

## June 3, 2020 Pemphigus and Pemphigoid Q&A Transcript

**Becky:** Welcome, everyone. This call is now being recorded. I'd like to thank you for being on the call with us today. And, a big thank you to our sponsors, Genentech, Principia Biopharma, argenx and Caballeta Bio for making today's call possible. Today's topic is a question and answer session about pemphigus and pemphigoid with Dr. Animesh Sinha. So, before we begin, I just want to take a quick poll and just to get an idea of our listeners, which disease do you have? Are you in the pemphigus family or the pemphigoid family? And while I do the poll, I'm going to introduce Dr. Sinha. Animesh Sinha is a Professor in Dermatology and the Department of Dermatology University at Buffalo in Buffalo, New York. Following the completion of his M.D. degree in 1982 from the University of Alberta, Dr. Sinha received his Ph.D. degree (Medical Sciences in Immunology) in 1986 from the same institution. Subsequently, he pursued post-doctoral research at Stanford University in the Department of Microbiology and Immunology. Dr. Sinha's subspecialty training in dermatology was completed at Yale University and Yale-New Haven Hospital. Dr. Sinha is a board-certified dermatologist whose professional goals are aimed at bridging the bench to the bedside. His research is focused on understanding the genetic and immunologic basis of complex skin disorders. He has published extensively, over 150 peer-reviewed articles, including 4 in the journal Science, and received numerous honors and awards for his academic activities. He is highly sought after as an invited speaker worldwide on a broad range of clinical and research topics. So it looks like we have about an even split Dr. Sinha. 49% of the people listening belong in the pemphigus family and 51 in the pemphigoid family.

**Dr. Sinha:** Great.

**Becky:** So now it is my pleasure to introduce Dr. Animesh Sinha. Welcome.

**Dr. Sinha:** Thank you. Great to be here and look forward to this exchange and hopefully I can help answer some questions.

**Becky:** Great. Well, we have a lot of questions that were submitted prior to the call, and some that are currently also being submitted now. So let's go ahead and start with a real basic primer

question for us. And I think it will help set the difference between the diseases. What is the difference between pemphigus and pemphigoid?

**Dr. Sinha:** Great question to start with and really appropriate since we got about equal numbers of people on the call with pemphigus and pemphigoid. So really quickly just to set the frame for the discussion for these diseases. Pemphigus and pemphigoid are both autoimmune diseases and autoimmunity is when our immune system, which normally does not react to our own tissues, there are things that break down in the maintenance of self tolerance, leading to an attack that's abnormal against your own tissues. And that can happen in any organ system, including the skin. There are a number of autoimmune diseases in the skin, including psoriasis, vitiligo and alopecia. But these diseases are the blistering disorders and they can roughly be divided into the pemphigus group and the pemphigoid group. The prototypical disease for the pemphigus group is pemphigus vulgaris but there's also pemphigus foliaceus, IgA pemphigus. Then there is the pemphigoid group and bullous pemphigoid is the prototypical disease but there's also herpes gestationis, in pregnancy, and some related conditions. So the main difference is the level of the split of the blister in the skin. In the pemphigus group, like pemphigus vulgaris also known PV, the split is within the top layer of the skin, the epidermis. It's at the bottom layer of the top layer of skin, the bottom layer of keratinocyte. So it's called the supra basilar split. But in the pemphigoid group, the split is below that. Just below the epidermis and therefore, we call it the sub epidermal split. The difference, therefore, is that the blisters in pemphigoid diseases are a little bit more tense because the split is deeper. So that's the main difference between pemphigus and pemphigoid.

**Becky:** Great, thank you. Our next question that was submitted before the call asks, is there a common denominator between blood type and either bullous pemphigoid or pemphigus with patients, example like an RH negative?

**Dr. Sinha:** Right, when we think of blood types there are a lot of markers or proteins on cells that mark them in different categories, including red blood cells. As we all know, whether you have blood type A, B, or O they are linked with different conditions. But in this case, there's no evidence to suggest, no data suggests, that there's a linkage to the autoimmune blistering disorders. There was, in fact, a study in 2016 out of Iran that looked at that specifically and they didn't find any link.

**Becky:** Great, thank you. Kelly asks, in pemphigoid, why do blisters occur on the same spot? If it's due to weakened skin membranes in that location, is there anything that can actually strengthen the membranes in order to alleviate blisters at the site?

**Dr. Sinha:** Well, that's a great question. Where exactly, and why do blisters happen? Well that is a whole host of reasons that we, in our group, and others, are studying but, we don't have a great answer of why blisters happen in a given individual or patient at a certain location in the body. There's some ideas about why blisters occur in the mouth versus the rest of the body or mucosa lesions like the mouth and other mucous membranes versus the non mucosa lesions, the rest of the skin. There's some ideas about that but in general, even within the mucosa or the skin, why does a certain person have a blister in one place or the other? There are some general patterns, but we don't know. And it can vary, it can come back in the same spot but most often it varies. We don't have a great explanation because if you think you have these antibodies that are causing the disease or attacking your proteins that are important in holding skin cells together, why doesn't the whole skin sloughed off? So there's gotta be some local factors whether they're genetic, mechanical, or other factors that ultimately tip the balance, whether a blister happens or not in the patient that's genetically susceptible and has developed these antibodies. We don't know, it's a great question. So then the second half of that question is, can we do something to strengthen the skin? Right now, we need to understand more about the reason's locally that contribute to a blister formation. So we don't have any really good treatments at the target tissue or skin level. Down the road, perhaps as we learn more about the exact mechanisms by which the skin falls apart, not just because those antibodies, but exactly how those antibodies are acting under what conditions they lead to a blister and under what conditions they don't, then we might be able to come up with better strategies. Not just attacking the immune system, but strengthening the skin, as Kelly asked about.

**Becky:** Great, thank you. Wendy asked a question. You talked about strengthening the skin. And she was asking if there is anything such as a cream that might help with the fragile skin that might help with the chafing that comes along with the disease?

**Dr. Sinha:** So like I said, we have nothing to really put on the skin that will really prevent blisters from a mechanistic way. As we learn more about how the skin actually falls apart, perhaps that will be the case. Nonetheless, perhaps there are things that patients can do to just be mindful of wound care and lesion care. Keeping the areas of blistering and the erosions clean and lubricated and then proper dressings and so forth. I think the way we approach management is to try and stop the immune system and block that train from running and causing havoc in the skin. And then trying to protect the skin to limit the consequences of the damage. But we don't have anything that actually protects the skin in a real mechanistic way yet.

**Becky:** Great. Thank you. We're going to take a little step back here and we have a question that came in that said, what is the best way of getting assessed and a diagnosis? What are the first steps that should be taken?

**Dr. Sinha:** So it's a really important question and very relevant to most people's lives. Our own group has done studies in line with what other groups have recorded in either literature or anecdotally. It takes about 12 to 13 months from, on average, between the first symptom of when the blisters occur, especially in pemphigus, and the proper diagnosis. Patients often go through, sometimes, it seems like a dentist and it's not recognized or other physicians. They bounce around, often it is repetitive, and sometimes it's diagnosed as an infection they don't get a proper diagnosis for a while. But what the criteria for diagnosis is one history and physical of course. When did this start? How did it start? What do the lesions look like exactly? And then the location of lesions? And then, the gold standard is a skin biopsy that will tell you, that the skin, it will show in particular at the edge of the blister, it will show in most cases that you have a lovely split in the epidermis in bullous diseases and below the epidermis pemphigoid diseases. Then to confirm the diagnosis, there's other things that we can do. So the first biopsy gives us usually, a characteristic pattern that tells the pathologist and the dermatologist staff you could have pemphigus or pemphigoid. Then there's immunofluorescence. We can take a biopsy tissue, stain it with other reactants that will light up tissue. You will see that there are some antibodies or immune reactants and that is not normal so that would be another clue, that those symptoms, the antibodies in the skin that's relevant to explain what is happening, clinically, the blisters. You can also take the serum, the blood of the patient and in the serum will be the antibodies. We can layer it over tissue and show that those antibodies will light up the keratinocytes, the skin cells come with another agent that is a color maker and you can literally see a green on a microscope. And so there's immunofluorescence. So there's clinical, history and clinical, there's a regular biopsy, immunofluorescence either direct or indirect and finally, you can do antibodies studies. You take the serum and you can check them on a tissue culture plate that has the proteins that we know are attacked in these diseases. In pemphigus it's desmoglein 1 and 3 and in pemphigoid it's BP antigen 180 and 230 and these are the known targets of these antibodies. So if a patient has those their blood they will attach to those proteins on the plate and a second agent mix is put on and the plate will turn say purple and it will tell us that there are antibodies. So these are the diagnostic steps we take to confirm the diagnosis of pemphigus or pemphigoid.

**Becky:** Great. Thank you. A question, Ricky says that her doctor is insisting that may be that they have a viral infection, like the herpes simplex and prescribes an antiviral. What would the next step be after that? Would it be the biopsy?

**Dr. Sinha:** Well lots of things can cause blisters including herpetic lesions and other infections. So sometimes a culture is taken for a viral reason like herpes or other viruses or even bacterial sometimes have a bullous staph infection, and so forth. So if the culture comes back negative and antibiotics or other treatments. If antivirals don't work, then I think the biopsy is warranted. Or if there's reasonable suspicion to do a biopsy earlier on that diagnostic pathway to determine if the lesions and the blisters are an autoimmune cause and are indicative of pemphigus or pemphigoid.

**Becky:** Great, thank you. Kind of going along the diagnostic and testing, Marlene wants to know if her daughter would be more susceptible to having mucus membrane pemphigoid because she has it?

**Dr. Sinha:** Yeah, great question. So there is a genetic basis to all autoimmune diseases including the blistering disorders but it's not a one gene disease that's comparative breakdown can be down the family line that you could pass on or perhaps you don't pass on. But there are diseases like that. These diseases, autoimmune disease are by definition complex meaning they are multifactorial, meaning there is a genetic component and also an environmental component such as infection, or stress, or other things are also perhaps more important than the genetic. Now the genetic component itself is complex, but it's not one gene, it's multiple genes. We know, in fact, I see that the genes that are most relevant during susceptibility for pemphigus such as HLA genes which are master regulators of the immune system. They help get immune and autoimmune responses started, and that's why pemphigus patients seem to have the predominance of a certain subtype of these genes and proteins. But most people who carry these particular genes of protein do not get pemphigus but most people who have pemphigus do have them. All other autoimmune diseases have these HLA associations. It's very, very strong in pemphigus and strong in different ones in pemphigoid and other bullous diseases. But there are other genes that we mostly have no idea what those genes are, we are working on it and we hope you'll have a better idea of a broader panel of genes that confer genetic risk. Now, because there are multiple genes involved, the chance of passing it onto the child is very small but it's possible. It's not very common, not like you have one gene that causes a disease. So, while there is an increased risk, slightly of having another autoimmune disease in oneself, or in a family member has a disease like pemphigus or pemphigoid, it's still low, but there is a genetic basis, but the chances of passing it down to a child are actually quite low.

**Becky:** Great, Thank you. We're gonna move on. We have a whole lot of questions that have come in about foods. Everybody wants to know, what is the best thing to eat if you have pemphigus or pemphigoid? And if there is any research being done looking at taking targeted

probiotics, how the microbiome affects the immune system and if there's any foods that make it better or make it worse?

**Dr. Sinha:** Great question. So there are, as I said there are genetic factors and environmental factors as well. So infections, medications, perhaps food, sleep, stress, psychological and physical stress, and maybe microbiome, too. So, let's talk about food. There's no particular diet that would prevent the development as far as we know of the development of disease, or terrifically improve disease once somebody is diagnosed with it. There are some foods that seem to exacerbate, maybe triggered flares, and those are some of the allium group of vegetables, like onions and leeks and so forth that maybe just because of their irritating nature and can trigger disease. Hard foods like nuts and citrus foods can irritate lesions and that can certainly exacerbate lesions and make them feel worse, or trigger perhaps the development of more lesions. But there's no exact diet that we can do or probiotics that we know of but I'll talk about the microbiome. It is interesting, there is no doubt that we're now understanding the microbiome that there is a huge role in health and disease, including the susceptibilities to autoimmunity. There have been very limited number of studies on microbiome and the blistering disorders. There's a couple of reports saying that there are some increased species of bacteria in the mouth or the lesions on the skin. Again, is that positive or is it because you have these lesions then the colonization of these pathogens? Our own group had a study published regarding HSE or herpes simplex virus and pemphigus. There's been some reports in literature outside our group we looked at for antibodies against these viral lesions and we did see some increases. Again, is it positive? But we do know that virus and bacterial are important in triggering autoimmunity. We don't always know exactly how that happens or the strength of these correlations, because these pathogens are often ubiquitous. So there's needs to be, and there will be more work done on understanding the role viruses and bacteria and maybe even fungi in figuring out autoimmunity and the blistering disorders and how the microbiome and the gut microbiome, in general changes and or effects, the susceptibility to disease or the course of disease. So, lots of interesting research that still needs to be done in this area.

**Becky:** Great. Another question came in regarding food. Is there any research or anything that has shown a link to cow's milk from the cows that have been treated with antibiotics or anything in that way? Any additives like to genetically modify our foods or anything like that, that you know of?

**Dr. Sinha:** Not that I know. I take a scientific approach, I'm open to any things but it has to be proven and tested. And sometimes when we don't know if nothing's proven doesn't mean it couldn't be, it just means that we don't have enough information to really rule it in or even rule it out. As far as I know, I don't know of any studies.

**Becky:** Okay, great thank you. We have a bunch of questions as well about Rituxan during COVID-19 and what is amongst a consensus. I know there's not one solid answer but what are the recommendations for use of Rituximab during this pandemic?

**Dr. Sinha:** Yeah, that's a great question. It's up for discussion and debate and we'll see what the results are. We just don't know the answer yet. So that we're all on the same page, many of you have heard of Rituxan or Rituximab, it is an antibody that is targeted to a protein on B lymphocytes. B lymphocytes, which are part of the white blood cells in our systems, or a component of our immune system and they are the cells that make the antibodies that are important for health and infection in general. But they also make the antibodies in the case of disease or autoimmunity that then target some of those keratin sites or skin cell proteins that cause the skin to fall apart. So, the strategy for Rituximab is clever. We see if these are the generators of these antibodies, let's have an antibody attacking those generators and knock them out. Rituximab was approved from pemphigus in 2018 and it really has been kind of a game changer. It's been pretty well tolerated and pretty effective. But remember, that you're knocking out a lot of your B cells for six to twelve months and we need those B cells for other things. So there's likely some increased risk for infection. So far, the safety data has actually been pretty good so there's not a severe compromise state in patients that get Rituximab but it's a risk benefit analysis of severe disease, etcetera. So you also don't wanna have severe disease. Also prednisone and most of these drugs used for pemphigus are basically immunosuppressants, most of them, not all of them. So what is the risk of Rituximab versus prednisone and there's some studies that say that actually the risk is a little higher with high dose prednisone. So, it's a discussion to have with your dermatologist and your physicians that are taking care of you. You have to discuss the risk benefit. If Rituximab can be avoided if there is mild disease or you are heading into remission that would be great. But if you really have a flaring or severe disease, that may be wise to also get that disease under control with Rituximab. Then in any case, if people are taking any immunosuppressive medication including Rituxan and non steroidal stuff such as Imuran it is even more important to practice precautions. So wearing masks, social distancing, hand washing, wound care especially if you have an autoimmune disease or on immunosuppressant therapy.

**Becky:** Great, thank you. So all of our listeners know, our call next week on June 11th will be on COVID-19. So if you have a lot of COVID questions, that would be the call to submit your questions to. Also, what is the dosing? There's some questions that have come in about using the dose 2 weeks apart versus given weekly for a while, and then what is the dose for that? And then when would a booster dose or a patient would need to be redosed or have another infusion?

**Dr. Sinha:** Sure. That's an evolving story, but as the data comes in people adjust there to dosing. So Rituximab was first designed for and utilized against B cell lymphoma, so B cell cancer to directly knock out those B cells. And so there's a lymphoma dosing, 375 milligrams

per meter squared of body surface area. And it's given weekly for 4 weeks. Then there was another protocol developed for rheumatoid arthritis for autoimmune disease not cancer. That was one gram on day one, repeat on day 15 and then there can be another cycle of these two doses in 6 months. So just because of ease, and because rheumatoid arthritis is an autoimmune disease I think people started in pemphigus and the blistering disease community with the rheumatoid arthritis dosing, mostly the last while. But there has been some data recently saying that lymphoma dosing, the weekly injections maybe 2 to 3 times more effective in some patients. I guess it's still evolving. I think the rheumatoid arthritis dosing is still active and also a little bit better for logistics. Somebody doesn't have to come in every week for injection are they able to tolerate it with their schedule, etcetera. So then for maintenance dosing, if the disease is not controlled there can give you 500 milligram dose, again after 6 months. The dosing schedule, the general comment is there's a couple of basic protocols and a maintenance dose protocol. But it's evolving a bit and we will have to see the data and it's worth having the discussions with your dermatologist to see what dose works best for your disease and for your overall condition and lifestyle.

**Becky:** Great. Thank you. Our next question asks, do you recommend getting a shingles vaccine during the initial prednisone treatment and what is considered a high dose of prednisone?

**Dr. Sinha;** So, in terms of the dosing for prednisone, that's all relative, I guess. Any dose of prednisone could be considered unwanted and undesirable. But, I think low doses are below 20, and then mid is 20 to 60 and higher is more than 60 and that is the basic range. Often in pemphigus and pemphigoid we start off at 60 to 80 milligrams per day, and then come down to usually about maximum, 1.5 milligram per kilogram per day, and then get the disease under control and then taper down. In terms of the vaccine, there are 2 types of Shingles vaccine. There is the one that is a live attenuated so it's actually a live virus, but it's a small dose of it. And if you have an autoimmune disease and are on immunosuppressants including prednisone, you don't want to get that. More commonly now, there's the inactivated vaccine, which is safe to get, but still, preferably not on high dose prednisone and probably not any closer to a month within the time you're going to get Rituximab or 4 to 6 months after you get Rituximab. And that's because you want your immune system to be able to not be totally down but you need to suppress it for your autoimmune disease. But if it's too far down, you won't give it a good enough chance to sort of muscle up and develop the immunity you need against the virus that you're trying to immunize against. So you just have to be careful to make sure you don't get the live vaccine, and the timing of when you're getting it in correlation with your medications and your overall immune suppression. So just make sure you discuss it with your doctor.

**Becky:** That's a really great answer. We had a question, Julie is asking when tapering prednisone, is it common to experience fatigue and what can be done to help fight that?

**Dr. Sinha:** Well, prednisone causes all sorts of side effects. Their common, prevalent, and not everybody gets the exact same ones. Nobody feels great on prednisone, it's safe to say that prednisone can cause fatigue to begin with. So it can occur whether you're going up or down the scale. We've just got a taper carefully because prednisone suppresses some of our natural hormones secreted by the adrenal gland and therefore if you go too far down you don't give your body a chance to pop back on the production of those hormones. And that could cause fatigue if you have to be really careful at the pace in which you step down on prednisone.

**Becky:** Great. Thank you. Our next question, Allen says, her 99 year old mother-in-law has been a bullous patient for eight years and currently taking methotrexate weekly. She has no new outbreaks, but terribly sensitive skin. It's so painful she can't wear clothes. And of course, there's the intense itching and the nerve pain. Is there any medication or anything that can be done to help with us?

**Dr. Sinha:** Well, congratulations on her being 99, that's a great achievement in itself. There are a number of things to watch out with methotrexate but I won't go over all of them here, but there's some toxicity with the liver, renal function that should be monitored and the blood, and so forth. In terms of bullous pemphigoid, there are antibodies that attack the proteins in the skin that are important for cell adhesion and that is what can cause the blisters but there also seems to be in more so than the pemphigus group, a large inflammatory component to their other immune cells not just the B cell and antibodies that are causing the problem but also the mast cells, the eosinophiles, etcetera, that seem to come along for the ride and secrete some of the things they do when they're trying to do the job. They are over-exuberant and they release some chemicals from histamines, etcetera, that can cause inflammation and irritation and itching. That can be actually a serious issue in pemphigoid and under-appreciated. Often not you don't only get blisters you get these hive plaques and the itching can be difficult. In the setting of a 99 year old person, our skin normally thins and dries out and that can be a chronic problem to begin with. So in a disease like pemphigoid that can certainly exacerbate that. So how do you approach this? One, try to keep the bullous pemphigoid disease under control with the normal things like prednisone or methotrexate or immunosuppressants. There are specific agents that have been investigated, looking at knocking out the eosinophiles that were in trial recently that were not completed for certain reasons targeting eosinophils. Zolara has been tried, it knocks out the IgE antibodies that are involved in itch. Then there are topical therapies. Keeping the skin moist and hydrated as well as Sarna lotion which has Camphor and Menthol that can be used to cool the skin and help mitigate the itch. Then antihistamines can be used but then those are often sedating and I would be careful in elderly. So there are a number of approaches and it might be trial and error to see what works. What is the balance between too

many medications on board especially in elderly when managing disease but the question illustrated that itching can be a major issue in people with bullous pemphigoid.

**Becky:** Great, thank you. Kind of leading into that, Joanne says she lives in a hot dry climate in the south-west and she tries to stay out of the sun during most of the day as a precaution having seen that bullous pemphigoid might be triggered by sunlight. What is the research on sunlight and pemphigoid and do I reduce the risk by following the usual precautions for skin sensitive people, if I have to be in the sun only exposing my outer extremities?

**Dr. Sinha:** So it's a really good question. The link between UV light and sunlight triggering autoimmunity. There may be some data, I don't think there's strong data linking UV light but there's certain diseases where UV light does trigger disease like in lupus, dermatomyositis, etcetera. So not so much that we know of in pemphigus or pemphigoid although perhaps a sunburn irritation would be considered a stressors to the skin that may contribute to triggering of lesions, it's possible. But otherwise following normal guidelines of sun safety such as sunscreen, wearing proper covering, staying out of the mid-day sun. Also liberal application of sunscreen, broad spectrum sunscreens, UVA and UVB sunscreens that are applied at appropriate times every couple of hours. So, still susceptible to skin cancer and melanoma, etcetera. So I think following the normal recommendations for sun protection to help with reduction of cancers and so on that would be my best recommendation.

**Becky:** Our next question says, is Rituximab considered to be the best option to try and have remission for pemphigus vulgaris or are there other choices you would suggest? With a follow up question of what is the success rate of Rituximab of achieving remission and does IVIG after Rituximab increase the remission rate and by how much?

**Dr. Sinha:** So, great questions about how effective Rituximab is. The first part of the question Becky was what? Will you remind me?

**Becky:** Is Rituximab considered the best option to achieve remission? And, if so, what is the success rate, and then with the IVIG?

**Dr. Sinha:** Sure. So Rituximab is considered a game changer and the success rate has been pretty good. About, 60% of patients go into a complete remission, that means no lesions for a couple of months at about 50% or 60% after just one cycle. And then, that's without any therapy. In another 15% or so, go into complete remission for a couple months, at least a couple months with no lesions, but still on some minimal therapy. So overall, if you look at multiple cycles, the remission rates achieved are around 80%, that's pretty good. But there are

still people that flare. In fact, about 50% of people flare in 12 months, and up to 75% of people flare sometime within two years. So it does work it does seem to in a large majority of patients, but not everybody. Not everybody responds exactly the same but it seems to be quite efficacious and effective but there are still people who flare. Now the question of, is it the best treatment for somebody? Again, it's very hard in these complex diseases. Everybody's a little bit different, you really have to work with your doctor and your dermatologist to tailor your medications and your schedule for medications which ones you're going to use and the timing of which ones you start with and add on closely to your disease. So, somebody who has a really mild disease, will have a little bit of a different strategy than someone who has rampant disease and that's where IVIG can be helpful. It's not immunosuppressive in fact with it you flood the system with all this immunoglobulin and it has been deeply studied, but not completely understood still, that it can be a complementary medication, used with Rituximab or other immunosuppressive. The setting that I think it's most effective is in, if there is really prominent disease and it's rapidly evolving because Rituximab works much more slowly because it's blocking out the B cells that make antibodies. Those antibodies have already been produced in the body and can cause problems so it takes a few months for it to work in general. IVIG works quicker and therefore can be used in combination, especially in a certain type of clinical settings, particularly rare diseases happening very strongly and quickly at the beginning. But the overall point is Rituximab is a good option, IVIG can be a good option in certain settings. But we don't have a sort of strict protocol for knowing what medications are used for what patients. We don't have the right biomarkers that tell us who is going to respond to a given medication or a combination of medications. As we do more research, as we try to identify factors that contribute to treatment response, hopefully, we'll come up with better algorithms and schedules to tailor therapies based on objective findings and clinical findings. Overall, Rituximab has been really tremendous for autoimmune blistering disorders.

**Becky:** Great. Following up with Rituximab again, Sarah wants to know if it's common to see longer remission periods after each round of Rituximab treatments for BP. Her skin was clear for eight months, between her first and second treatment, then 13 months between her second and third. She's hoping this trend continues.

**Dr. Sinha:** I hope so, too. And I think it makes sense, and I think it is illustrative of the way we think things work in Rituximab. You're knocking out the B cells in each subsequent round knocks them down more. But between each round they start to come back because you're not knocking out the generation of the B cells, you are knocking out the ones that are in the body. And then have the potential to make the antibodies that are causing problems. So, the data show that too. You achieve about 50 to 60% complete remission off therapy with one cycle Rituximab. Two, plus cycles, gets you to 80%. So, that patient's experience highlights the way we think this is working, and what the data are showing us.

**Becky:** Great. So, as well as it sounds like it's working for Sarah, Susan wants to know how many rounds of Rituximab without remission do I do before giving up on this therapy?

**Dr. Sinha:** Yeah, again, no hard and fast rule. I would think if it's, and I think this is something that each physician has to figure out with their patient how long you give it. If there's no improvement for a year or more than I would say, if you've probably already switched to some other immunosuppressants along the way as well. Sometimes it's hard to tell if something is working or attribute success or not success to getting a regime especially success because the disease waxes and wanes, the natural history of disease is to wax and wane for all autoimmune disease. I think that's because there's an internal struggle in our body in the immune system drivers that propel us towards having disease. And the counter regulatory mechanisms that are trying to operate to apply brakes on those drivers of disease. And that's happening I think internally. The immune system is incredibly inter-connected in counter-balance and in disease it tips over in autoimmunity where you get these drivers that override and create these runaway clones that produce the antibodies that cause disease. Nonetheless your body's probably trying to control that on an immunological level. The medications help you to tip the balance back in a favorable way. If a particular medication is not working enough to tip the balance back than other combinations need to be tried. Again, not everybody responds to Rituximab. Overall it's been good but not everybody, some people have flares or more frequent flares than others on Rituximab. And we don't have biomarkers that will tell us who is going to respond and who is not. That is really something we'd love to have at some point for this medication in this disease, and many other diseases But at this moment, we don't have that information so we have to sort of go trial and error and adjust on the fly.

**Becky:** Great. Thank you. Our next question says I'm concerned with gum health and tooth loss. I see people on all of the discussion boards talking about losing their teeth. My dentist believes that MMP is not the cause. What is your opinion on this?

**Dr. Sinha:** Sure, so obviously mucous membrane pemphigoid often severely affects the oral mucosa and the gingiva. And probably there's not a direct cause but what can happen, I believe, is that if you have constant irritation and eating and lesions around your gum and mucosa that there's a good chance you don't really love to brush your teeth are very long, or maybe just try and rinse out your mouth. That could perhaps lead to increased caries or cavities and just the chronic inflammation may not be great for the gum health and cause gum disease. Those two things indirectly would then lead to dental problems and tooth loss. I don't know, I'm not familiar with the literature on this. There may be data but that it may not have been studied really rigorously. But I think the disease itself won't attack the teeth but the sort of collateral damage of having constant problems in your gums and pain would lead indirectly to conditions that are not good for your teeth. And so that's certainly a possibility. So perhaps take gentle but extra care, and discuss these things with the dentist. They may have some

ideas and some tips on how to manage your oral health, and maybe more frequent monitoring for gum or tooth decay.

**Becky:** Our next question asks, do you have any recommendations for treatment of having ulcers in your nose?

**Dr. Sinha:** I think all the same things apply. When we're talking about mucosal involvement I think we're often talking about the oral mucosa, but it's really the nasal pharyngeal as well, so from the nose. It can be significant and severe so I would suggest that if this is an issue, certainly discuss it with your dermatologist but perhaps also, have a visit to the ear, nose and throat doctor, the ENT doctors. They can scope down and see how far or extensive the lesions are. The basic approach to therapy will be the same, to knock down the immune system with prednisone, Rituximab or other immunosuppressive, maybe even some local care to keep things moist. Again, the ENT person will examine the scope to see the extent of the lesions where a patient or dermatologist couldn't see and make some recommendations on local care. Certainly, mucosal lesions outside the oral cavity and even below the belt in the genital region, in the nose and larynx, etcetera could also be involved. I think, if it's something that is an issue then perhaps a consult with an ENT as well.

**Becky:** Thank you. Our next question asks, for oral MMP, should a patient go see a dentist, a dermatologist or both? And why?

**Dr. Sinha:** I think certainly a dermatologist should be consulted and be part of things but the dentist, as we talked about, the issues in the oral cavity could lead to dental problems. It's important to involve a dentist and that they're aware of the condition. It can help with promoting good oral health and help prevent tooth disease. Then, for MMP patients, sometimes there can be ocular cicatricial pemphigoid, so the eyes can be involved. In that case an ophthalmologist should be consulted immediately with conjunction of the dermatologist to really be on top of any progression and scarring in the eyes that can lead to blindness. So I think it is very important to work in teams when necessary. To work with an ENT, ophthalmology, dentists, depending on how the disease is presenting and the involvement the patient is having.

**Becky:** All right. Thank you. This has been a really quick hour Dr. Sinha and I want to be respectful of your time. We have a lot of questions left. Would you mind hanging out with us for a little bit longer, just to help answer.

**Dr. Sinha:** Sure

**Becky:** Awesome, thank you. So, this question says that I got bullous pemphigoid after a knee replacement, only on my knee. Will another knee replacement cause it to go to my other one, and the replacement was titanium and does the titanium cause BP?

**Dr. Sinha:** Okay, so we don't know all the triggers of disease. So, there has to be some sort of genetic susceptibility. And, as I said, and that involves those HLA molecules. But as I said, there are environmental factors such as infections, medications, stress, etcetera that we don't know much about. Anecdotally, there's a lot of evidence in autoimmunity that there are some sort of traumatic life events and that could be physical or emotional. Psychological. Often people say, there was a death in the family or I lost my job, or divorce, or had surgery or had some sort of trauma. And that's not uncommon. We're actually in the lab, my group, is looking at these factors right now in our database to see the correlations we can make. And we have some data and we are writing a paper on that. But again, it's correlative, it's necessarily positive. But it seems to be, what happens is that you have a predisposition to an autoimmune disease. And then something has to push it over the cliff from having the potential for disease to actually having the disease and getting lesions. So, it is quite possible that a tough surgery or a knee replacement could have triggered disease, and caused attacks on the patient's body, and that weakened it even more to tip over. But again, it could also just be coincidental and sometimes we just remember these things. So it's hard to know. Will another knee replacement trigger a flare? Possibly, but I think if you need a knee replacement, you need a knee replacement and then just coordinate the timing of the surgery and the recovery steps with your dermatologist so they are aware of things, and take it from there. So it could be correlative but you have to go on with the care of the other parts of your body, too.

**Becky:** Absolutely. Our next question comes from Robert, and says that his wife was diagnosed with OCP, and also has RA. He mentioned that her sister has RA, and he wonders if there is any blood or DNA test to determine if her sister is susceptible to OCP as well. And also, if there's any connection between OCP and RA?

**Dr. Sinha:** So that's a really interesting question and it gets to, I'll take it back to the observation that if one has an autoimmune disease, such as pemphigus or pemphigoid or OCP, ocular cicatricial pemphigoid, that there is an increased risk of having a second or even third autoimmune disease in oneself or in a family member. We and others have published on that. And it's clear that the closer the relation, first degree or second degree relatives, the higher the possibility. It's still low, but it's going to be more than just by chance. And then we also found something interesting, a couple years back, and we published this in the British

Journal of Dermatology and that is, that certain autoimmune diseases seem to cluster together. It's not an even distribution of which disease, you or a family member might get an additional disease. So there seems to be a cluster with pemphigus vulgaris with rheumatoid arthritis, autoimmune thyroid disease and diabetes mellitus. And so, when you look at all the data that we had, we saw that those diseases run a little more frequently together, then you might expect by chance than with other autoimmune diseases. Statistically, it's not a high chance but it's a little bit more chance. And why could that be? It's not known, this lends to the common cause hypothesis or maybe the common gene hypothesis. Maybe there's common genes that link these diseases that are related to susceptibility to auto immunities. And they may not be fully overlapping, but there may be a set of overlapping themes between those conditions, those clustering diseases, that predispose somebody to autoimmunity. And then there are other genes that then push you towards rheumatoid arthritis, pemphigus, or mucous membrane pemphigoid, OCP, etcetera. And there could also be common environmental factors as well that we don't know about. Maybe they have certain infections that are common among these clustering diseases, so we don't know. But there is no test that we can do that would say right now, that would say you're more likely to get rheumatoid arthritis if you have OCP or which patients who have one of these blistering disorders is most likely to get thyroid disease or diabetes mellitus. We know there is a real increase but can we predict which ones are more likely to get it and or a family member? We can't do that yet. We are looking into the genes that perhaps may be overlapping in some sort of Venn diagram that may show some of the common susceptibility but that's really tough work to do. But we are making some efforts to do that. Right now we have no markers, genetically, or otherwise that would help us predict who is most likely to get a second autoimmune disease in the clustering diseases.

**Becky:** Great. Thank you. Selina says she is the caregiver for her 89 year old mother who has bullous pemphigoid for the past year. Her mother's regime currently includes doxycycline 2 times a day, Niacinamide 2 times a day, and Tacrolimus or Clobetasol twice a day. She heard that Tacrolimus could be associated with cancer, so is Tacrolimus okay to use on a long-term basis?

**Dr. Sinha:** First is it effective? There's some reports that it could be, it's not clear what the mechanism would be as Tacrolimus is immunosuppressive agent applied topically. It mostly goes after T cells where this is mostly a B cell mediated disease. Again, although B cells come from T cells and potentially those white blood cells would help each other out. So, in terms of safety, though, there were some reports about Tacrolimus and having increased cancer risk. Most of the studies have shown that risk is negligible, and the Tacrolimus is used especially in people with atopic dermatitis including kids. And the follow-up studies, going out a few years, haven't shown any increased risk of cancer, pretty much. The long term studies, you never

know but in general, I believe most of the studies have been showing that it's relatively safe in terms of cancer.

**Becky:** Great. Thank you. Are there any special considerations I should know and precautions I should take when I'm taking methotrexate?

**Dr. Sinha:** Sure, so methotrexate is an immunosuppressive drug. It works as many of these nonsteroidal immunosuppressants work by ultimately blocking the nucleic acids or a process where our cells replicate. Since lymphocytes are rapidly dividing, the idea is that you throw a wrench in the chain there, in the machinery that will stop the lymphocytes from working because the lymphocytes are important in producing antibodies that cause disease. So it's been used successfully in autoimmunity including pemphigus and pemphigoid. It's less used now because we're using more immunological based and targeted therapies. First of all, you don't want to have any evidence of liver disease or alcoholism because Methotrexate can affect the liver. And in terms of other certain medications that can't be used in conjunction with Methotrexate, you have to watch out for folate deficiency, because that's how it works. It blocks that pathway but you can supplement with folate and monitor for CBC, complete blood count and make sure that your blood counts are okay and monitor for liver function, renal function. But overall Methotrexate, the overall safety profile is not so bad and can be an alternative for certain patients. You just have to take it with care and in close conjunction with monitoring from your physician.

**Becky:** Great, thank you. Our next question asks, What is the best kind of dressing to use for lesions on my legs?

**Dr. Sinha:** This is really important. And sometimes an aspect that we don't consider as we're working on treating how the antibodies are made in the immune system. But when you have lesions, that's a real practical issue that we deal with day-to-day. It's worthwhile to keep areas of erosion or blisters clean. They're certain skin cleansers are wound cleansers that have a surfactant, lubrication that can help. I think you want to have a non-stick, perhaps alginate-based dressing that forms sort of a gel and keeps things moist and helps with wound healing. And then a secondary dry dressing. You don't want to put on a dry, woven dressing. So, I think local care is important. We get help from our colleagues sometimes in surgery and ulcerative wound care and there are excellent nurses that know a lot of tricks and the right types of dressing. But basically, you want a non-stick dressing and keep the area clean. If the blister is on top, it needs protection and then take care of the open wound areas by keeping things clean and then the non-stick dressings.

**Becky:** Great, thank you. Beth says that she has bullous pemphigoid and mucous membranous pemphigoid, not BP with mucosal involvement. How often do you come across patients with both forms of pemphigoid?

**Dr. Sinha:** Well, it's interesting, it can happen. There are some reports even with patients with pemphigus vulgaris and pemphigus foliaceus or even pemphigus vulgaris and bullous pemphigoid and some overlapping diseases. It can happen perhaps because there's a common genetic susceptibility also because one hypothesis is that once the antibodies start having local effects and causing havoc and destruction of the skin, other proteins or antigens as they are created by the immune system they become the least recognize and then new antibodies develop that target these other proteins that are marker for these other related but distinct diseases. And so that's one hypothesis and bullous pemphigoid has certain antibodies, two key proteins that seem to be a hallmark of that disease. Mucous membrane pemphigoid related also subepidermal split of the traditional targets, therefore additional targets that are involved. It's not that common but I suppose you could see it in convention. And it may be, again, related to genetic susceptibility and or the release of these other antigens that now trigger antibodies to those antigens that are relevant to MMP.

**Becky:** Great, Thank you. Our last question, and I appreciate you hanging with us for so long with us today. Is a connection between hormonal changes and bullous diseases? Kelly says that she wants to know if there's any research regarding hormonal changes activating the disease and it seems like she's talked to a lot of people that have presented after a surge of synthetic hormones.

**Dr. Sinha:** It's quite possible. I have a couple of thoughts, one, most autoimmune diseases including the blistering disorders especially pemphigus is a female predominance. We don't know why that is, I could be partly genetic and or genetic link to hormonal changes. There is data on that but a lot of work to be done on that. And secondly as there are hormonal changes, especially in women throughout the course of a lifetime these changes impact the immune system and in ways that are intricate and still being figured out. So, I don't know if there's direct evidence. Therefore again, the level of impacting the immune system, or the level of inflammation, or overall stress as we go through life cycle changes in the course of a life span. All those things in general could be impacting and shifting and autoimmune response around all of it. I'm not myself familiar with exactly how those mechanisms work, there may be literature that is a little more defining but probably all those questions and those relationships and correlations are still being studied.

**Becky:** Great. Thank you. I really appreciate you hanging on with us. We had a lot of great questions, and I know that there's a lot of questions that still haven't been answered. But thank you for being on the call with us today.

**Dr. Sinha:** My pleasure, I hope that was helpful for for you all and good health and stay in touch with your dermatologist and take your precautions.

**Becky:** Thank you. I'd also like to give a huge thank you to everyone on the call and submitting great questions to be asked today and of course a big thank you to Genentech, Principia Biopharma, argenx, Cabaletta Bio for helping to make today's call possible. Before we go, I have a few announcements:

Our next Patient Education Webinar will be on June 11 with Dr. Emanuel Maverakis, Dr. Aimee Payne, and Dr. Mary Tomayko to answer your questions about COVID-19. Please submit your questions to Amethyst Yale at [amethyst@pemphigus.org](mailto:amethyst@pemphigus.org). You can register online today!

We want to thank everyone that donated to the IPPF's Hope Fund and to our generous matching partners, Principia Biopharma and argenx for helping us raise almost our funds. As you know, the IPPF's main focus is to improve the quality of life for all those affected by pemphigus and pemphigoid through early diagnosis and support. Day in and day out, we're here for you, whether it's by providing support through our peer health coaches, supporting the research of new treatment options, advocating on behalf of the rare disease community, or accelerating the diagnostic process. What you may not know is that we accomplish all of this with just 4 full-time and 6 part-time employees. Though our commitment is international in scope, the IPPF operates as a small nonprofit organization. With your generous support we are able to keep hope alive and continue supporting you and our community in the way you have come to expect. Also, for those of you that do online shopping through Amazon, you have the unique opportunity to give back all while shopping. Visit [smile.amazon.com](https://smile.amazon.com) and search for the International Pemphigus and Pemphigoid Foundation as your charity. Amazon will donate 0.5% of all purchases made through amazon smile to the IPPF.

If you have not registered for the IPPF's natural history study we encourage you to do so. The IPPF Natural History study is a 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](http://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 Strong, at [becky@pemphigus.org](mailto:becky@pemphigus.org), or call (916) 922-1298 x:105, and we would be more than happy to help. This call recording will be sent out with a survey following this call. Thank you everyone, good-bye.