March 16, 2021 Back To Basics: Treatment #4- Rituximab Patient Education Webinar

Becky: Welcome everyone to the Back to Basics: Treatments #4 webinar series to discuss Rituximab.This call is now being recorded. I'd like to thank you for being on the call this evening with us and to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, argenx and Cabaletta Bio for making today's call possible. Information is a key factor in treating and living with a rare disease or any condition. However, everybody's situation is unique. The IPPF reminds you that any information found on the internet or during these presentations should be discussed with your own doctor or health care team to determine if it applies to your specific situation. Before we begin, I'd like to take a quick poll, to see how many of you on the call have had Rituximab for treatment of your pemphigus or pemphigoid. If you could just take a moment and answer that, and while you're answering the poll, let me introduce you to our speaker for this webinar. Dr. Victoria Werth received her MD from Johns Hopkins School of Medicine, followed by residency and a postdoctoral research fellowship in Immunodermatology at New York University. Dr. Werth moved to Penn in 1989 as Chief of Dermatology at the Philadelphia VA Hospital. At Penn she directs the Autoimmune Skin Disease study unit, and performs clinical and translational research studies in autoimmune skin disease funded by NIH, autoimmune foundations, and industry. She has performed a number of industry trials for pemphigus, including the Roche/Genentech rituximab study. She has a basic research lab at the VA devoted to autoimmune skin disease and photobiology, funded by NIH and the VA. Dr. Werth's clinical practice specializes in the diagnosis and treatment of patients with autoimmune skin diseases, including autoimmune blistering disease, lupus erythematosus, and dermatomyositis. Dr. Werth has received numerous honors for her work, including the lifetime achievement award from the Medical Dermatology Society, the Rose Hirschler Award from the Women's Dermatologic Society, and the American Skin Associations Research Achievement Award in Autoimmune & Inflammatory Skin Disorders, the Lifetime Career Educator Award from the Dermatology Foundation, and the Naomi Kanof Clinical Investigator Award from the Society of Investigative Dermatology. Now quickly, I'd just like to show our poll results. And it looks like about 65% of our listeners today have had Rituximab as a treatment. So we hope that this will be very informational for all of you. Now, before getting into Dr. Werth's presentation, I would like to go over a few housekeeping slides... (Goes over Housekeeping Rules). Now, it is my pleasure to introduce Dr. Werth to answer your questions about Rituximab as a treatment option for pemphigus and pemphigoid.

Dr. Werth: Thank you very much for that kind introduction, and it's great to be here. So, we're going to be talking about Rituximab and this is an amazing time to be able to discuss this. I do want to mention I have some conflicts, and I think these are wonderful to have conflicts in a time when we need to have more studies and more therapies for pemphigus and I really advocated for that for many years. I work closely with the IPPF. We've worked hard to develop the outcome measures that can be used for some of these trials that are ongoing in both pemphigus and pemphigoid. I've never seen at a time that's more dynamic and more beneficial for patients with these diseases, as what I anticipate will happen now and in the next few years.

So we know that in the past, pemphigus had a high mortality rate before steroids and steroids made a huge difference. Although there were delays in diagnosis and there still are delays and diagnosing pemphigus, I think there is getting to be more awareness and I do think that that's important. In the past, there were very few controlled trials, and I'm going to show you some examples where that's finally changing. I think the patient community and the physicians who take care of these patients are coming together to try to advance therapies. The case series in the past are still guiding some of our diseases, and I'll talk a little bit about that and we're getting more evidence, but we need more for making decisions.

Dr. Werth: Rituximab began as several case reports and a small case series of efficacy. I have referenced some very early studies here. You can see from a study in 2006 and one in 2007 there was thought of the disease improving with a combination of Anti-CD20 and IVIG. And then another where 18 out of 21 patients, 86% of patients had responded to one course of four weekly infusions of Rituximab and that was published in the New England Journal of Medicine, that was 15 years ago. And as many of you probably know, it took many years after that to finally get FDA approval. But this is really the beginning of what revolutionized therapies. So Anti-CD20 works by depleting B cells that have CD20 on their surface. They also downregulate desmoglein-specific CD4+ T cells that are also part of the immune reaction in causing pemphigus. So to better understand this, you can see that there are stem cells and Pro-B cells that don't have CD20, then there's all these different cells from Pre-B cells, immature B cells to transitional mature B cells, and memory B cells and all of these have CD20. And what that means is if you take a drug, like Rituximab which binds to CD20 and removes these cells, all of these cells kind of go away in the setting of getting Rituximab but what doesn't go away are the plasma cells, which make a lot of our long standing antibodies against infection or when we get vaccinated. You can see that there's also the ability to make new B cells so that after these cells are depleted, there's still new cells that can be formed and then they're ongoing plasma cells. So although we are depleting these cells, there are still many aspects of the B cell immunology armamentarium that are still there.

Dr. Werth: So I was asked to talk a little bit about how this is different from other therapies that we use in pemphigus and pemphigoid as well. We know that prednisone has anti-inflammatory and immunosuppressive effects and that the effects are more prevalent on T cells than B cells. What that means is to have effects on B cells, you have to give very high doses of these steroids often. And those, as we now have many side effects and that's one of the fundamental problems, I think, in trying to rely mostly on steroids. Then we often have used immunosuppressive drugs, such as Mycophenolate Mofetil and Azathioprine for steroid-sparing effects. What they do is inhibit B cells and T cells but as solitary agents, usually they're not sufficient. So we start with steroids and then we use these immunosuppressants as a way to be able to get off at the steroids.

Dr. Werth: Now another approach is IVIg. IVIg blocks the FcRn receptor and what FcRn does is, normally it basically protects IgG and IgG immune complexes from degradation and then prolongs them in the serum and so they don't go away. But if you can block FcRn, then what happens is that you get rid of these immune complexes that are circulating. And they don't get spewed back into the circulation, to cause problems with blistering diseases where these antibodies can then go on and bind in the skin. There are a number of approaches being tried, either again, with IVIg or Anti-FcRn, that are yet again another way of trying to have effect on both pemphigus and pemphigoid. Now, what I will say is as opposed to Rtixuan where you're knocking out the cells making the antibodies, this approach is probably better at removing the antibodies that are already there but you can make new antibodies. So, that has led people to think about for instance, using Rituximab in combination with IVIg as a way to turn off new antibody production but then using something like IVIg to be able to clear the antibodies that are already circulating. These are again trying to contrast some of the mechanisms.

Dr. Werth: This is from the 2007 study, that Pascal Joly did showing that Rtiximab was a new treatment option for pemphigus. What you can see here, this is looking at the desmoglein 1 antibody, which we see in pemphigus vulgaris but we also see it especially in pemphigus foliaceus. You can see very quickly after getting Rituximab, this is only 60 days, that these antibody levels are coming down pretty precipitously and then kind of leveling off. This was getting at the mechanism of how this is working. So if you're knocking out those B cells that are making the more short-lived B cells that are making these antibodies, then you would expect that rather rapidly the antibodies are going to be metabolized and cleared and that's what this is showing.

Dr. Werth: So Dr. Joly went on ,again looking at the time. It's a decade later and he published this article that he was the lead author on in The Lancet. This is what we call the Ritux 3 trial. This was a study done completely in France of 91 patients and they received 1 to 1, so randomized like any trial, there are people who get the drug and there are people who don't get the drug. So in this trial, everybody got steroids, oral steroids, although the doses depended on the severity level of the pemphigus and then they were tapered over a period of time. Basically half the patients, the ones that Rituximab, got one 1,000 milligrams on day zero, and then again on day 14. Then they got 500 milligrams at months 12 and 18. This was combined with a shorter term prednisone regimen. As you can see it was a little bit lower dose and was tapered more quickly than in the control arm that wasn't given Rituximab. Then the patients were followed up for three years. So at month 24, it was seen that 89%, of the 46 patients, who got Rituximab plus short-term prednisone, were in complete remission and off therapy versus the 34% of the 44 who were assigned to prednisone alone. And as you remember, received higher doses of prednisone for longer periods of time. This shows that in fact, the Rituximab was superior in accomplishing that endpoint of complete remission off therapy.

Dr. Werth: This is just showing you the cumulative probability of getting the first episode of complete response and what that means is being able to be off of or very low doses of steroids.

As you can see, the probability of complete response happened much more quickly and earlier in the group that got Rituximab versus those who got steroids, which is much further out. And many fewer people actually got a complete response. So, this is helpful, I think, in understanding the advance that has been made here.

Dr. Werth: Then the amount of disease free survival. So remember, the patient's got two courses of Rituximab or two treatments of Rituxan, two weeks apart, and then got a lower dose at 12 months than 18 months. What this is showing is how people did, in terms of not having their disease relapse, and clearly there were many more relapses in the group who got just the steroids relative to those who got Rituxan.

Dr. Werth: Then if you looked at the prednisone dose, again, the same ideas that people had much less prednisone when they were treated with Rituximab here as opposed to getting the steroids without the Rituximab. So this can translate into quite a bit difference in the amount of steroids and the length of time that one is on higher doses of steroids.

Dr. Werith: Then the number of people that were on minimal therapy or off therapy is also very different. So the Rituximab and prednisone group here, you can appreciate that the number of patients who achieved minimal therapy or no therapy was a much higher percentage and number of patients, and happened again much earlier than what was seen in the group that just got steroids. So these are all reasons why I think the community has been very excited about having Rituximab as a possible option.

Dr. Werth: This is showing for this particular trial, the one that occurred and published in the Lancet, that the antibody levels also came down in both groups, but came down more and more rapidly in the patients who got Rituximab. This is looking at both desmoglein 1 here, where there's a dramatic effect. And then desmoglein 3 with again, very rapid decreases in both arms. But again, one can see that what translates into is more complete remission and more time on lower doses of steroids.

Dr. Werth: So Rituximab has in fact changed the treatment of pemphigus and it can be given either and 375 milligrams per meter square, it's a way of calculating based on weight and body surface area, every week for 4 weeks. Or 1,000 milligrams, every other week for two weeks. Now, relapses do happen and it's not infrequent. And they average about 18 months out for people who've gone, for instance, the 2 or the 4 treatments early on but there are some relapses that can happen earlier and there's some people who take more time to clear and require more treatment. So, one does, at times, need to be retreated at 6 months if there's still activity or consider a treatment between 6 and 12 months to prevent relapse. But we really need more data to know how to optimally manage the retreatment with Rituximab.

Dr. Werth: So Rituximab has rapidly become first line therapy. It's part of guidelines now, international guidelines. It doesn't say you have to get Rituximab first but it says it's among the first line therapies and I think as we get more data, that may shift even more. But this has been approved by the FDA for pemphigus in mid 2018. Then more recently, there was a phase 3 study that was sponsored by Genentech, and this was called the PEMPHIX Trial. It was reported at a European dermatology meeting in 2019 and is actually now being accepted for important publication that we will certainly be hearing more about later. But this was comparing steroids with Rituximab some versus steroids with Mycophenolate. It was shown in this study that Rituximab was superior to MMF, which is the other abbreviation for Mycophenolate, in achieving sustained, complete remission, tapering steroids, preventing flares, and also it had good effects on quality of life. So the way this study was done was to treat either with Rituximab or placebo, and then again at 6 months and then an endpoint at 52 weeks. This is a pretty involved study and the people had to be on a lot of prednisone and still have quite a bit of activity. So these were more severe patients who went into the study.

Dr. Werth: And the primary outcome was looking at the proportion of patients who could get sustained, complete response without experiencing treatment failure. This was defined as a score, the PDAI score that the pemphigus community worked together to develop, and the score had to be zero, and the patient on zero milligrams per day of prednisone or the equivalent for at least 16 consecutive weeks during the 52 week treatment period for that to be accomplished to be a sustained, complete response. Then secondary points that were looked at were the amount of steroids, the number of flares, time to sustain complete response, time to disease flare, and the change in health related quality of life. These are all aspects of clinical trials that are really important to capture, to show that medications are actually working, and working in an important way. Then, of course, capture serious adverse events and any problems so that we understand better about that and using the medication.

Dr. Werth: So, just to give you an idea, it's pretty hard to do these kinds of trials because pemphigus is not that common. So it involved an international study with 49 academic sites. Again, it gives you an idea of the complexity of being able to do the kinds of studies that we're showing you, here and also to select for patients who have enough severity of their disease that they can actually be able to capture the change that you need to be able to demonstrate. There were 135 patients that were randomized, and this shows you each arm, Rituximab and MMF and it tells you how many patients withdrew from the study and why they withdrew, versus the one patient who withdrew from the Rituximab arm. Then these patients were followed out, again, for the 52 weeks. For every study you have to look at who went into this study, what was the age of the patient. It was around 50 here, and around 45 here in the MMF. Then also looking at what race and weight, and all these things that are captured very carefully in such studies.

Dr. Werth: So the primary endpoint, at 52 weeks, was sustained, complete remission off prednisone for a greater than 16 weeks. What this is showing you is that Rituximab was superior to MMF, in combination with a tapering course of oral prednisone. At week 52 a significantly higher proportion of patients in the Rituximab group achieved a sustained, complete remission off prednisone then the MMF group. Here is 40.3% versus 9.5% in the MMF group. So, that's a very large difference, it's a very large, statistically significant difference. Really, I think it gets to the point of saying that if a person is treated with Rituximab there's a rationale for thinking that the outcomes might be even better than what has been in previous standard of care with steroids and immunosuppressants. Having said that, there are many reasons why people may not go on to Rituximab and why this kind of treatment with MMF and steroids might be used. So, again, you can't take this study and then extrapolate to say this is how I need to be treated but you can learn a lot from these kinds of studies and then put them in the context of the situation for an individual person or for a particular point in time.

Dr. Werth: So this is looking at steroid exposure and again, showing that the median daily oral steroids dose, you can see in the group that got Rituxan, is really coming way down to almost nothing relative to needing much higher doses in the patients who did not get Rituxan. And since we know steroids have so many side effects, it’s really beneficial to be able to have a therapy that allows people to get off of prednisone. Then this is looking at disease flare, and clearly one can see that the total number of disease flares is quite different between the Rituxan group and the MMF group. And so again, an indication of how successful this particular type of therapy has been.

Dr. Werth: Then looking at a sustained, complete response off the therapy, this is looking again at the Rituximab group and looking at patients with sustained complete response. And it turns out that the likelihood of achieving a sustained complete response on Rituximab was five times greater than on an MMF. So you can see the difference here versus here. This is obviously very important as well to capture, as well as the time to first flare. You can see here, that the number of patients without a disease flare is falling pretty consistently in the group that did not get Rituxan whereas those with Rtixuan, again remember getting retreated at 12 and 18 months. The numbers who flared were obviously much smaller and further out.

Dr. Werth: Then looking at quality of life, which is very important because I think it's really an endpoint that is important for trials. If people don't feel better, that's a problem in therapy and then we should really re-examining things. But what this is showing is that the quality of life, this is looking at the change in the DLQI and clearly, there was much more improvement in the Rituximab arm relative to the MMF arm. And it was, again, statistically, significantly different.

Dr. Werth: Then, in terms of safety, it's important to know that there are AE’s in any trial, and they're often many AE's, that means adverse events. They're captured very, very carefully and in the context of a trial to learn as much as possible about the therapy and about the

comparator arm. So what this is showing you is that looking at the side effects that were found, and more than, or equal to 10% of the Rituxan treated patients, there were problems with infusion related reactions, headaches, lymphopenia, one of the cell types that can be a little bit lower, and upper respiratory infections. If you look at the MMF patients the side effects were diarrhea and nasopharyngitis. It's important to recognize that, although their outcomes are better with the Ritxuan, there certainly are some side effects that come with that.

Dr. Werth: So in conclusion for that trial, in patients with moderate to severe pemphigus the efficacy for Rituximab is superior to MMF. We've really gone through this, but the primary endpoints of sustained, complete remission off prednisone for greater than or equal to 16 weeks was statistically significant in favor of Rituximab and all their ranked secondary efficacy endpoints were statistically significant in favor of Rituximab. The safety profile was manageable with Rituximab with an acceptable tolerability, consistent with the known Rituximab safety profile and the approved autoimmune indications and Rituximab has a superior overall benefit risk ratio or profile, compared to MMF in patients with moderate to severe pemphigus. Now remember, these are patients who have pretty significant disease and were really refractory to steroids.

Dr. Werith: Now, what about other diseases? And it's much harder. I'm showing you several elegant trials in pemphigus and we are still waiting for similar elegant trials of Rituximab on the subepidermal bullous diseases and most of the evidence is really coming from more case series. But there is evidence that Rituximab works for MMP, bullous pemphigoid and Epidermolysis bullosa acquisita. The amount of control depends on what case series you look at and how quickly it happens. There is a fairly high relapse rate, but it works, for many patients. In bullous pemphigoid there were quite a number of people who got partial or complete responses, again, high relapse rate and potentially a little longer response than we see in pemphigus. But clearly, this is not the only autoimmune bullous disease to consider and we really need to also think of these other sub epidermal diseases in the pemphigoid group as well.

Dr. Werth: So I mentioned before that there are two typical doses that have been used. And the FDA approved the one that was done in the French study, which is 1,000 milligrams every other week for two treatments. Then the other one is more the lymphoma dosing and their has been retrospective data suggesting that potentially there's less chance of remission and maybe quicker remission in the people who get the weekly for four weeks. But there's a little bit of controversy about whether there's actually a difference, and there has never been a head to head comparison of the two treatment arms. So at this point, it's really hard to say that you have to get one or the other and it really often is dictated by the insurance companies.

Dr. Werth: So, how long to see a response? Well, often disease control, meaning you're not making new lesions and the old ones are starting to heal, can be as quickly as a month on

average, and 76% have a disease remission in six months. The main duration of remission is 15 months, 40% have a relapse, and early treatment may be beneficial. So these are all things to keep in mind in terms of pemphigus and I don't think we have even this much data to be able to draw on for pemphigoid. So when do you get retreatment? and with theirs? Again, because this has really not been examined very systematically. We usually think people have early relapses, often are those who have worse disease. So potentially people who start out with really bad disease should get retreated sort of automatically even if they're doing better but again that's not something that we have total evidence for, it's a concept of looking at the severity and who gets their disease back. And given that the antibody levels often correlate with the severity of disease, it would also follow that the persistence of higher levels of autoantibodies at three months may suggest that this is a situation where there's still cells around that are making these antibodies and therefore it may be reasonable to think about retreatment and also if there's ongoing disease activity. So if somebody got treatment and it's six months later and they still have disease activity, that may be a reason to think about retreatment as well. I think these are all suggestions, since we don't have studies to totally say, if this is happening, this is what you have to do.

Dr. Werth: So, how is Rituximab given? It's given, usually, at a doctors office or an infusion suite. The office can be a separate room that you'll be in for several hours. In some hospitals, they have infusion suites and that's where you go to have the infusion. The idea is that people who are getting it need to be monitored to make sure you're not having a reaction to the medication and that you're tolerating it, to make sure that the infusion rate doesn't need to be adjusted. So, giving it at home is not really something that's routinely done. It's really done, a more monitored setting. In terms of who does the infusion, they're typically done, I would say, in an outpatient setting with hematology or oncology that's giving a lot of the Rituximab for lymphoma patients or with rheumatology or at an infusion suite. But clearly, Dermatologists, in the context of these studies, also gave Rituximab and it is something that can be done by dermatologists, but in some ways it's more set up to routinely do it often through these other mechanisms. It really depends on where you live as to where to get it done, and also where are the infusion areas you can go to. Often, you'll need to work with the referring physician and with the primary to locate the best arrangement for getting the Rituximab.

Dr. Werth: Premedications are very standard and involve Tylenol, often steroids through IV, and then also antihistamines. This is just to cut down on any infusion reactions that could be seen where you might get a fever or might get rash and itching. So, these are really a standard part of premedications. Then, how long is the immunosuppression after Rituxan? These are all really good questions that I was given. Essentially, the B cells are depleted almost immediately but as I mentioned to you, the plasma cells don't have CD20 and they still make a lot of our antibodies that are made by the longer lived cells that don't have CD20. We do develop new B cells typically starting around six months after depletion but then there is a reset and then you do start to make more B cells, although it may not be back up to normal for longer than six months. It's best to get the vaccine for COVID before the next dose of Rituximab and six months or more since the last dose in order to have the best response that's possible to the

vaccine. So, that has led to a lot of us having to consider delaying redosing of Rituximab or even dosing for the first time prior to getting the vaccine. Now that it's available, we want people to get immunized. So that's something that you may have questions about, but this is I think to a certain extent, may change the flow of when people are getting Rituximab.

Dr. Werth: So can Rituximab be combined with other treatments for pemphigus and pemphigoid? If the disease requires this, often will use prednisone with Rituximab because the prednisone works quickly and the Rituximab takes time because you're again not making new antibodies but the antibodies that are causing problems are still there. And if needed you can give IVIg, two weeks after the last Rituxan dose as I mentioned that's a way to clear the existing antibodies. There are people who have severe enough disease that it would be helpful to clear those antibodies with IVIg, but certainly not every single person who gets Rituxan gets IVIg. There is a risk of clearing auto antibodies with IVIg, as I told you, the IVIg increases clearance of antibodies in general, including normal immunoglobulins we have. If one gives something like IVIg too soon, you have a risk of clearing the Rituximab before it's really finished working. And so we try to stagger it a little bit, to remove the IVIg dose out a little ways away, a few weeks out from when they got the Rituximab.

Dr. Werth: So there is blood work needed before Rituximab and that's just to make sure that there hasn't been a previous exposure to Hepatitis or to Quantiferon or TB or HIV that could then lead to reactivation in the setting of getting Rituximab. It's really helpful to find this out, because we have so many good treatments for these conditions now. So it doesn't mean, for instance, if somebody is a carrier for Hepatitis B, that they can't get treated with Rituximab, it just means they have to get treatment for their Hepatitis B in order to get Rituximab. And similarly, if they don't get treatment because there's no Hepatitis present in the blood, you can still monitor that during therapy to make sure that there's no evidence of reactivation. So knowing this is really helpful. If there's Hepatitis B core antibodies, and again we talked about needing treatment or to make sure it doesn't get reactivated. Then the other thing is we often will have a console but with the physician or the infusion suite, that's going to do the infusion. There needs to be a prior approval by insurance. So this is not something you order one day and you get the same day. There's a process involved with scheduling with the insurance company to make sure they will cover it and then also getting the infusion suite and the scheduling. It does take a little bit of planning for some patients to get to this point.

Dr. Werth: Now I already alluded from the other studies that I mentioned about the side effects of Rituximab and infusion reactions can happen and the premedications do help. If they do happen then the Rituximab may be stopped for a while or then we infuse at a slower rate. People sometimes get chills, they may have body aches, fatigue, and maybe an increased risk of infections. Again, I told you about the reactivation of viruses and that's certainly a side effect that can happen. Then there's some other effects that are really rare such as early or late onset of loss of neutrophils or decrease in neutrophils. And also, progressive multifocal leukoencephalopathy due to JC virus, which is again, extremely rare and we really haven't

seen examples of this but it's been described in other non-autoimmune bullous disease conditions.

Dr. Werth: So in summary, Rituximab is effective in many cases. It may require more than one course of treatment. Relapse is frequent, requiring retreatment and the exact frequency of retreatment to recommend is still unclear. Adding IVIg in refactoring patients can help and may have a broader effect with regulating, as we talked about various antibody receptors. It has a number of different ways that it can work, in addition to clearing the antibodies quicker. It is an adjunct that can be added as necessary. Again, the idea that there may be new treatments coming along and they certainly ongoing trials to see if antibodies against the FcRn receptor are going to be helpful in and actually treating pemphigus. A lot of these approaches with Rituxan or with FcRn, I think eventually the goal might be to be able to get by and not necessarily give everybody steroids. In Europe, there's been something called immunoabsorption, and there have been cases where people get Rituximab and then instead of giving something like IVIg, there's a column where they can remove antibodies on a column by basically filtering the blood. This is another way of turning off new antibodies, but then also removing the antibodies that are there. It also enhances all the different work that's going on to try to improve the way that people can be treated. So I think with that, that ends my talk and I'm really happy now to entertain any questions.

Becky: Great Dr. Werth, that was amazing. And a lot of information there that I know that our community is glad to have. We did have one question come in when you were talking about patients having flares and relapses, how a flare defined?

Dr. Werth: Basically there are many different ways to think about flaring. It can be just a need to re-institute treatment, to have to increase the amount of prednisone, it may have to do with the increase in the score. In that particular trial, it often would be that you had to increase the dose of prednisone in order to get the disease back under control.

Becky: Great. Thank you. We've had a lot of questions come in during the webinar about the COVID vaccine. When is the right time to get the vaccine, and it does the brand matter? Those are the big questions about the timing, and if there is a particular or a preferred brand.

Dr. Werth: So in terms of the brand, I do think that there's some advantage, there are people that have been waiting to get, maybe they have active pemphigus and maybe they're having trouble eating, there on steroids, and they're holding off on getting Rituxan because they want to get the vaccine. It would be really great for those people to get a vaccine that you only need to get once like the J&J vaccine so that you can, as soon as possible, move on and get treated with Rituxan. We don't know exactly how far out, but probably by 2 to 3 weeks out it would be fine to think about getting treated with the Rituxan. So I think if the timing of everything else going on is such that you're waiting to get Rituxan, then I think getting something you only need

to get once instead of waiting 3 or 4 weeks to get the second dose might make some sense. Then in terms of timing, I think it's problematic because we didn't know for sure that there was going to be a vaccine. So people will continue to have their flare or to get their disease and given that we had no idea a lot of people got treated with Ritxuan over the past year appropriately. So. Those people probably need to wait a little bit longer by six months or so before getting the vaccine, in order to be able to have a chance of mounting a response. I think that has meant, though, that now that the vaccine has been available now for a few months, that's led to really delaying getting treatments with Ritxuan. But the problem is, people don't know where they're going to be able to get the vaccine so that's really building in delays that are very frustrating for people. But I think waiting probably at least six months is the way to go from the last Rituxan dose.

Becky: Great. And is measuring the immune response to the vaccine recommended if you've had Rituximab?

Dr. Werth: So, I have not seen any recommendations about that. I don't think that for people getting the vaccine it's recommended to go and get the antibody levels checked but I think it's an interesting question, and I think that's something that clearly, there are places that are studying that. What happens in the setting of immunosuppression with Rituxan and how does that alter the immune response? I'm not sure that I would routinely recommend it because I'm not sure what you would do differently. I think it's an area that we need to learn a lot more about, and I think there will be much more coming out in the near future.

Becky: Great. Thank you. Then we've received quite a few questions asking if the COVID vaccine can trigger a flare in patients?

Dr. Werth: Yeah, that's a great question. As you know, there have been very rare cases of pemphigus that have been triggered by various vaccines, and so it obviously weighs on some people's minds. I don't think we have any evidence that that's happening. We just don't have any data, it's going to be something that we'll learn more about, I think, as we start to vaccinate people with autoimmune diseases and we systematically collect data. But, so far, I haven't seen any of my own patients personally, or any data that would suggest that that's happening, and we are recommending to get the vaccine. I think that getting COVID is not a good idea.

Becky: Great, thank you. Can Rituximab cause issues with balance and equilibrium?

Dr. Werth: There are people who seem to have symptoms around the time of the infusion of somehow related to maybe an infusion reaction or maybe their blood pressure drops. I would think, in general, that has not been something that we have seen. It's not a common side effect.

Becky: Great. And what are the long term side effects of Rituximab on the heart, kidney, and liver? We've had a few patients right in saying that their liver enzymes went up on other medications, and they're wondering about the effects for Rituximab.

Dr. Werth: It turns out Rituximab is a very focused kind of drug and in general, it has effects in terms of the blood lines to some sense as I mentioned about how the lymphocytes or the leukocytes can be lowered. But in general, it does not seem to have effects on the organs in the same way that, for instance, we might anticipate with other systemic meditations. We have to check the liver enzymes in people who are on Methotrexate or Mycophenolate. We have to worry not so much about kidneys, usually with those medications, but if somebody has problems with the kidneys, we certainly want to make sure about that. So I'm not so worried or we don't know so much that Rituximab has big effects on either the heart, kidney, or liver.

Becky: Great. Thank you. Max asked, what is the efficacy of Rituximab for treatment of pemphigoid which is no longer responding to Mycophenolate after 1 to 2 years?

Dr. Werth: I think the issue there is, Mycophenolate is a solitary agent, it’s good at maintaining remission, but usually not getting to remission. I’ll start by saying that, if the pemphigoid is getting more active, often that requires retreatment with steroids along with MMF, because again MMF helps get off the steroids and maybe stay off them longer. Rituximab, I think for people that don't want to go back through prednisone and immunosuppressants is a very realistic option. It's not that the person's refractory, it's just a relapsing and that happens with steroids or immunosuppressive and it happens with Rituxan. When there's a relapse then you have to decide, what approach makes the most sense for you? And Rituxan will work for many patients. It won't work right away, and so you may end up back on steroids for some period of time while you're waiting for the Rituxan to work.

Becky: Great. Thank you. Our next question asks, how high is the risk for a veterinarian to get to a zoonotic disease if she is treated with Rituximab?

Dr. Werth: There certainly are zoonotic exposures for vets. With the immune system lower, I'm certain that there are some issues with that. But that would be true with steroids, that would true with immunosuppressives. I don't know how frequently veterinarians have those problems in the first place, but it probably does increase the possibility of that happening.

Becky: Great. Another question that came in, is hair loss a common side effect of Rituximab?

Dr. Werth: Usually, not a big problem, but there's so many things typically happening around that time. If you've been on steroids, those can cause alterations that lead to some hair loss. Some of the immunosuppressive, if one was on them, could cause hair loss. Just the stress of having an autoimmune blistering disease, in itself can cause you to be really ill. What that means is that the stress of even going through an infusion or having a reaction might lead to the hair cycling more at the same time and so they shed at the same time. But then the hair is going to grow back again. So, it can be part of the sort of the stress response, is how I would put it.

Becky: Great, thank you. We've also received quite a few questions, as soon as somebody gets their infusion of Rituxan they tend to either breakout in more lesions, or the itching associated with the pemphigoid is getting worse. Could that be the stress response as well? And your body's reacting to what's going on and getting the infusion or is that due to something else?

Dr. Werth: We know that stress brings individual lesions. It's not a good thing. So I think to the extent whatever's going on around the time of Ritxuan, I don't typically think of the disease getting worse. But, there are other effects of Rituxan on other cell types. For instance, the T regulatory cells and B regulatory cells, there are other parts of the immune system that can be affected and they may be transiently affected in a way that an individual person could lead to exacerbation as well. The immune system is pretty complicated and I think that it could be one of those immunologic effects. But I think when that happens it's pretty transient.

Becky: Great. Thank you. We had another question come in, and you had mentioned about measuring Desmoglein 1 and 3 levels. How often should that monitoring be done after a diagnosis of pemphigus and what are the stats you're looking for, and what are the stats that you're hoping for?

Dr. Werth: We know depending on the ELISA and the lab, what's in the positive range, which might be in some labs, like let's just say above 20, then in severe disease might be 100 or higher. If somebody's up in the higher range, then typically they're going to have worse disease. And it may take time given the half-life of clearing these antibodies to get those levels back down. So there's not an absolute level that I think we're looking for. We're just more or less looking for the drop in the antibody levels. I don't think there's an answer as to how often to check, because we really don't have good guidelines as to when to retreat. So, it may be reasonable to recheck at let's say three months just make sure that the antibodies are coming down. And then maybe at six months because if they're not continuing to come down, maybe you want to retreat earlier. But I don't think we have enough data right now to really provide guidance as to how often to get those ELISA tests.

Becky: Great, thank you. Andy is saying that his adrenal glands have gone to sleep after being on prednisone long term. Does that need to be resolved before starting Rituximab?

Dr. Werth: So that's a great question. It turns out, if you're on prednisone for three weeks or longer and many people with pemphigus have been on much higher doses for very long periods of time, the adrenal suppression can last for up to a year. Essentially what you just have to do is be on a low dose of steroids and recheck to see if the adrenal gland is gradually waking up but it can take awhile. There's no reason to wait to get treated. There's really no connection with the adrenal gland and getting Rituximab. It's just important to know that if the adrenal gland is suppressed and if there is stress, and this is true about steroids, that if you need surgery, or if you get sick or something's happening, you may need additional doses of steroids to deal with the stress. But there's no reason not to get Rituxan.

Becky: Great, thank you. We've also received a bunch of questions about biosimilars, and Sally asks, is it possible for a new and improved version of Rituximab to be more focused versus impacting the good B cells too?

Dr. Werth: So right now CD20 is on, as I showed you, lots of these cells and some of them are good and some are bad. The biosimilars are essentially identical in terms of binding to either CD19 or CD20, which are on the B cells, and they are going to deplete the same B cells. That approach is probably not going to change much. I mean, the only way to deplete the bad ones would be to have a more specific targeted therapy, which would required more of an engineered type of approach different from an antibody that's going to bind to many of the B cells. The biosimilars are going to be exactly the same as Rituximab.

Becky: Great, thank you. Going back to getting infusions, we have another question, is there any nutritional advice to optimizing the benefits of Rituxan like hydration, or micro biome? Or any foods that you should eat or avoid that could interfere with the treatment?

Dr. Werth: In general, no. My one comment I will make is what to avoid. I think right now, if you go into a CVS or Rite Aid, or any store, you're bombarded by all these herbal preparations and some of them stimulate the immune system. Often, when people have immune problems, they think that they need to take something to help their immune system. I would say, be very, very careful about herbal medications that you're taking and that's irrespective of Rituxan or any other treatments. But if you have an autoimmune disease, be really careful. So other than that, I'm not aware of any particular food or any kind of diet that's going to make a difference in how you respond to the drug.

Becky: Great, thank you. Anna is asking, is there a maximum amount of Rituxan that a person can have?

Dr. Werth: We don't know the optimal dosing, I'll start with that. They just kind of were concocted by various clinical trials for hematologic problems or rheumatoid arthritis. And, and so we don't know the maximum dose that people can get that way and then individual treatment. But on the other hand, I will tell you that for rheumatoid arthritis, when people get it, they're getting it every six months. It's not, are the antibodies not coming down, or my disease is coming back. It's more like every six months like clockwork, they're getting it for years and there's no end points to that. But I think that some of the people who get it for a very long time in that way, every six months for years, their immunoglobulin levels can be lower and they can be more susceptible to infections. I think that that's the kind of thing that needs to be monitored. But there's no maximum dose per se, and I think we're way below that, in the way in which most people are treated in terms of autoimmune blistering disease.

Becky: Great, thank you so much. There was a question that summarizes that this person's desmoglein levels are low, but they're still having lesions. Should they be redosed with Rituximab and why would something like that happen?

Dr. Werth: Yeah, good question. Sometimes there can be other autoantibodies that are playing a role. Not every single person has desmogleins and I don't know if this person's desmogleins were ever high. There are other antibodies against other things other than desmogleins that can very rarely cause pemphigus. There's also issues about what is circulating versus what's in tissue, and so maybe there's enough in tissue to cause problems but it's not that high a circulating level. It really depends, I think, for each individual person. It may be a little bit of a different story as to why that might be the case.

Becky: Great. Thank you. Virginia is asking, can you just get Rituximab without prednisone or any other medication to go with it?

Dr. Werth: I think that is a wonderful goal. There are certainly people who have mild disease, who would opt to get Rituximab who maybe don't need to get prednisone and who might just get Rituxan. And in a similar way, there are people that we used to give very high doses of steroids too because the goal was to knock out those B cells with the steroids. And now the goal is just to keep people comfortable while the Rituxan is starting to work. Even if we have to use steroids, we may not have to use the higher doses that we used to have. But yes, there will be people, for instance, again, with mild disease or people who are relapsing, who know that they need to get retreated, who may never have to go back on prednisone and just get retreated.

Becky: Great, thank you. We've had a few questions about the cost of Rituximab and also if Medicare or Medicaid covers Rituximab infusions?

Dr. Werth: So, it's FDA approved and Medicare and Medicaid do covered as far as I know. There are sometimes co-pays for insurances and they may not cover that, and that is an issue for some people. Most of the time, by the time it's FDA approved and there's an indication, and there may need to be enough of a severity level, the private insurance will cover it.

Becky: Great! Thank you so much. Another question came in from Trevor. In pemphigus foliaceus, is Rituximab the treatment of choice if continuing problems are happening?

Dr. Werth: It's hard to answer an individual case. There's a lot of variability about how severe pemphigus foliaceus is. I'd have to know so much more about the disease and the extent, and what's been done, but it has been used in pemphigus foliaceus successfully. In fact, pemphigus foliaceus wasn't studied necessarily for the trials that we just talked about, because it's less prevalent in the United States, but it works for pemphigus foliaceus and can be used.

Becky: Great, thank you. Robert is asking, besides for COVID, are respiratory infections an extra concern when you're getting Rituximab?

Dr. Werth: So people are at increased risk of getting infections. There are some people who are on high doses of immunosuppressants, who have other medical conditions, and also getting Rituximab who might need to go and some kind of even suppression therapy to prevent them from getting a lung infection. That's something that is a concern but the same thing is true for steroids and immunosuppressants, there's an increased risk of getting viral infections and lung infections there as well.

Becky: Great, thank you. Dr. Werth, I can't believe our hour is up already. That was really quick and a lot, a lot of great information. So, thank you for joining us and for sharing all that information. And I'd like to give a huge thank you for everybody who joined us on the call. I know that there's a lot more questions and I apologize, we can't get to them all. But, please, if you have any questions, we can try and get you the answers that you're looking for afterwards, so please email me. And I'd like to give a huge thank you to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, argenx and Cabaletta Bio for making today's call possible. Before we go, I just have a few announcements. Our next and final webinar in the treatment series will be next Tuesday, March 23rd to discuss anti-inflammatories such as the Dapsones and the Tetracyclines. This is going to be with Dr. David Fivenson, Board Certified Dermatologist and Immunodermatologist and member of the IPPF Medical Advisory Council. Registration will open tomorrow. March is Autoimmune Awareness Month. We have paired up The American Autoimmune Related Disease Association (AARDA) to spread awareness about

autoimmune diseases such as pemphigus and pemphigoid. Keep an eye out for emails about ways you can help us spread awareness this month.

Do you have bullous pemphigoid? You are invited to participate in an interview as part of a research study to better understand the challenges of diagnosis, treatment, and everyday life of living with bullous pemphigoid. Contact Magnolia Innovation at ilymanscott@magnoliainnovation.com or call 914-414-6767 for more information.

The IPPF has been looking towards the future and how we can continue to help you and our community. We need your help to grow our community of Healing Heroes. Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small, even a $5 or $10 monthly donation goes a long way and continues to allow us to provide for the greater good of our community.

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. 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 contact one of the IPPF's Peer Health Coaches on our website by visiting: www.pemphigus.org/peer-health-coaches/ or you can call me, Becky at (916) 922-1298 x 105, and we would be more than happy to help.This call recording will be sent out with the survey following this call. Thank you, everyone, good night.