

June 2018 Patient Education Call- Transcription

Dr. Victoria Werth: Hello?

Becky: Hello, Dr. Werth are you there?

Dr. Victoria Werth: I am, it's four o'clock.

Becky: It is. It is four o'clock and here we are going to start the recording, 1 o'clock Pacific time. So welcome everyone! This call is now being recorded. I would like to thank you for being on the call today. Our speaker is Dr. Victoria Werth, Dermatologist and Professor at the University of Pennsylvania. Thank you for joining us today!

Dr. Victoria Werth: Absolutely.

Becky: The call today will focus on Rituximab as a treatment for pemphigus and pemphigoid patients and Dr. Werth will be answering questions from the community. Dr. Victoria Werth is a Professor of Dermatology and Medicine at the University of Pennsylvania. She has been a member of the Medical Advisory Board for the IPPF for many years. She is funded by the NIH to perform Patient Oriented Research in autoimmune skin diseases. After an NIH meeting in 2005, she led international efforts related to definitions and standardized disease severity measure for both pemphigus and pemphigoid. She was funded by the IPPF to perform initial validation studies for the pemphigus disease area index (PDAI), a disease severity measure that is currently being used in a number of international trials. She was a co-organizer of the most recent NIH meeting related to autoimmune blistering diseases, which culminated with a paper published in the Journal of Investigative Dermatology. She performed the first multicenter placebo-controlled trial in pemphigus vulgaris, and has helped in design and completion of several early phase trials, as well as an NIH funded trial of infliximab, which was recently completed under the leadership of Dr. Russell Hall. She has organized and participated in a number of yearly patient conferences sponsored by the IPPF. She has a practice at the University of Pennsylvania that is devoted to patients with autoimmune skin disease.

Becky: Now it is my pleasure to introduce Dr. Werth to discuss a little bit about Rituximab as a treatment option and to answer your questions. Dr. Werth are you ready for me to pass over the control?

Dr. Victoria Werth: Absolutely, I am ready to go. Alright, hopefully you start to see my screen pretty soon. See it now?

Becky: I can see your screen.

Dr. Victoria Werth: (*New Slide*) Alright, so I am going to talk briefly about autoimmune bullous disease as it relates to Rituximab and in particular, pemphigus. And it is really great to be able

to speak about this today because in the last two weeks actually a lot has changed and I hope to update you about that.

Dr. Victoria Werth: (*New Slide*) Let me start out by telling you that I have some conflicts of interest. Really this relates to the idea that we need to do some studies and trials about what would work and what didn't work for pemphigus. So I listed here a number of trials. I am going to talk about Rituximab which you can see list here, which is the last trial listed here and that is actually still an ongoing trial. (*New Slide*) And here are some more trials. I did help develop a disease severity tool for evaluating pemphigus in skin. I have been a member for many, many years of the Medical Advisory Board for the IPPF as well as a consultant for a number of different organizations that are involved with trying to get better treatments.

Dr. Victoria Werth: (*New Slide*) So we are going to talk about Rituximab as a new treatment option in PV and I say new really in parentheses, we have been using this medication for a long time off-label and I will share some of the results of that. And Rituximab is a CD20 and that is actually a receptor that is on cells, I will show you in a minute. But this antibody monoclonal antibody targets this receptor and is a treatment option for a number of autoimmune diseases as well as a other diseases where B-cells are a problem, not just autoimmune diseases. The antibody targets cells that express the CD20 receptor.

Dr. Victoria Werth: (*New Slide*) So this is just a picture of different B-cells as they develop. You can see on the left side it says, "Bone Marrow" so these are the B-cells before they get released into the bloodstream and you can see there are some stem cells, you can see there is a Lymphoid stem cell. And again if you look all the way to the left you can see that these actually don't have any CD20 receptor. And so what that means is when you get an antibody against CD20 you don't deplete B stem cells in these early B-cells. And that actually is a really good thing because that means that you can still make new cells in the future and it turns out the plasma cells, that are all the way on the right-hand side of this graphic, after the B-cells differentiate can still make antibodies. So it turns out the risk for infection is a lot lower than you might otherwise expect when you deplete the B-cells that have CD20. And those are all the cells that you see in the middle there that are usually being released into the blood and it can be found in lymph nodes. So that would be the Pre-B-cells, B-cells, and Activated B-cells that all express CD20 that they are indicated by those little orange arrows. So what happens is the antibody can bind to this CD20 and basically get rid of the B-cell that it turns out that these CD20 cells are the ones that by-and-large are making the antibodies that are causing problems in pemphigus. So by removing rather specifically these lineage of B-cells that have CD20 you can eliminate the cells that can make antibodies that cause problems with binding in the skin.

Dr. Victoria Werth: (*New Slide*) And this is just to show you that the primary mechanism of action for Rituximab, the red circle thing is B-cell and you can see that there is a receptor CD20 protein that is on the outside of the B-cell. And Rituximab is this antibody that can bind to the CD20 and in the process of doing that causes destruction of these B-cells.

Dr. Victoria Werth: (*New Slide*) So like i said Rituximab is a relatively new treatment option and it has been found over about 500 patients to be fairly safe and efficacious for severe pemphigus vulgaris. Prior to very recently there have been several small trials and case series and when you added them all together there was about 500 people who received Rituximab. Many of them had a clinical remission occurring, some within 6 weeks, I would say that for some it can take longer like 3-4 months. So the range can be on the higher end because you are depleting the B-cells but the circulating antibodies are still there and they take time to go away because the half life for the antibody is probably 3 weeks. And so if you if you have high antibodies that are in the blood it can really take a number of months for that to go away. And that is why when people get Rituximab their disease doesn't go away right away because all we are doing is eliminating the cells that make the new antibody but the old ones are still there and have to be cleared.

Dr. Victoria Werth: (*New Slide*) So a long time ago, at this point 11-12 years ago, there had been a number of studies in the New England Journal that had talked improvement with Anti-CD20. In one case it had been combined with IVIG and in another case it was just a matter of giving 21 patients a single weekly infusion of Rituximab and finding that 86 percent of people had responded to just one course. This was published in 2007 and it was really after this that people became very excited about the possibility of this medication becoming an alternative to very high doses of steroids and immunosuppressants and other approaches when people had moderate to severe disease.

Dr. Victoria Werth: (*New Slide*) In 2017 Pascal Joly who is a French dermatologist, organized a very important study that linked a number of centers together in France and they studied Rituximab in a very organized way and this study was published in the Lancet. They included 91 patients, 74 of which had pemphigus vulgaris and the rest had pemphigus foliaceus. Half of them either got either oral Prednisone alone at a dose of 1.0-1.5 milligrams per kilograms per day, then tapered rather slowly over 12-18 months. And that was at one arm of the trial and then the other half of the patients got Rituximab and here the dose was 1000 milligrams of Rituximab and day 0 and 14 and then 500 milligrams at months twelve and eighteen and that was combined with a short-term Prednisone regimen of 0.5-1.0 milligrams per kilograms per day tapered over 3-6 months. What you see is the dose of Prednisone is much less in people who got Rituximab because it was tapered much more rapidly and it was a lower dose to start with in many of the people. Then the follow up was for three years in this study. So at month 28, 89 percent of 46 patients assigned to Rituximab plus short-term Prednisone were in complete remission off therapy versus 34 percent of 44 assigned to Prednisone alone. So this gave a very significant difference for the p-value of less than 0.0001 and in general it was less than 0.05 so people thought this was important study. So this obviously is a huge difference and functionally

a difference of 55 percentage points between the patients who got Rituximab versus those who got Prednisone alone.

Dr. Victoria Werth: (*New Slide*) And this is just showing you graphically that 89 percent versus 34 percent had remission rates at 24 months. And also the disease-free survival rate was quite different between the Rituximab group where it was 75 percent versus 36.7 percent in the patients that just got Prednisone. On terms of safety there were no treatment-related deaths and there were fewer severe grade $\frac{3}{4}$ treatment-related adverse events in the Rituximab arm. This speaks again to the safety, relative safety of Rituximab relative to high doses of steroids, in that side effects were much less.

Dr. Victoria Werth: (*New Slide*) So Rituximab has changed the treatment of pemphigus and it can either be given as a weekly dose which is a little bit different or in the trial I just showed you it was 1,000 milligrams given twice, two weeks apart. And one thing to say is that relapses are quite frequent and they average about 18 months out but sometimes there can be early relapses or people may not clear completely after the first course. So some people need retreatment at 6 months if still active or possibly however we don't know this but more people should get retreated between 6 and 12 months to prevent relapse. Probably additional studies will be needed to figure out exactly how often and when people should get more treatment. But it is very clear from the data that I have shown you that Rituximab is really doing quite well for people who have moderate to severe pemphigus. But again we need more data to know that optimal management in terms of retreatment.

Dr. Victoria Werth: (*New Slide*) So what are the downsides to Rituximab? Well some people have infusion reactions. I would say that that is not nearly as often as we see in for instance in people who might get Rituximab for other indications such as other hematological malignancies. So because there are not so many cells in the blood we don't see as many severe reactions and that is a good thing. And then the other thing is sometimes there are some effects in terms of viruses and so we know that if somebody had Hepatitis B and if they have something known as surface antigen for Hepatitis B or another antibody which could be a sign that there is still some latent virus around that could reactivate. Most people say you need to get other treatment for the Hepatitis B at the time you are getting the Rituximab. So we do need to do testing prior to giving Rituxan to make sure that there is no hidden virus that could get reactivated by getting the therapy. In addition some people have had something called progressive multifocal leukoencephalopathy which is due to JC virus. This is quite a rare complication and has not been seen in pemphigus at all yet even though many patients have received Rituximab. But it is optimal to know what the potential downsides are but again that particular side effect is quite rare. And then sometimes people can have chills, infections, or body aches or feel tired just during and around the times of the infusion. Occasionally there will be a low white blood cell count and may more infections such as respiratory infection. But in general as I said, it is much better tolerated than steroid for long periods of time.

Dr. Victoria Werth: (*New Slide*) Now there is one other trial that Genentech Roche has done and I told you I was an investigator in this trial and it was a phase 3 trial called the PEMPHIX Trial

and that was a randomized, double-blind, double-dummy, active-comparator so in other words a very sophisticated trial where everybody is blinded and they were actually testing in one arm CellCept and in the other arm Rituximab and everyone got steroids. And what was a little different about this study as opposed to the previous study that I told you about from this group, was that this one was blinded. So that means that the investigators didn't know what the patient got and neither did the patient. In this trial nobody knew what they got including the investigator so it is called double-blinded as a result. So they put a lot of effort into doing this study and recruited 124 patients with moderate to severe active pemphigus who would have failed fairly high doses of Prednisone, 60-120 milligrams a day and had been diagnosed relatively recently and would have had to have had pretty severely active disease. So it was not easy to find people with this particular subset of disease but it would have been somebody who would particularly benefit from the trial. So people either got Rituximab, and this was the same dose that was used by French group at day 1 and day 15 and then also at 168 and 182. And the placebo group would get MMF twice daily which is the CellCept. So then everybody got the steroids which were subsequently reduced. And then the other group, which I should say the people in the blue (on the slide image) the people who got Rituximab got a CellCept placebo so it really wasn't CellCept it was a placebo. The other arm actually got CellCept but got the placebo Rituximab. And that is why it is called a double-dummy. So this trial went on for 52 weeks and everyone has been enrolled and the database is in the process of being locked which means we will have data sometime in the very near future. They are going to be looking at complete response determined by an outcome measure that we all worked on called the PDAI and then there were a lot of other secondary endpoints that you can see there that were looked at including: time to and duration of complete remission, time to and number of protocol defined disease flares, change in health related quality of life, adverse events, and changes in the pemphigus disease score.

Dr. Victoria Werth: *(New Slide)* So this is a trial we will be getting results from in the near future but what is really interesting to see what has happened from a regulatory standpoint in the U.S.. So in March 2017 the US FDA granted Breakthrough Therapy designation for the treatment of Rituximab for the treatment of pemphigus. And then in 2018 in February they granted Priority Review, which meant that based on data that had been submitted related to the French study they were going to evaluate the possibility of approval of Rituximab. So the idea was, actually when I was originally going to give this talk a couple of weeks ago that there was going to be an approval expected mid-to-late 2018.

Dr. Victoria Werth: *(New Slide)* So 2 weeks ago was when the FDA approved Rituximab and it was given approval for treatment of moderate to severe pemphigus vulgaris. It was again based on the Ritux 3 French trial and in addition there was mention that there had been a recent international panel of experts that had provided new recommendations of the diagnosis and management of pemphigus and that was published in the Journal of the American Academy of Dermatology just a couple of months ago. So I think all of this has come together to really allow much better access for Rituximab for people with moderate to severe disease.

Dr. Victoria Werth: (*New Slide*) Again the phase three study is finished and we should have data shortly.

Dr. Victoria Werth: (*New Slide*) So in summary, Rituximab is now approved. It is the first new therapy in 60 years for pemphigus, which is amazing! And in particular pemphigus vulgaris. And it is remarkably effective for many patients and reduces the need for high dose longer term Prednisone. So that really ends my formal presentation about Rituximab but on a very happy note that it will be much easier, we hope, for people to access Rituximab and insurance companies will have to look to the fact that this is now been approved specifically for pemphigus. So Becky I think I will turn it over to you for questions.

Becky: Great! Thank you Dr. Werth. That information will be invaluable for many people listening on the call with us today. The first question came in from Debbie and she is asking, "The risks and benefits of Rituximab versus other immunosuppressants, are there any specific recommendations on using Rituximab or other treatments where the PV is solely in the patient's mouth?"

Dr. Victoria Werth: Yeah, so that is a great question. You know people can have severe pemphigus just in the mouth. They may not be able to eat, they can not be responding to steroids, they have lost weight and so that is not a trivial presentation and not an uncommon way for people with pemphigus to present. And so I think that Rituximab is legitimately a very good option for people who have moderate to severe pemphigus in the mouth.

Becky: Great, thank you. Our next question comes from Cindy, "She says that when she was diagnosed that the first line of treatment was high dose steroids. Does Rituximab work to control pemphigus vulgaris as a first-line treatment? And if you use it as a first-time treatment is it always necessary to use steroids with it?"

Dr. Victoria Werth: Ok, another excellent question. So the recommendations for the international group was to have Rituximab available as a first-line therapy. And what that means is that you would not have to have failed steroids to be given Rituximab. From my presentation you can tell that it doesn't always work right away so you know if somebody has moderate to severe disease and it is going to take some time for that disease to get better because you have to clear the antibodies that are still circulating. Then, we often have to use steroids in order to allow for some enough improvements so people can eat and not be miserable. And so we still use quite a bit of steroids in people early on. Another option is we sometimes use for people who can not use steroids who might not tolerate it would be IVIG, Intravenous Immunoglobulin. And that is thought to work in a different mechanism and potentially clear the antibodies much more quickly. So that becomes another option once you turn off new antibody production to be able to clear the antibodies. But a lot of people still need to get steroids for some period of time but usually not quite such a high dose and usually for a shorter period of time and it can be tapered as the antibody level comes down.

Becky: Great, thank you. Asma is asking, and it is question that I am going to combine everything all at once so it is going to be a multi-step question here. "If a person has an allergic

reaction like an anaphylactic reaction during a Rituximab infusion, can they take the medication in the future and also there have been questions about pre-medication. What medications are given and why are they given with Rituxan?”

Dr. Victoria Werth: Yeah, good question. So very often people are given a combination of steroids and antihistamines prior to treatment to try and prevent allergic reactions. Sometimes when people have reactions we find that you can slow down the infusion rate and they can tolerate the infusion. If someone truly has an anaphylactic reaction it would require assessing what that exactly means. But in that sort of situation would require premedication and careful evaluation by the person who is doing the infusions to decide whether it is safe to go through with another infusion later and again whether slowing down the rate of the infusion would be helpful.

Becky: Great, thank you. Another patient is asking is Rituxan possible for a patient with latent tuberculosis. And if they have to take Rifampin does it interrupt the effects of the Rituximab?

Dr. Victoria Werth: So the treatment for latent TB, I am not sure if Rifampin would be sufficient I know often we use Isoniazid and so that would require usually either working with primary infectious disease. And it is possible to get Rituxan but probably to get initial treatment for some period of time for the TB to prevent the reactivation. I am not convinced that Rituximab would be quite enough in that situation. I mean I think it might also require Isoniazid in addition to Rifampin.

Becky: Okay, thank you. Rodica asks, “Is there more than one brand of Rituximab and given the process required to make medication, is there one preferred brand over another?”

Dr. Victoria Werth: So Rituximab is currently on patent and that is the drug that Genentech is making, the one that was approved for pemphigus vulgaris. There are other formulations of the anti-CD20 that are not called Rituximab and those have not been approved for pemphigus and have not been studied, per say. There have been some reports for people who haven't tolerated Rituximab to potential think about using these other agents as well but there haven't been organized studies.

Becky: Great. Our next question comes from Becky and I think this kind of speaks to what is considered moderate to severe for approval. But she gets lesions when she gets stressed and sometimes when she eats certain foods, but only a couple of lesions at a time and then they clear. Is it best to treat this flare or would be wise to treat the lesions before it gets worse? She says that her labs don't change when she has lesions or doesn't and she is asking if it is best to treat the lesions or to treat the lab work?

Dr. Victoria Werth: Yeah, I think you can't really answer one right answer there. Sometimes people have done really well and they have responded to Rituximab and then its 18 months to 24 months later and things are relapsing and getting a few lesions would be the first sign of a relapse. And then there is that sort of situation where there is starting to get more lesions might require retreatment. I think that sometimes people wait to get retreated and that creates a

situation where their disease gets worse before they get the treatment. So we try to tell people maybe not to wait. If they have been clear and then they are starting to get lesions that is a good time to go see your physician. Having said that, there are times where people have disease that sort of comes with certain stress of foods but it is more like waxing and waning at a low level. It isn't like the sense that it was better and now it is getting worse. And when that happens I think you can take more of a wait and see attitude and not necessarily get another treatment. So it really does require reevaluating the situation for each person. And I say that the FDA approved the medication for moderate to severe disease and I think that this is a relatively conservative stance. There are a lot of people who feel that because of its relative the safety that even for mild disease, early on it's a decision. Again it also becomes a decision with the insurance company but it may well be if somebody is early on and sort of getting worse that they may benefit from getting early on treatment with Rituximab. So although approved for moderate to severe, I think it remains to be seen how to optimize things.

Becky: Great, thank you. Ali submitted the next question and he said that he was diagnosed 8 years ago and then he was recommended to a dermatologist who suggested that they give Rituxan. He said that he has been prescribed that medicine on and off over about 5 years ago and he has has to repeat the infusion cycle every 6 months. Is this a typical time to repeat Rituxan, every 6 months? Or is there a different protocol now that the FDA approval has gone through?

Dr. Victoria Werth: So you know, what sort of missing in that question is to know a little bit more about why he is getting retreated every 6 months. So if the disease was getting better and then got worse or it wasn't completely gone then you can sort of see that he might need to keep getting treatment. I think that if somebody is better, whether they need to keep getting treated every 6 months for years is a little less clear. And I think that most of us you treat at the most, 1 more time and then maybe back off and see how things go.

Becky: Yeah, I think it has been for persistent activity.

Dr. Victoria Werth: Then it might be reasonable. Rituximab has been used for Rheumatoid Arthritis with a typical dosing every 6 months. So there has been a long-term history of it being used more than what we tend to do in patients with pemphigus.

Becky: Great, thank you. Laurie is asking a question. "Insurance companies have been reluctant to approve Rituximab treatment. Now that it is FDA approved, what will this mean and how long will it take my insurance company to let me have this medication?"

Dr. Victoria Werth: Yeah, that is a great question and I think it is early days so I can't really answer that with any information. I mean normally that is one of the ways that insurance companies try to not pay, by saying oh well it is not FDA approved. I think once you have articles that show the efficacy and you have FDA approval it is much harder for them to deny access. But again I think it probably depends a little bit on the insurance company. But I think you have a lot more ammunition now to say, "hey this needs to get covered" and I would try to

make sure that your physician is really advocating for you and writing letters and sending in the documentation that might be necessary in order to access the medication.

Becky: Great, thank you. Rosa asks, "What drug induces more immunosuppression, the Prednisone or the Rituximab? And are there any immunosuppressants that patients should be on after their infusion and how long will they need to be on them?"

Dr. Victoria Werth: So the data from this trial suggest that the side effect profile including infections was less with Rituximab than with Prednisone. So I think that was pretty clear data that came from the trial. In terms of how long to be on immunosuppression, it really kind of goes along with how long it takes for the antibodies to clear. I think people are getting Rituximab early on now it may be less necessary to be on immunosuppression except for on some steroids if they are unable to eat or they are uncomfortable. And you may not need immunosuppression. We used to use a lot of immunosuppression if we weren't giving Rituximab. Then the tapering of the steroids and possibly the immunosuppressants after the giving of Rituximab would be determined by how clinically the person is doing.

Becky: Great, thank you. You kind of touched on this and talked about, what is the difference between Rituxan and IVIG? Why wouldn't you give IVIG all the time, regularly with Rituxan?

Dr. Victoria Werth: Okay, so they are very different. IVIG is pooled immunoglobulin that is taken from over 1,000 patients and pooled. And it works through a mechanism that gets rid of the antibodies that are circulating through the blood. Rituximab works by clearing the B-cells that make the antibodies. So you can clear the B-cells and still have antibodies hanging around for a long time. And in that setting if somebody is continuing to have a problem and despite maybe background steroids then IVIG can help clear the antibodies. The reason maybe not to give IVIG is number one you don't want to get it right away when you are getting Rituxan because it might actually clear the Rituxan and you need that drug around to help clear the B-cells so you usually want to wait a few weeks. And IVIG does have some side effects. It can cause clotting, it can cause headaches. It is not a perfectly safe medication and so we use it when we need to but we don't use it in every single person if it is not necessary.

Becky: Great, thank you. John is asking, "What are the cardiac risks associated with Rituximab? Are they more serious if one uses the lymphoma protocol versus the Rheumatoid Arthritis protocol?"

Dr. Victoria Werth: Yeah, the cardiac risks are fairly rare. I think there can be some arrhythmias. I am not aware if there is a difference in the cardiac risks between the two different dosing regimens. I mean there can be issues with arrhythmias but it is pretty rare.

Becky: Great, thank you. Felicia says her husband has pemphigus vegetans. She is wondering if Rituxan is able to be used to treat her husband's disease.

Dr. Victoria Werth: Pemphigus vegetans is really just a morphology of the lesions, they are just a little more heaped up but I would really just say that it is the same as pemphigus vulgaris and

the epidermis is a little bit thicker. Yes in that situation, Rituximab would be used in the same way as we use for other forms of pemphigus.

Becky: Great. Thank you. Our next question is asking, "Is Rituxan always done as an outpatient procedure at the hospital or can it be given has a home infusion?"

Dr. Victoria Werth: So Rituximab because people can have infusion reactions and might need pre-meds. In general it is given more as an outpatient infusion than at home. It is not typically done because of the potential and the need for more monitoring than you can really do in a home situation.

Becky: Great. Thank you. Faith said that she received 2 infusions of Rituxan 2 years ago with no ill effects and she went into remission but she is currently experiencing a flare. Would another round of Rituxan help her chances of achieving remission and what are the long term risks to this treatment? And do they increase according to the number of treatments that you have?

Dr. Victoria Werth: So the B-cells get depleted very quickly after the initial infusion and they they come back usually at about 6 months but it is kind of reset so that really people who are having pretty normally functioning B-cells. So the risk of getting another treatment is really not that different than getting the initial one. Sometimes the B-cells don't come back completely to normal but it is usually close to normal and I would say that in general we usually find that patients do need to get retreated. That reflare about 4 months out is pretty routine and then when that happens we just retreat. And sometimes over time it is less likely to have the disease come back again and so I think it is actually really helpful to go and get retreated if she is starting to flare.

Becky: Great, thank you so much. Prateek also asks a question, "Can my doctor prescribe Rituximab if it is not FDA approved for my specific condition?"

Dr. Victoria Werth: Well if they have pemphigus vulgaris then it's approved. That might be an older question.

Becky: I am not sure on that one, I am sorry.

Dr. Victoria Werth: If it is pemphigus foliaceus then I don't believe it is approved and then you would have to go back and it could still be prescribed but it might require some education of the insurance company before it might happen. It is not as much guarantee of that then.

Becky: Great. I think that you have already kind of covered this question but you might just want to reiterate. Lauralyne is asking, "What is the approved infusion schedule and would she still be able to get the medication according to the other protocol if that is not the one that she is on?"

Dr. Victoria Werth: Yeah, I don't think that we have the answer to that right now. The approved one is the 2 infusions, 2 weeks apart. And the another infusion every week is not the one that is approved so I don't have yet enough experience to know how insurance companies are now

going to handle things if we try to order weekly. So I think that is a thing we will find out in the near future.

Becky: Great. Thank you. Iva says that her dermatologist told her that she doesn't need to get another infusion if she doesn't get any new blisters but she is worried that her immune system isn't suppressed enough so she wants to verify that this is true.

Dr. Victoria Werth: So has she has stopped making blisters?

Becky: It sounds like she doesn't have any lesions currently.

Dr. Victoria Werth: So if there are no lesions now and she has gone through the whole infusion series, I mean there is no right answer. In Dr. Joly's study they did a lower dose at a year for everybody that got Rituximab and then at 18 months. We don't know whether to retreat and how much, that is still kind of unknown. So I think a lot of the patients get 1 series of infusions and then we wait to see what happens. There is not a right answer right now, so there is not enough information to answer that.

Becky: Great thank you. Nancy is asking if there is any dental or surgical procedures that should be avoided after receiving Rituxan?

Dr. Victoria Werth: That kind of speaks more to maybe if someone had been on steroids and was on a bisphosphonate like Actonel or Fosamax. Some of those are the bisphosphonates that are used to prevent osteoporosis can very rarely cause problems with avascular necrosis of the jaw when people have dental or surgical procedures. We usually ask people before they start getting treated if they are up-to-date with their dental cleaning and their oral surgical approaches. But for Rituximab I am not aware if there are problems with dental work or surgical work in the mouth.

Becky: The follow-up question she is also asking is, "Does Rituxan do anything to help with TMJ?"

Dr. Victoria Werth: So I don't know the answer to that. I mean that is not any way related to pemphigus. It seems that TMJ is more of an inflammatory process and not a B-cell mediated process or antibody mediated so I guess off the top of my head I would be a little surprised if it was helpful but I really don't know the answer.

Becky: Okay. Sachin is asking, "For patients who are using another immunosuppressant to control their pemphigus, what do you advise is the best method to change or reduce the amount of immunosuppressants after being administered Rituxan?"

Dr. Victoria Werth: So typically if it is Prednisone it is sort of one answer. It's more like if we are talking about Mycophenolate, Mofetil or Azathioprine or Methotrexate, that is a different thing. Again there is not a one sentence answer there. You don't have to taper immunosuppressants and if somebody was not on them and I was going to give them Rituximab I might only give them steroids and not even immunosuppressants if they are going to get Rituximab. So the

situation might be if somebody was being treated with steroids and immunosuppressants and wasn't doing so well and some point and then got Rituximab. And in that setting it would probably be okay to stop the immunosuppressant because really where that helps is to get people off of steroids and to prevent relapse but if they are getting Rituximab then you are kind of interrupting the process of antibody formation and it is kind of a little bit different. So eventually you would want to just stop the immunosuppressants and then gradually taper the steroids as Rituximab is working. But there is no cookbook for that and there is not a right answer, it depends on a lot of different variables I think for that particular person.

Becky: Great, thank you. Dana says, "How do you know if you are getting enough Rituxan? She is on a 6 month schedule and up until her last infusion she was fine. She had her last infusion in May and she got sick 3 weeks ago and some blisters came up on her leg and then they went away."

Dr. Victoria Werth: So people can still have circulating antibodies a few weeks after getting the infusion so if it is just an isolated few lesions I wouldn't worry so much about it. I mean that is really a standard dose for treatment so it doesn't mean that you are not going to get new blisters after getting the infusion.

Becky: This is a follow-up question and it is kind of from a few different patients and it kind of goes to what you just said. Some patients get worse after they receive Rituxan and don't start getting better. Why specifically does that happen?

Dr. Victoria Werth: Well I think more often it is not a matter of getting worse it is not getting better right away. And the reason is, the antibodies are still there and they are still circulating. All you have done is turn off the cells that make new antibodies but it takes like I said the half-life is like 3 weeks for antibodies to go away. If you have a high titer it make take 3-4 months for the antibodies to go to a low level that you don't have disease. So I think that it is more that the antibodies are there and they are not going away right away. And in that setting if somebody is really severely impaired than thinking about something like IVIG could be helpful.

Becky: Great, thank you. Shauna says that she has been on Cellcept and she hasn't seen any improvement and the doctor wants her to start taking Azathioprine is there any preference of Cellcept or Azathioprine to be taking with Rituxan? And does one have to take Cellcept longer or Azathioprine longer after the Rituxan treatment?

Dr. Victoria Werth: I think that it would be the same for either one and in terms of the length of time it really depends on how they are doing with the Rituxan and if the antibodies are going away. I think they can both work quite well. Usually when someone has active blistering it is not going to be very helpful on either one because usually what works with active blistering early on is steroids and these immunosuppressants work in order to be able to taper steroids, they have steroid sparing effects. Sometimes people do with isolated immunosuppressants control their disease but it problem doesn't matter which one.

Becky: Great, thank you. There a bunch of questions coming in on fertility issues and I am going to ask them kind of as a group here. One is how long after a woman get Rituximab do they have to wait to get pregnant? And two does Rituxan have any effect on male fertility and how long should the couple wait to get pregnant if he is the one receiving it?

Dr. Victoria Werth: For woman it's felt that they should wait a year after getting Rituximab to try and get pregnant. I actually think for male fertility, I am less familiar with data on that. It is a little hard for me to answer that question to tell you the truth. If they are thinking of pregnancy it would be very worthwhile for them to speak to their doctor about that but for woman it is a year.

Becky: Great, thank you. The next question is, what level of activity for PV do you feel warrants Rituximab?

Dr. Victoria Werth: That is an individual question. There is not a right answer. I think that Rituximab is so effective that if in an ideal world, and this is not FDA approved, if the disease is anything more than very mild it could make sense to get treated somewhat early but that is not anything that is recommended by FDA and there really aren't good guidelines about that. I think that if somebody has a significant amount of disease, more than a few lesions and they are getting more than that kind of person in particular then one would want to start thinking about Rituximab for.

Becky: Great, thank you. This patient said that they were diagnosed in November of 2016, they were given Rituximab and Prednisone and in April 2017 they were given another dose and went down on the Prednisone by a little and finished that round in the beginning of January 2018. In February and again in March the lesions appeared again and then they received Rituxan again in April and already feeling improvement. Can Rituxan be given over a short period of time? I know you discussed 6 months, but can it be taken over a shorter period of time?

Dr. Victoria Werth: Well from what you described it doesn't sound like it was much shorter than the 6 months. They have had 3 infusions over the course of a little over a year. In general it is 6 months because the B-cells get depleted and then they come back at about 6 months but there really is no data to make you think that a more frequent dosing is needed for that but I would not be afraid to be retreated if things seem to be settling down and it is requiring multiple treatments. But it sounded like it was April 2017 and then, yeah it doesn't seem like it is too out of line.

Becky: Okay, Daphne is asking "What is the most effective combination with Rituxan to achieve remission?"

Dr. Victoria Werth: Well I think that alone Rituxan can help you achieve complete remission off therapy, it doesn't work for every single person but for many people. So then the question becomes do you have a lot of activity that the antibodies are disrupting things even though you have turned off new antibody production then I think what works is often some dose of steroids

and if it really severe enough and not clearing then you can think about IVIG to remove the circulating antibodies.

Becky: Great thank you. Charrie is asking, "Is it possible to treat PV and RA at the same time with Rituxan?"

Dr. Victoria Werth: Absolutely. And the drug is now indicated for both diseases so that would make a lot of sense.

Becky: Great, thank you. That was sort and easy. Nancy says that her husband has already had the Rituxan over the course of 2 sessions and he didn't go on remission and is still on 20 milligrams of Prednisone and 2,000 grams of Cellcept daily. What do you consider success with the infusion and treatment? And if one doesn't go into remission after the infusion could it be more effective to get another round of Rituxan?

Dr. Victoria Werth: So again that would be a matter of knowing how many times it happened and so on but sometimes it does take 3 or 4 infusions to see improvement. I think that 20 milligrams of Prednisone is a lot to be on chronically and there are newer treatments that are in development for people that are refractory to Rituxan. There are some people who don't get all the way better and so I think that there will be other options in the future. But depending on how often they have been treated with Rituximab it would have to be individually assessed whether or not more treatment would be helpful.

Becky: Great thank you. Dana says that she has pemphigus vulgaris and was diagnosed 7 years ago and is on Dapsone. She was given Rituximab 4 years ago and underwent 6 treatments in total and went into remission with no other medicine. This past fall, the pemphigus came back in full course and she is only taking CBD full spectrum oil and rubbing alcohol because she is afraid to go back on Rituxan. Is this treatment as effective and safe for the immune system as Rituxan? Having 3 kids and being a teacher, she is a little bit afraid to go back on the Rituxan. Should she be concerned?

Dr. Victoria Werth: Well I don't think that we have any information whether CBD oil helps pemphigus. I am not aware of that much data, in fact any data about it. So I would say that if the Rituxan worked before I would be thinking that it would be reasonable to go back and get it again, just to prevent it from getting worse. But I would have to know how they were doing with their current approach. But it doesn't sound like they had a problem with taking it before and yes there is a little more risk of infection but I don't think that that is a reason not to get the treatment.

Becky: Great. Thank you so much. The next couple of questions are kind of related. Is Rituxan effective against other bullous diseases? They don't mention which one but other patient mentions EBA.

Dr. Victoria Werth: I mean there really isn't as much data and there are no trials but there are case series that suggest that Rituxan can be quite effective for all of this MMP, BA, and bullous

pemphigoid. And it may not work as often as it does in pemphigus vulgaris but it can be quite effective and it is worth giving it a try for refractory disease.

Becky: Great, thank you. Heidi is asking if Rituximab might fit into treatment regimes for paraneoplastic pemphigus? And the follow-up to that would be if there are any contraindications with chemoradiation?

Dr. Victoria Werth: Well it depends on what the malignancy is. There are people for instance with leukemia that are treated with Rituximab and if that can improve them then potentially the pemphigus can improve. And I think usually in that sort of situation with an underlying malignancy I think you would have to get more details about what that malignancy is and work with the oncologist to see if they think it would be a problem to be on Rituximab along with other things they are being treated with.

Becky: Great, thank you. Is Rituxan okay or are there any contraindications for a patient who is 94 years old with PV?

Dr. Victoria Werth: You know I think that it is usually quite well tolerated and I think if you think about giving someone that age Prednisone that is probably more risky. From the trials it looks like Prednisone is certainly not as safe as Rituxan but you know it probably is better than having untreated pemphigus depending on how severe it is.

Becky: Great. There are a couple questions related to cost related to Rituximab. Melissa is want to know if there are any programs to help patients to reduce the cost for Rituxan?

Dr. Victoria Werth: So for the people that have private insurance I think there are now. Through Genentech there are ways to have some kind of assistance in terms of copays and stuff like that. So you should have your doctor or the patient can check with Genentech to see what kind of programs they offer to offset some of the costs.

Becky: And I also want to put it out there too that I believe that they also can help you figure out with your insurance company if it can be covered. Correct Dr. Werth?

Dr. Victoria Werth: Yeah, I think that is what I was just saying. Yeah they will help with all those aspects of treatment.

Becky: Great thank you. Is there a limit on how many times you can have a Rituxan infusion before you become immune to it or risk other side effects?

Dr. Victoria Werth: You know, in general there doesn't seem to be a limit. There are people who get treated for rheumatoid arthritis as I mentioned every 6 months and I think it more relates to if the blood count is okay and things like that. But I am not aware of any particular limit on how many infusions people can get in terms of safety.

Becky: Great, thank you. Sandy is asking, “Now that the FDA has approved Rituximab as treatment for PV, is there any guidance given to insurance companies in the terms of the number of treatments and the approval of treatments?”

Dr. Victoria Werth: So you know, I think a drug can be approved for an indication but I think that the insurance company can also make their own determinations to some extent. So I think that what it is is certainly more ammunition to say, hey this is such a good treatment that it has now been approved by the FDA. So I think that it is a matter of giving the insurance company that information but I can't say for sure that they will pay for it. It really does become that insurance company is in the driver seat for that.

Becky: Alright, thank you. Triny said that she read that Rituxan is giving between flare-ups to minimize the severity of future flare-ups and is asking your opinion on this practice. And what do you feel are the biggest risks of doing so?

Dr. Victoria Werth: So in the study that we talked about, the French study, they mentioned that they gave every other week dose at the beginning then they gave 500 milligrams of Rituximab which is half the dose of the infusion that was given the first time go around at months 12 and 18. And so I think that is what she is talking about. We don't know if doing that will change anything and I believe that because of the high recurrence rate some people even think that giving a retreatment even earlier than 12 months might be the way to go. But we just don't have enough data to really know what the right answer is and there certainly are people that only get 1 course and they don't relapse. So it is really hard to know what the right answer is.

Becky: Thank. Just to let our listeners know, we only have about 10 minutes or so left with questions. If you don't get your questions answered on this call please submit them to me at becky@pemphigus.org or through our Ask A Coach line and we are happy to help to support you in any way that we possibly can. So moving on to the next question. If someone has initial simple severity of PV is Rituxan better or are steroids better?

Dr. Victoria Werth: So you said they have mild disease?

Becky: They said initial level simple severity of PV.

Dr. Victoria Werth: I am not sure what that means. I mean if someone has very mild disease you can certainly try steroids first and see if it improves. For mild disease I think that there are a number of different options and ways to go. If they have mild disease, and then they are starting to get more lesions and it is become less than mild then that is when you want to think about escalating treatment to Rituxan.

Becky: Great, thank you. Is there any evidence or information related to subsequent administration of Rituxan being less effective than a first round treatment?

Dr. Victoria Werth: You know the data would almost suggest that with each additional infusion there is probably a higher likelihood for people doing better and maybe not relapsing as much. So I don't think there is any evidence that it gets less effective over time.

Becky: Okay, and I think that this is more of a clarification. Cynthia says that she is currently only on 2,000 milligrams of Cellcept and has been off steroids for over a year. She would not necessarily have to restart to get Rituxan. Correct?

Dr. Victoria Werth: No, absolutely not. There is no reason to escalate therapy just to get Rituxan.

Becky: Okay. Pertika is asking if there is any danger of cancer or any diseases after taking Rituxan?

Dr. Victoria Werth: So the reactivation of Hepatitis we talked about and also TB we check for and also to make sure that there is not a prion disease. But in terms of cancer I am not sure that there is any increased risk.

Becky: Can Rituxan be used on dialysis patients or will the dialysis machine clean the Rituxan from the blood?

Dr. Victoria Werth: Wow, that's a great question. I am not sure that I can answer that. The depletion of B-cells is very quick. However dialysis patients are more susceptible to infection and I would really need to be talking to a nephrologist and making sure about safety in that particular situation.

Becky: Great. Thank you. A patient has a condition called senear-usher, which they are saying is pemphigus with lupus. Is Rituxan effective in treating this condition as well?

Dr. Victoria Werth: I mean yeah, that is a complicated question. There have been trials that have done for lupus haven't shown Rituximab to be effective but in this particular situation there is no reason to think that it wouldn't be effective in terms of the pemphigus.

Becky: Great. What other conditions is Rituximab approved to treat besides pemphigus vulgaris?

Dr. Victoria Werth: Well Rheumatoid Arthritis, Vasculitis, and certainly a number of B-cell cancers of different types. And it is being used off-label for a number of different autoimmune problems. I don't know if it is FDA approved for ITP, thrombocytopenia. It is kind of used pretty broadly for a lot of autoimmune conditions.

Becky: Great. The next couple of sort of combined. Is Rituxan used in mucous membrane pemphigoid or bullous pemphigoid?

Dr. Victoria Werth: Yeah, it has been used for both and has worked in both. It doesn't have to work but it can work.

Becky: Great thank you. Debra says that you have mentioned that the risk of infection is a lot lower than you would expect with depleting of the B-cells with the CD20, so she is asking, "Is an unusual slow regeneration of B-cells following a course of Rituxan a reason not to repeat it in the future for future relapse?"

Dr. Victoria Werth: No, it is fine. It's just what happens is the B-cells that have the CD20 are depleted but then you still have the immature B-cells that are developing into B-cells and you still have plasma cells. So those are protective against infection but at some point if there is a relapse then that is the reason to get retreated. To deplete the CD20 cells again that are causing the problem.

Becky: Great. Thank you. Lisa says that she did her 2 treatments 2 months ago and she is getting better but she is still on 3,000 milligrams of Cellcept. How do you know when is the right time to start weaning the Cellcept?

Dr. Victoria Werth: So that would have to do with how the disease is doing. If the lesions are getting better and you are not getting new ones, you can pretty much reduce it relatively rapidly but then keeping track, if things start to get worse again maybe then not too quickly.

Becky: Great, thank you. Well we have gone over our hour as it is, so in closing I would like to say thank you Dr. Werth for being on our call with us today. You have provided a phenomenal amount of information and education on this call. I just want to say thank you on behalf of everybody who has joined us on the call today.

Dr. Victoria Werth: Thank you for being such a good host.

Becky: I would also like to remind our listeners that the IPPF second quarter fundraising is dedicated to increasing Awareness of Pemphigus and Pemphigoid. We have a few more weeks until the end of June to reach our goal of \$30,000 by June 30th. So if you haven't already, please consider visiting our website today to make a tax-free donation to support the Awareness Program's continued efforts in reducing P/P diagnostic delays.

The IPPF is pleased to announce the date and place of the next IPPF Annual Patient Conference. The 2018 conference will take place in Raleigh-Durham, North Carolina from October 12-14th. Registration is now open! Visit our website at www.pemphigus.org to register for the conference. This is a great opportunity to meet others within the pemphigus and pemphigoid community and learn more from the world's leading experts about the disease. We are also excited to announce that we will be including a visit to the University of North Carolina Dental School for a day filled with learning and hands-on workshops for the patients.

Becky: Also our next webinar is scheduled for July 25 to discuss Treatments Option Question and Answers with Dr. Marinkovich from Stanford University. Registration will open shortly for this call. Don't forget to register for the IPPF Natural History Study, a new patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Register today on the IPPF Website under the research tab. And a reminder the IPPF is still looking for Awareness Ambassadors to visit local dental offices. Please click on the Awareness Ambassador link for more information.

Becky: Lastly, I know that there were still a lot of questions that we couldn't get to today so if you have a question that didn't get answered on the call, or have additional questions please e-mail our Outreach Manager, Becky, at becky@pemphigus.org, or call me at (916) 922-1298 x:105, and I would be more than happy to help. This call recording will be sent out with the survey following this call. Thank you everyone and thank you Dr. Werth. I really appreciate your time today.

Dr. Victoria Werth: Thank you.

Becky: Thank you. Bye.