetic predisposition and there is research going on to look at a kind of genetic factors that might predispose you. And the IPPF is involved in that research. So you can follow up afterwards with Becky about how you might submit just cheek swab for DNA to kind of see if your genes might be predisposing you. But we also think there's probably some second hit to your immune system and whether that's an environmental trigger? So, we really don't have much research at all into that. There are studies currently being done to figure out what might be kind of triggering the disease in genetically susceptible individuals. A lot of that work has been done in patient populations that are more commonly affected. So, where we know that the genetics are playing a role and then we're just looking within that population at the environmental triggers. But right now, that it is an active area of research but we don't really have any outcomes of that yet. And then in terms of whether we can go and fix genes the answer is no, we're not quite there yet. That's a very kind of advanced technology that's really used more to treat kind of true pure genetic diseases. And as I said, pemphigus is a little more like some genetic but also some environmental.

Becky: Great. Maybe it might be important just to take a step back and to talk about like what tests are needed for a definitive diagnosis of pemphigus or pemphigoid?

Dr. Culton: So, in general we use three kind of major criteria. So, the first is the clinical appearance of the patient. The second would be the biopsies that we do where we're looking at the architecture of the skin. That type of biopsy, it's called biopsy for H and E and H and E just

stands for their abbreviations for the stains that are used. So that's a regular biopsy. And then the third would be immunological testing. And so that can be a biopsy done for immunofluorescence, which is the gold standard or blood taken to look for antibodies circulating in the bloodstream. And so that's called indirect immunofluorescence or ELISA can be done a couple of different ways. So those three, the clinical, the kind of regular biopsy and then the immunological biopsies are the three main ways, the criteria we use to decide if a patient has pemphigus. And ideally to have a firm diagnosis, you have all three being positive.

Becky: Great. Thank you. Brenda says that she has PV, lung and squamous cancer and that she's been on chemotherapy as everyone is afraid to do immunotherapy treatment. She says now that she's starting Abrexane and that all the doctors are afraid of the possible catastrophic effect of her PV. Do you know of any treatment that can be used with PV besides chemo? And is it common to treat a pemphigus and cancer?

Dr. Culton: Yeah, I would say many patients are unfortunately afflicted with both pemphigus or pemphigoid and some type of malignancy. And of course, internal malignancy, as we say, solid organ malignancies like lung cancer you know, are life threatening and require treatment. And so, some of the newer treatments to treat solid organ or internal cancers do kind of trick the immune system a little bit and allow the immune system to become more active in hopes that the immune system will attack the cancer. But in doing that, there have been reports of patients where by activating the immune system, they actually get autoimmune diseases so they get pemphigoid. And so, I do think a lot of physicians treat patients that already have a history of one of these, pemphigus or pemphigoid do become nervous to use the immunotherapies. So, I think it's a valid concern and of course, in that situation it becomes all about the individual risk benefit for that patient. How bad is their pemphigus or pemphigoid, how bad is their internal cancer? So, the details of that question would be difficult to get into. But in terms of other treatments that can be used I do work with the oncologist. And certainly, I have patients that we use Rituximab in patients that have you know some other sort of malignancy, for example, breast cancer patients where we need to treat their pemphigus. But we don't want to suppress the immune system too much. And the treatment that's coming up more and more as the ones that the oncologists are more comfortable with and kind of the safest is Rituximab compared to some of the other

medications like prednisone, Azothaprine, Mycophenolate. Those are all felt to suppress the immune system and globally suppressed the immune system. So, a little more dangerous for patients that have history of cancer. Whereas because Rituximab only kind of targets the B cells, it doesn't suppress the entire immune system and it's felt to be a little bit safer.

Becky: Great. Thank you. Gale is changing gears on us here. And says that she has bullous pemphigoid and that when she was diagnosed, she was put on 60 milligrams of prednisone for a number of months. But then after Rituxan she's still on 10 milligrams and that she's heard that is not good to be on Prednisone for long term. She said last year she was diagnosed with type two diabetes and this year she was diagnosed with cataracts and two weeks ago she was diagnosed with cardiac blockages and she has her scan in a week. She says her cholesterol, triglycerides and stress levels have always been normal. But are there any cardiac problems that related to prednisone?

Dr. Culton: You know, I think in general, prednisone reduces inflammation. So, on the flip side of that, certain diseases that have a lot of associated inflammation have increased risk of cardiac problems. And so, Prednisone reducing inflammation in those diseases could be somewhat protective. In general, though I do think prednisone we all know a difficult medicine to be on long-term has numerous side effects, most of which are less in terms of like true cardiac related, but more related to things like an increasing risk of diabetes. So, it's more direct link to that. And then of course other risk factors that the patient might already have that are unrelated to prednisone. So, cholesterol but high blood pressure, prednisone can also cause high blood pressure, and that's a risk factor for cardiac disease. So, I think several of the side effects of prednisone do channel in to overall risk for cardiac disease. I think it's important to kind of keep working with your providers to see if you can get your prednisone lower. I think in general five milligrams of prednisone a day is considered the equivalent to your body's normal prednisone level, which is actually cortisol. And so, five milligrams a day is really, I of course you don't want your patients on any prednisone if you can help it. But if you get down to five milligrams of prednisone a day that that seems a little safer than being on 10. I always say it's unfortunate if you have to be on prednisone. It's also unfortunate to have diseases like pemphigus and pemphigoid and so the risk benefit ratio is the most important. Now I think because of diabetes and cataracts and many of the other side effects

that are, you're experiencing to kind of keep the conversation going, whether you need something in addition to Rituximab to help you get lower on the prednisone dose that you're needing to keep your disease in check.

Becky: Okay, great. Thank you so much. We are getting a lot of questions about the itch specifically in pemphigoid patients. What can be done for the itch?

Dr. Culton: It's a good question. So, the itch is obviously the blisters are debilitating, but the itch is what can make you crazy. It's just miserable.

Becky: Exactly. That's how it's being described.

Dr. Culton: Yes, yes. So honestly as physicians we see the blisters and so we are very aggressive with treatments to heal up those blisters for patients. The itch is something that is harder to see. But I think our patients do a great job of letting us know how miserable are with the itch. And many of us feel like residual itch even once blisters have healed is a sign that you haven't quite controlled the disease yet. And that potentially blisters are just on the brink of coming back, right if you have so much itch still remaining. And so, I treat itch just as aggressively as I treat blisters. Ideally the two kind of approaches, one is to treat the disease. So again, your immunosuppressive agents to really get the itch under control. But then we also use adjunct therapy for itch as well. So those are medications that may not do anything to change the disease process but can just alleviate the symptoms of itch. And again, I think those definitely have a place they should not be used alone cause you're not really treating the disease if you're just treating the itch. But those would be medications like anti-histamines. Sometimes medicines that are used to treat nerve damage. So, we use a lot of those types of medications just when nerves get irritated, sometimes that causes itch. And so, we'll use a lot of those medications and then even topical anti-itch cream. So, all of those, again, I think of as adjuncts to just give a little relief from the itch while we're really treating the disease itself. But I know it's miserable and I would just encourage you to keep working with your doctors. Obviously, those other medications I mentioned have their own side effects. So it's not an easy thing at all, but I would again keep working with your physicians and make sure that you're voicing just how miserable you are because that that gets us positions to act a little more aggressively with therapy.

Becky: Great. Great advice. Thank you. Basha is talking about gestational pemphigoid. She wants to know, is it common to be diagnosed with gestational pemphigoid? Then after months being diagnosed with celiac disease or another autoimmune disease, she says that she's a year and a half post-delivery with her baby and she's managing. And she would also like advice on contraception.

Dr. Culton: Yeah. So, pemphigoid gestationis is a form of pemphigoid that comes either during pregnancy or right after postpartum. So, otherwise it's identical to bullous pemphigoid. It's just in of course younger patients and occurs right around the time of pregnancy. Many patients were able to get the disease under control and then once they're postpartum and get everything settled down, they go into remission. And then many patients will have a recurrence with the next pregnancy or really anything that kind of shakes up the hormonal status. So oftentimes oral contraceptives can reactivate pemphigoid in this setting of the kind of gestational pemphigoid. And so, it is tricky knowing kind of how to proceed with a rechallenge of oral contraceptives. But I would say once if the disease is completely under control then potentially challenging with oral contraceptives and being kind of posed and ready in case a flareup happens. And then you'll know, okay, you can't really use any hormonal type of contraception in that regard. And then getting back to the first question whether it's common for patients to get other autoimmune diseases specifically with pemphigoid gestationis, luckily Becky shared this question with me ahead of time, so they're able to look up some of these answers. I would say typically we don't see it. There was, in the literature some older data where they looked at women that had this gestational form of pemphigoid. And a small percentage of these patients did have other autoimmune diseases. The majority of patients that had another autoimmune disease that was thyroid disease. So autoimmune thyroid disease and then, and specifically relating to celiac disease. There have been some papers that look in the blood of women with gestational pemphigoid and have noted that there are an increased number of antibodies that are associated with celiac disease. But that particular paper really didn't talk about whether those women actually have gastrointestinal symptoms of celiac disease. So, there's definitely some data suggest there's an association, but we really don't have great data on that matter. So in general I think we worry about our patients with autoimmune diseases of the skin being more likely, something's a little bit off with your immune system and if you can make one autoimmune

disease, there's a lot of data suggests you at more increased risk of other autoimmune diseases as well.

Becky: Great. Thank you. It's a great answer and it's something that we don't talk about very much. It's not one of the more common things that come across the foundation, so any information is great. Thank you. Amrit says that his mother is off of all medicine and she's been in partial remission after her Rituximab five months ago. However, she still has some small patches of blister of oral blisters, which come and go. Her dentist said that aren't completely healed. Are there any vitamins or supplements that can help or, or how to proceed?

Dr. Culton: So that's a one. I think in general most of the physicians that treat pemphigus and pemphigoid are trained in more Western medicine and so are not as familiar with kind of how vitamins and supplements can play a role. And I think what is tricky even when we try to recommend those things is that there's not a lot of evidence about vitamins or supplements actually being helpful. And a lot of the studies are not done in a rigorous way, the way that we're used to with our medications that we use. And so it's hard to recommend those things. I would say avoiding, more than just being able to recommend a supplement, if you're thinking about a supplement or vitamin, you know, be careful because those vitamins and supplements actually do have effects on the body. Right. It's easy to think, Oh well it's just the vitamin supplement, it will only help me, but it's possible it can hurt you too. And there are some of those vitamins and supplements that actually people take them because they want to boost their immune system. They think, my immune system is suppressed by all these medicines. I'm going to boost it with vitamins and supplements. Well, some of them actually really do boost the immune system. And so it's like counteracting the medications that you're being given. So, as opposed to recommending vitamin and supplements, I think a multivitamin and a healthy, balanced diet are all helpful and then avoiding any triggers that might stir up new blisters. So, I have some patients who say, every time I eat citrus fruits or vinegar based something, there are certain things that really can aggravate their mouth and bring on more blisters. And so if you notice any of those things, just remember that you do have a little control if you avoid those to avoid getting blisters. And then partial remission is actually, in some ways a big win but in some ways miserable because you're so close to not having anything at all. And so I do work with each patient and if we're really

going for zero blisters, it's all worth going for us just at what cost. So, talk with your doctor about what other medications again and in addition to Rituximab might be helpful. But make sure you talk about potential side effects too because sometimes going to try to clear those last few blisters can come at a cost.

Becky: Great. Thank you so much. Our next question says, can you please guide me about nail manifest manifestations with PV? My mom's hand nails have been affected for about six months now with occasional liquid oozing out, yellow pus, bleeding, inflammation and pain. Our dermatologist says nothing can be done much except for avoiding soaps and detergent and applying liquid and antifungal drops on the nail beds. Also, the dermatologist doesn't feel that adding any more immunosuppressants due to my mom's age, 62, and history of fairly controlled diabetes. Any advice?

Dr. Culton: So, I do have a lot of patients that do have nail manifestations with pemphigus vulgaris and it is extremely challenging to treat the nail manifestations. I think it sounds like the dermatologist that is working with this family is recommending a lot of really great advice in terms of avoiding unnecessary exposure, prolonged exposure to water with the hands, cause that can always aggravate nail issues. And then I do think applying any fungal drops, we sometimes apply steroids straight to the nail. So, putting a steroid ointment on top and then covering them with bandages. And then I'm fortunate enough to have a nail expert that I work with who I've sent some of my patients to. And what they have been doing is injections of steroid into the skin surrounding the nail. So, it can be a potentially painful treatment but that can also be effective and so something to definitely to consider.

Becky: Great. Thank you. Joanne has bullous pemphigoid and she asks, what are some first attempt drugs that can be tried, followed by more effective and complex drugs?

Dr. Culton: Yeah, so I think most of us who treat bullous pemphigoid do have an algorithm that we go through meaning the medicines we would try first followed by the medicines we try second. And truthfully, a lot of that has to do with the patient sitting in front of us. So what other diseases, right? If somebody has raging diabetes that is completely out of control, most of us use Prednisone right off the bat to get kind of a quick control of the disease while we're waiting for

other medications to kick in. But in a patient that has horrible diabetes you might not use that medication. So, I can get some general first attempt drugs but just know that it's very patient specific and all the physicians that are treating pemphigus and pemphigoid are considering other diseases that their patients might have. So in general, the first medications we use to treat pemphigoid really would be prednisone, again for immediate control of the disease, knowing that it's going to have side effects, but we kind of need it to get things under control quickly. And that's mostly because so many of our other medications take a while to kick in. So, and then in terms of what other kind of first medications, I use a lot of methotrexate for both pemphigoid other physicians do as well. I think it's a great medicine. Sometimes it's not ideal in patients that have very bad renal disease. And so again, there's some things that for some patients we might not use it in. Other medicines would be Azathioprine or Mycophenolate. And then of course there's Rituximab. And again, I think we're still figuring out how to use a Rituximab in a lot of these diseases. And so, some physicians might use Rituximab first line in both pemphigoid and others might save it and try one of these other medications first. So that's my algorithm. I think it also depends, I should say on how severe the diseases. So, for some patients with really mild disease, your first line treatment may not be those medications I just said, it might be something more like some antibiotics. Some people do Doxycycline, Niacinamide, other people do Dapsone. So it really depends on a lot, but one is the severity and then also the other diseases that patient might have.

Becky: Great. Thank you. Joanne says that she's 65 years old and she has been having problems with her gums and she's wondering if this could be related to the bullous pemphigoid? She says she does have regular dental cleanings and dental work and dental work done.

Dr. Culton: Yes, absolutely it could be. We know that pemphigoid is typically on the skin, but it can affect the mouth as well. And then there's another condition called mucus membrane pemphigoid, which typically only affects the mucosal surfaces, but, but does sometimes affect the skin. It's kind of where the disease is more often. And I have had a patient that started with classic bullous pemphigoid for many, many years, had her under great control. And then she started having problems with her gums and ultimately a biopsy for a direct immunofluorescence, so that kind of fancy biopsy, the immunology biopsy was what proof that she had it in her mouth

as well. And so that was the patient that I would say, certainly didn't start with any, anything in her mouth, but ultimately did have disease that began to affect her mouth as well. So, I would say, it may not be but really, I think one of the main ways that you would be able to tell would be to have a biopsy done. Again, no small tasks to have a biopsy done in your mouth. And again, a biopsy for direct immunofluorescence is what would probably be needed.

Becky: Great. Thank you. Christie says that she's 39 and she was diagnosed after being hospitalized with blisters over 90% of her body and in her mouth and throat. She keeps reading that the disease is self-limiting and will go into remission in about five years. But from what she's seeing from other support groups online, it's not looking like that. Can you shed some light on what to expect in the years?

Dr. Culton: Yes, I would say you know certainly I think most patients, it kind of depends on treatment. But most patients who have that severity of bullous pemphigoid are unlikely to go into a spontaneous remission without treatment. So self-limiting and going into remission on its own, I think maybe with the right treatment that could happen, but not without treatment in my experience. So, I do tell patients when we're at talking about going into a remission, like a clinical remission that it's possible, but we can't say for sure. And so the first order of business is to get things under control and then once things are under control, begin to slowly taper the medication. And if we can taper the medications all the way off, then that's somebody who we can get into a remission off of therapy. But many patients do require therapy lifelong for these diseases. And it's always about getting used to the lowest dose of medication that can keep things in check for you. So, I think there's no way to predict for every patient or each patient what their course is going to be like. But I think remission is a possibility but typically requires treatment to kind of get you there. And certainly, doesn't happen for everybody, unfortunately. We wish it would.

Becky: Great. Thank you. I'm kind of getting back to the biopsy questions. Is it possible to have an immunofluorescent biopsy come up negative even though the doctors that I've seen say that all my sores like PV? And why would something like this happen?

Dr. Culton: Yes, that's a great question. Biopsies all of you who have hands on experience know this, it's a very small piece of skin that's taken. And it really does depend where it has taken from. And so a lot of patients, if the biopsy is not taken from exactly the right place, some biopsies needs to be right at the edge of a blister. Other biopsies need to be like the biopsy for immunofluorescence, we want a little bit away from the blister. And so if the biopsy is taken from the wrong place, you can get a false negative. And so many patients do have to have repeat biopsies and it's not that anything was done wrong the first time, it's just we have data to suggest that sometimes it's just the wrong piece that happened to make it to the pathologist or the immunofluorescence lab. So, if the physicians really feel like it's pemphigus, then more biopsies need to be done. And I don't see that, again, as a fail, I see that as being persistent in getting your diagnosis. And, again, it's sample selection and you know, we don't always pick the right spot that's going to show all the classic features on the first time. I do have some patients that come to me that have had negative immunofluorescence and asks, can we say that they have pemphigus? And, I really think you cannot say that somebody has pemphigus without some sort of immunofluorescence testing, whether it's the biopsy or the serum like checking the blood for the antibodies. The biopsy is the best, but sometimes if the serum is positive and it looks like pemphigus and we kind of feel like that's enough. And again, it's all about kind of getting that firm diagnosis. And certainly, there are some patients that we never reach a firm diagnosis and I treat them anyway after discussion of risks and benefits but I can see a way where you could have a negative biopsy even though it is pemphigus. And so I just say don't give up and maybe consider another biopsy even though that's not the most fun thing to consider.

Becky: Great. Thank you so much. I'm going to start grouping some questions together about IVIG, what is the difference between IVIG and Rituxan?

Dr. Culton: So I'll start with the similarities and that is just that they're both infusions. They both kind of get lumped together in the minds of many patients because they're both infusions. But IVIG stands for intravenous immunoglobulin and immunoglobulin is the fancy word for antibodies. So it's IV antibodies. And what is done is healthy antibodies from healthy donors are collected, purified away from the rest of the blood and mixed all together. So, you have a batch of healthy antibodies from a lot of healthy donors that have been pooled and then those healthy

antibodies get infused by IV into a patient. And the way I like to think about it is that your body is used to having a certain number of antibodies floating around. And so, when you flood the body with healthy antibodies, it kind of dilutes out and your body kind of goes back to a normal level. And so what happens is you end up diluting out the auto antibodies. You're not doing anything to affect the cells that make the auto antibodies though and so I think at one point I likened it to musical chairs, right? There's only a certain number of chairs. If you have three chairs filled by auto antibodies and you flood that room and the game with lots of healthy antibodies, just by nature of, of musical chairs, the healthy antibodies won't get a seat next time so they get eliminated, but you're going to have new auto antibodies coming back. So the downside of IVG is that it's only temporary, it's not permanent. I always think of IVIG as the last thing about a month because that's about how long it takes before your body's making new antibodies again, right? Or for the old antibodies are kind of dying off, whereas Rituxan eliminates the B cells and the B cells go on to become plasma cells that make antibodies. So Rituxan is getting at these diseases from a different way in which it's eliminating the cells that go on to make the antibodies to begin with. So if you're thinking about how this disease forms, Rituxan is actually getting at a little earlier in the disease process where you're riding the B cells, whereas IVIG is a little later in kind of how disease formed and that you're only really targeting the antibodies, but you're not really targeting the B cells that make. So I would say there's a role for both of them in the treatment but they are very different in terms of how they act, how we use them, how quickly you can see results from them and then how frequently you have to do them, so very different. And I think the IPPF on the website has a good overview of the two different drugs and how they act. So I would refer you back to that.

Becky: Great. Thank you. I'm Susan is asking what antibody is present in the serum that you're, you're talking about?

Dr. Culton: So, it depends on the disease. For pemphigus vulgaris and pemphigus foliaceus, it's antibodies to the desmogleins. So those are the antibodies that are causing disease. The desmogleins hold the skin cells together. And when antibodies against desmogleins are present in the blood and present in the tissue they kind of break apart the skin cells from one another and form the blisters. For bullous pemphigoid it's antibodies against BP 180 and that's the

protein that holds the top layer of skin to the middle layer of the skin. And so, it really depends on which diseases to which antibodies we're looking for. But, there's several ways to look for those antibodies. Indirect immunofluorescence, direct immunofluorescence both can show antibodies in the blood and then the tissue respectively.

Becky: Great. Thank you. Is IVIG safe for cancer patients?

Dr. Culton: Yeah so, I will say one of the benefits of IVIG is that it does not suppress the immune system. So, we use it for patients that have active infection, right. So many of the other drugs we use suppress the immune system. IVIG does not, it's not considered immunosuppressive. The downside is that it's a lot of protein. If you can imagine collecting antibodies and pulling them and then infusing it, it's a lot of protein going into the body. And so, there is a risk of making clots, so that's something we call that thrombosis and then what you worry about is that those clots would travel. So thromboembolic events would be things like a blood clot traveling to your lungs. We do worry about that and patients with cancer are at higher risk for thromboembolic events anyway. So, I think there is a concern sometimes to use IVIG and cancer patients for that reason. But again, it's back to that risk benefit. If there's nothing else that's considered safe with all the other medications because of the cancer, then maybe IVIG is worth the risk. And just knowing that you have to be on the lookout for anything that would be a symptom or sign of a blood clot forming.

Becky: Great. Thank you. The next question says that I've had my first two IVIG treatments this week and since then I felt dizzy and have had headaches and just had some bad muscle pain, especially in my back. Is this a side effect of the IVIG?

Dr. Culton: Yeah, so certainly I think headaches are a pretty common side effect of IVIG. I have had some patients describe the other symptoms that were mentioned such as muscle pain. But, headaches by far in a way, I would say are very common after IVIG. We do a lot of pre-treatments at our infusion center to help minimize that. And then I think also staying well hydrated around the time of your infusions can help a little bit. And then we, again, sometimes we do, you know, headache treatments before and after. So even simple things like ibuprofen or Tylenol before and after your treatment can really help. But, that is unfortunately a pretty common side effect. And I think being two treatments in, it's hard to know. I think, typically the way IVIG is given and, we all

do it a little bit differently, but usually it's like divided over two to three days and then potentially repeated at some point down the road. So maybe a month later, six weeks later. It may be worthwhile trying to stay the course and see if it happens again after the next IVIG cycle because then you'll know for sure it's probably related to the IVIG. Those symptoms should, if they're related to IVIG, should dissipate between your infusions, maybe not the infusions that are spaced just a day or so apart. But if you have a cycle and then another one six weeks later in between those six weeks, things should feel better and that if they come back again after IVIG, then it probably is a side effect.

Becky: Great. Thank you for that information. Barry says that he was just approved for IVIG Panzyga, two hours on consecutive days each month for 12 months. Do you have any experience on the success of this treatment? For full remission.

Dr. Culton: And tell me again, what was the diagnosis?

Becky: Bullous pemphigoid.

Dr. Culton: Yeah, so I do think, different people use IVIG different ways. I think being approved to have it essentially monthly, the two infusions, but monthly for a year. It is, is worthwhile kind of getting into and seeing. And I have heard some reports of patients having a remission after that. Some patients who get an improvement though will require that you keep going with that treatment, which can be exhausting to two days out of every month have infusions done. And not to mention the cost. It's great that it was approved, but there's still sometimes an out of pocket expense associated. In terms of long-term remission, you know, again, there are some reports of IVIG, and Rituximab being used together. And then again, anecdotal and some patients that have been treated with just IVIG and go into a remission. I think you'll just have to wait and see it certainly worthwhile going forward with and seeing how you tolerate the infusions.

Becky: Great. Well, moving on to Rituxan, we've gotten quite a few questions about that. So, I'm trying to group them together for you to keep you on one train of thought. Will a booster of one treatment of Rituxan help extend remission? I'm curious, over four years and several infusion

cycles, the best or remission period only lasted a year. What would you propose the treatment plan to be moving forward?

Dr. Culton: Yes, that's a great question. I think one that we as doctors who treat pemphigus with Rituxan struggle with so some patients. I think many patients, and I hear this a lot and I think the IPPF hears this a lot is, you know, you never really want and you're always afraid of your disease going back to how it first started. So, the idea of a relapse, even if it's a small relapse, is kind of terrifying. Some patients are very enthusiastic about continuing to get their Rituxan every six months, even if there's no evidence of disease on the skin and no antibodies in the blood and all signs point to being in remission. They really don't want to take the chance of a flare or a relapse down the road. And right now, we as physicians don't know. We're always trying to weigh the risks and benefits. So, the risk of doing that is that your immune system, your B cells are chronically depleted and that comes with risk of infection. I do encourage my patients if there's nothing on the skin and there's no antibodies in the blood that we do not retreat particularly if they've had several cycles. So, you know, trying to read between the lines here, it looks like four years and several infusion cycles. I would always use the end point as if there's nothing on the skin and no antibodies in the blood at the time you would be due for your next infusion, consider not doing it and waiting and seeing what happens. Again, it sounds like this particular person has already had remission, the longest period lasted a year. I still think it's probably still the way to go just because otherwise the alternative is keeping Rituximab every six months indefinitely, which is really suppressive to the immune system. If you don't need it and the only way you would know is to not do it. It's tricky because I definitely understand the anxiety of like not wanting even to have to go through a relapsed once a year. So, I think it definitely is a decision that you make together with your physician and talk about your fears and what evidence is being used to decide whether you should retreat or hold off on treatment.

Becky: Great. Thank you. We've gotten a few questions about how long after a Rituximab infusion is your immune system compromised?

Dr. Culton: So most of the data shows that your B lymphocytes, which is what Rituximab is eliminating from the peripheral blood. Your B lymphocytes do not begin to come back until six

months. And that doesn't mean that at six months their back to their normal levels, that's just when they begin to come back. So, we really say six months is kind of your most risky period where you don't have any B cells, most patients. And then after that you're still a little bit risk but your B cells begin to come back. And, if you were to, say an immunization, you have some B cell there that could begin to respond to either an immunization or to an infection if you got an infection. So, the six-month period is generally what we recommend, to just again that your immune system suppressed. But, in reality it's probably suppressed a little bit longer than that.

Becky: Great. Thank you. One question that we get a lot here at the foundation is that patients will get their first couple of Rituxan infusions and they're waiting for that six months for the next two. But there are lesions actually get worse. Why does that happen?

Dr. Culton: Yeah, so there's definitely a lag time. I know I already mentioned a little bit how Rituximab works, so it eliminates the B-cell. And then I had mentioned B cells go on to become plasma cells that secrete antibodies. Well, the little tricky thing about Rituximab is it eliminates B cells, but it does not eliminate plasma cells. So, you might ask, well then how can it even help because it's not eliminating the plasma cells that make the antibodies? Well, the plasma cells, like everything have a lifespan. So, we have to wait for the plasma cells to kind of die off. And then we've eliminated the B-cell so they, there's no B cell to go on to make new plasma cells there. So, there is a lag time waiting for those plasma cells to die off of about three months. In that period of time, they'll have antibodies circulating, plasma cell, still making new antibodies so disease can get worse in that period of time. Typically, after two to three months, you should start seeing the results of the Rituximab. And I do have patients that the two and three months comes and goes and they're still pretty bad. And so that can happen. It's just that the first cycle of Rituximab was not quite enough. And it doesn't mean that we didn't eliminate all the B cells in the blood, but potentially there's B cells in other places of the body that Rituximab can't get into. So, I call those the B cells that are kind of hiding in the tissues and the lymph nodes in places where Rituximab does not get as easily. Sometimes you need a second cycle of Rituximab and I agree that's one of the most challenging situations to be in as you have had your Rituximab infusions, you've waited your two to three months and you're still not better and now you have to wait to get your next cycle. So, we do use prednisone and other treatments to kind of bridge people until we can kind of

do the next cycle of Rituximab. But, it's not uncommon that that happens. It's fortunate, but we see it.

Becky: Okay, great. Thank you. Laurence is from France and has a couple of questions about Rituxan and some biosimilars. She says that I've heard in the states that doctors are not too sure about them and continue to give MabThera Rituximab for PV patients. She says all the studies have confirmed identical results in both MabThera and the biosimilars. All prior reservations and restrictions have been lifted in Europe which makes the medicine widely available. What is your take on this? Keeping in mind, would it be better to take biosimilars as a first treatment in order to prevent having to change afterwards during follow-up treatments?

Dr. Culton: That's a good question. In the U.S. we really have not had as much availability of the biosimilars. Doctors are always a little worried to move away from something that we know and it's working. But I agree, in general, the biosimilars, the testing they have to go through shows that they're not inferior to Rituximab. What I usually go for is, let's get what your insurance company will approve for you. And if it happens to be a biosimilar, I would go for it. So, I don't think it's so much, we get Rituximab first and then that gets denied and we have to switch to a biosimilar. I haven't had any situations of that happening at all. But I would say if the situation arises in the US that a biosimilar is approved but Rituximab is not I don't think I would let that hold me back at all.

Becky: Okay, great. Great information. Thank you. Our next question asks, for patients that have been administered Rituximab more than three times over a large span of time, does the efficacy reduce over a time period as compared to earlier instances?

Dr. Culton: It is a good question and I don't think we have a perfect answer for it. So, I will say there's some studies that show, just like anything else you put into the body, this is going to get confusing, so stay with me here. Your body can make antibodies against Rituximab. So, if that happens, then yes, by your second or third cycle, Rituximab might not be effective because essentially, you're blocking it. Your body's making antibodies to block the Rituximab. At this time, there's no commercially available tests to test for those anti-rituximab antibodies. But if you and your physician are seeing reduced efficacy over time, it may well be that that has happened. And

then the other thing I would just say is that for some patients the Rituximab if it's used in a patient who's had disease for years and years and years, sometimes it doesn't work as well as if we use it right up front. And so, there's some changing ways to use it but I do have patients that saw a good response to the first infusion, but then not as good responses to second and third. And sometimes I wonder if it's just because they've had disease for so long that they have some B cells that are just kind of resistant to Rituximab.

Becky: Great. Thank you. There is another question on Rituximab. Are changes with fingernails and toenails an effect of pemphigus foliaceus or pemphigus vulgaris or could it be from the Rituxan infusions? I have ridges in my fingernails and it's happened twice, a few months after each flare up. And I can't tell if it's from the disease or from the treatment.

Dr. Culton: That's a great question. I think the timing is important. So already recognizing that if there's pemphigus flaring every place else and you have these changes to your nails, probably it's the pemphigus. If everything else has been pretty quiet with your pemphigus and it's just the nail changes, it may well be the Rituximab. A lot of times it depends on what kind of ridging is being seen. So, there's ridging that's kind of longitudinal and goes down the nail. And that one is less hard to blame on Rituximab as opposed to a ridge that kind of goes horizontal across the nail. In which case it could be the Rituximab. I'd say certainly nail changes are not common after Rituximab. So that the timing and I think the actual appearance of the ridges would be important to consider when answering that.

Becky: Great. Barbara says that have had two rituximab treatments two weeks apart. The last one being seven weeks ago. I was wondering if there's a pattern to the healing of the blisters in my mouth. It seems that the last one I got, which is a blister under my tongue is not going away yet. But the ones that I've had for a long time are gone. She was diagnosed with pemphigus vulgaris.

Dr. Culton: Okay. Can you remind me how long ago the infusions were?

Becky: She got her last one seven weeks ago.

Dr. Culton: Seven weeks ago. Okay. So definitely in the period of time where we are just maybe beginning to see what the Rituximab can do. Right. I said probably two to three months is about when we start to see it working. I would wonder if there's any other treatments that were being used to bridge that period of time. So maybe, prednisone. The only other thought is, as prednisone is coming down maybe some of the older lesions have resolved, but now as prednisone is coming down, some new lesions are coming. And then the other thing I'd say is that lesions under the tongue, on the tongue, on the tip of the tongue are among the most stubborn of all the lesions. So, it might be lesion location this is why. They just keep getting traumatized when you talk, when you eat and it just makes it hard to heal even if it wanted to. So that's my other thought on just maybe the location is the trouble there.

Becky: Great. Thank you. We get a lot of questions from women and men who want to know if it's okay to color my hair after I have lesions on my head. Should they clear up first, do I need to be in remission and what should I be careful of?

Dr. Culton: So, I would say definitely if you have open wounds on your scalp, maybe don't color your hair. If you have healing of all the lesions on your scalp, whether you're still requiring medication or no longer require medication, if all the lesions have healed, it's typically safe for you to get the hair colored. I would say the one thing to be on the lookout for some hair dyes, especially black hair dyes, people can have an allergic reaction to and maybe you've colored your hair for years and never had an allergic reaction, but now your immune system is a little wonky. So, I would just speak with your hairdresser about that and let them know. Ask them if, especially if it's going to be a black dye whether they think it's safe for you. I think hairdressers sometimes they get scared off, right? They don't want to do it because they're so afraid that the disease is going to come back and it's going to be due to something they did. But in general, it should be safe if your scalp is cleared up.

Becky: Great. Thank you. Another question that we get a lot is it ever safe to have a tattoo after you've been diagnosed with pemphigus or pemphigoid?

Dr. Culton: So, you know, in general you know, tattoos, I think people have differing views of them. I don't think there's anything innately worrisome about getting a tattoo after he'd been

diagnosed. Certainly, you don't want to tattoo into skin that has been affected recently or still affected. And then I think, we worry a little bit about diseases that might be transmitted. So, go to a reputable place if you're going to do it. I think some physicians would be a little more conservative and say no, never, no tattoos ever, ever. But I have patients that that's important to them. And so, I would say just like with the hair dye, makes sure that your skin is well healed then know that really anything can kind of tip your immune system off. So, it's possible you could get a little flare or something weird happened with your immune system. But in general, it should be safe. Maybe don't get like a full arm sleeve tattoo, maybe just a small one to test it out.

Becky: Great, another question that we've gotten, is it ever safe to microblade your eyebrows?

Dr. Culton: So same thing with a lot of these kinds of cosmetic procedures or procedures to the skin, make sure that you don't have any pemphigus or pemphigoid going on in your eyebrows at the moment. And then just be on the lookout. I've never seen or had this done, so I'm not sure if there's a way to do a small portion of that and just make sure that it goes well before like going crazy and doing all your eyebrows and then having something catastrophic happen.

Becky: Great. Thank you. Carol is saying that she has lesions on her genitals and what is the best way from keeping her skin to stick to her clothing? Is a diaper rash cream okay to use on that sensitive like peri area? Or are there better creams to use?

Dr. Culton: No, I think, even plain Vaseline, Aquaphor is kind of a Vaseline that has a little bit of water mixed in with it to make it a little easier to smooth. So, I think one of the tricky parts of Vaseline, we love it because it doesn't have anything that's going to give you an allergic reaction and it shouldn't burn open skin, but it is really thick. And so, it's hard to spread sometimes, especially if you have really sensitive skin, you're spreading it over a blister and then that as you rub that on, it just keeps extending the blister. So, aquifer might be a good option. And then I think regular kind of diaper cream really, we call it barrier cream. So, the paste that have zinc oxide in it are very safe and effective in that area. And then I think I like recommending patients line the area with a nonstick pad. Telfa is one brand, they're essentially non-adhesive pads, absorbent pads. So, if you think about it like the middle part of the band aid where it's like a little bit shiny cause it has a coating on it, but it's perforated. So inside is a little bit of gauze, but on the

outside it's smooth and so that will stick less but that alone is not enough. You definitely need some sort of barrier cream, whether it be like a Vaseline or Aquaphor or the zinc paste.

Becky: Great. Betty's says that she gets lesions on her skin and she's been using the same tube of Kenalog 80 milligram tube for the past year. Would you consider her disease under control?

Dr. Culton: So, control of disease is, again, how we define that depends. I would say, it is encouraging if it's the same one tube that she's been using the whole time, that's very encouraging. But certainly, I think it might depend on how long the blisters last, how long does she have to use the steroid before they go away and then how long of a break does she get before lesions come back. And then where are these lesions? If the lesions are always on your palms and on your hands and you have trouble, like doing activities of daily living, then maybe it's not well controlled enough for her. But maybe it's again, a lot about how much it bothers her. So, I would say if it's incredibly bothersome and worth taking the risk of doing a systemic medication then maybe go for it. I have some patients though that choose to live with a few blisters that come and go that they can put topical steroids on. They'd rather do that than be on a systemic medicine. So, a lot of individual factors that go into that decision.

Becky: Great. Thank you. Dolores says that she's a 76 year old woman with PV. She had her first two Rituxan doses eight months ago, and will have her third and December. In the past few months, I've had two UTI's, a persistent cough with chest congestion and throat and neck pain. And now I have skin cancer. Her question is, how can I determine the likelihood that new and recurring things that are happening are not immunosuppressant caused or related?

Dr. Culton: Yeah, it's tricky. And I think this is something I struggle with, with my patients. Their disease is getting better, but now they feel like they're getting sick a lot. And of course, I caution them that they might get infections more commonly after having these immunosuppressive treatments, particularly Rituximab. And it's always hard to know if you were going get that same, UTI or chest congestion, sore throat if you were not on Rituximab. I've had some patients say, you know, I just don't want to do it because I feel like I'm getting sick all the time. And other patients say, yes, I'm getting sick all the time, but I understand, maybe that was just the luck of the draw for that particular six months and I want to do it again. So, there's no way we can ever tell for sure.

There're no tests that can be done to see if a particular infection is because your immune system suppressed or not. But I think in general we usually do say, well probably it is, probably it is. So, things you can do, right? We don't want you to be a hermit, but avoiding places that have a lot of sick people, washing your hands a lot if you're going to be out around people, avoiding people who you know are sick. All of those are important things to do after Rituximab.

Becky: Well, great. Thank you. Debra says that she was diagnosed with mucous membrane pemphigoid by biopsy. In January she was started on a hundred milligrams of prednisone and she's tapered down to 10. And that she was on 10 milligrams of prednisone and Dapsone in the last month with no improvement. She is now taking 20 milligrams of prednisone and started CellCept a week ago. When should she started seeing improvement in her gums because they are very, very sore?

Dr. Culton: Yeah so unfortunately when we try our first, we have prednisone, we call that the steroid, and then the other medications are the, the steroid sparing agents, or other immunosuppressants that are not steroids. By far, they almost all take two to three months to begin to see improvement. So, I would say just having started CellCept, the improvement from the CellCept is not going to come for another several weeks, maybe another couple of months even. And so, we kind of go back to the drawing board where we have to have something that bridges that period of time and whether it be a higher dose of prednisone, which again, nobody loves having to go back up on prednisone, but we also don't love having you be miserable either. So that's an option. Sometimes we can get away with an increase in topical steroids during that period of time. So, swishes or ointments that you can use on top of your gums again, just to bridge you until the CellCept starts to kick in. So those are both options.

Becky: Thank you. Julie says that she was on five milligrams of prednisone and 15 milligrams of methotrexate. Is it ever possible to taper the methotrexate as well? It seems I'm having aching muscles from the methotrexate and would like to get off of it.

Dr. Culton: Yes. I think, in general physicians always have excitement about the next thing they want to try or if they see the patient getting better, they want to kind of keep going with the treatment. And if there are side effects though that are really limiting, I think either going down

on the dose or stopping all together to see if there's improvement afterwards is worthwhile. The job of the physician is to try to figure out whether the symptoms are really side effects of the medication or I should say, are likely to be. Again, we can't ever say for sure, but are muscle aches common with methotrexate? And so, in my experience some patients have muscle aches, but it's not a crazy common thing that we see on patients that are on methotrexate. And then the other thing would be at the end of the day, if the patient wants to stop the medicine, we have to support them in that. And so just making sure we do it in a safe way is important. And then finally, what other medications have been tried. So sometimes what happens is, we have been through every medicine there is to try, right? There's not a ton, there's maybe a handful of medicines that can be used to treat these diseases. And if we go through all of them, and now finally, methotrexate is the thing that's helping, but it's giving muscle aches or pains, maybe the decision is, would I'd rather have my pemphigoid or would I rather have my methotrexate induce muscle aches. And so, it's a difficult decision you have to make some time about when you're dealing with these sorts of treatments. And I might've missed the first part of the question or kind of answered only the second part, but was, was there a part of, of when should we do tapering or when should we see tapering happen?

Becky: She didn't ask that. But if you'd like to give an opinion, I'm sure she'd be glad to have it.

Dr. Culton: Okay. I would just say, I have a lot of patients that are very aware of their body. You have these awful diseases and their kind of paying attention to everything that's happening. So, if a physician seems to kind of dismiss the side effect, oftentimes it's not that they're trying to dismiss it, they're trying to say, well I don't think it's related to my medicine that I gave you. And the real fear of the physician again is that if we stop that medicine and move to the next one and then there's the side effect and then we moved to the next one and then there's the side effects that before long you'll be through all the medicines there are to try and we will have run out of medicines to try on you. And so, what often happens is we circle back to medicines that have been tried before. We call that a rechallenge, let's try this one again and see if you still get that same side affects you had before. Or maybe it just was a coincidence and it wasn't related at all. And then the other thing I was going say is, when you're coming down on prednisone, prednisone calms down so much inflammation. So I have people who are coming off the prednisone and they

start to get joint aches or other side effects, maybe muscle pains and it's not necessarily a side effect of the methotrexate, it's just your body kind of going back to life without prednisone, where inflammation that might have been in your joints from like arthritis felt so much better on prednisone and now you're coming off of it, you're starting to feel all that stuff again. So that's just something to consider. It's not always the answer, but I sometimes think about that.

Becky: Okay, great. Well, Dr. Culton, this has been a very quick hour and we've actually run over and I appreciate the time that you've given us. One last question we've gotten from a few patients is, are you taking new patients at the UNC that they are interested in coming to see you?

Dr. Culton: Yeah, so we do take new patients at UNC. I do a half day of clinic that is specialized for patients with these diseases, but I do tend to see patients and in my other half days that are not specifically reserved for patients with pemphigus and pemphigoid. And then we have two other physicians in our group that that have specialty clinics where we see patients with pemphigus and pemphigoid. So, the bigger answer is that yes, at UNC we are taking new patients into our autoimmune clinic. And then specifically with me. I know just recently my administrative person told me I'm looking out for new patients you know, by several weeks. But certainly, we are working always to get people in as quick as we can and maybe not even in autoimmune clinic, maybe an in a regular clinic. So certainly, I think my information is there on the IPPF website, but we'd be happy to have anybody who lives close or far.

Becky: Oh, great. Well, thank you for being on the call with us today. This was extremely educational and I always learn things when I talk to you, so I always enjoy having you on the call. I also want to give a thank you to everyone and want to give a huge thank you for everyone listening in on the call and joining us. And a big thank you to Genentech and Celgene again for helping to make today's call possible. I do have a few announcements. The IPPF needs your help with our Patient Services fundraiser this quarter. The fundraiser helps to benefit calls like this today. Because the IPPF provides free of charge services to the community, your small donation will instantly make a huge impact. Other patient services include the peer health coach program and local and regional support groups. Consider making a donation by visiting the website today

and making it a tax free donation to help support these programs, as little as a few dollars a day can really make a huge difference to the lives of patients with pemphigus and pemphigoid. Early registration prices for the 2019 IPPF Annual Patient Education Conference will be ending in 3 days! This year's conference will take place in Philadelphia from October 11-13th. This is our 25th year as an organization and we hope that you will join us this year for an educational and fun weekend in the city of brotherly love! We hope to see you there! If you have not heard, the IPPF has a natural history study! If you have not registered for the IPPF Natural History Study, we encourage you to do so. The IPPF Natural History study is a new patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). You can register today at www.pemphigus.iamrare.org. This online data system collects, stores, and retrieves patient data for analysis in research studies. The more data we can collect, the better the information we can give to researchers, the sooner they can find better treatments, earlier diagnosis, and one day – **A CURE!** Lastly, If you have a question that didn't get answered on the call, or have additional questions please e-mail me, Becky, at becky@pemphigus.org, or call me at (916) 922-1298 x:105, and I would be more than happy to help. This call recording will be sent out with the survey following this call.