

July PES Call Transcription

Becky: Welcome everyone! This call is now being recorded. I would like to thank you for being on the call this evening. Our Speaker today is Dr. M. Peter Marinkovich, Associate Professor of Dermatology at Stanford University. Thank you for joining us today!

Dr. Marinkovich: Glad to be here.

Becky: The call today will focus on treatment option for pemphigus and pemphigoid patients and Dr. Marinkovich will be answering any questions you have. Dr. M. Peter Marinkovich, M.D., is an Associate Professor of Dermatology, and faculty member of the Program in Epithelial Biology and the Stanford Cancer Biology Program. He has an interest in inflammatory skin disease and is Director of the Stanford Bullous Disease and Psoriasis Clinics as well as an attending dermatologist at the VA Palo Alto Medical Center. Dr. Marinkovich's research focuses on pathogenesis and therapy of epidermolysis bullosa, psoriasis, hair disorders and skin cancers.

Becky: One question that has come in is, is Dapsone an appropriate treatment for a mild to moderate case of PF? Should it be used by itself or with other medications?

Dr. Marinkovich: Hi everybody, it is nice to speak with you all. I look forward to trying to help out. So the first question about the Dapsone. Yes I think it is an appropriate therapy for pemphigus foliaceus and other forms of pemphigus and pemphigoid. However, the thing is it is mild. It is a very mild medicine. For best with pemphigus it is going to substitute for maybe 10 milligrams of Prednisone, not any more than that. So if you are having a flare, Dapsone is not going to help with the flare. You need Prednisone, you need to get the flare controlled, or whatever other medicines you are taking, but you need to get the disease under really good control. And then when you are just tapering down, you are in the later stages of your disease where you are having a low prednisone requirement, that is when Dapsone helps.

Becky: Well great, thank you. Sara asks a question, she has a concern about weight loss. She recently went through a trial with Rituxan and then Veltuzumab. The medicine is working great but getting rid of the extra weight has been very challenging. She has a friend who does the "Thrive" and it has worked very well for her but she is concerned about the extra vitamins and other stuff in it. The last thing she wants to do is rev up my immune system. She says she has had pemphigus for 20 years and has been able to lose the weight up until now. She is wondering if we had any great ideas?

Dr. Marinkovich: Okay, yeah this is a very common scenario. Unfortunately we use a lot of prednisone, especially in the early stages to stabilize the disease and as a result people gain weight. The whole goal when treating pemphigus and pemphigoid is to minimize the total prednisone. But you know there may be some that is still needed and unfortunately there are side effects. And weight loss is one of the most debilitating one. So when you are on a high dose of prednisone it is hard to lose weight but as you get down you will find that your weight

loss efforts respond better. I am a firm believer in a healthy diet and exercise and I don't think fad diets are really a thing to do. You really just want to adjust your lifestyle. Not just enter a diet thinking, I am going to lose 20 pounds in 2 months then go back to doing what I am doing after that. You want a diet and regime that you can live with for the rest of your life. It is a lifelong struggle and as you get older, you notice too that it makes it even harder to lose weight. As long as it is a healthy diet, you are eating a balanced assortment of healthy fruits and vegetables and try to stay away from processed foods. There is no diet that is going to make your pemphigus better. As far as weight loss, I would just opt for a healthy diet and that would be good for your entire body including your skin. I am not familiar with the Thrive diet but I do know that there are a lot of supplements that tout that they are immune-enhancing. So if the Thrive diet does tout itself as immune-enhancing then you should avoid it. If it doesn't tout itself as immune-enhancing then I would be neutral on it because I don't really know much about it.

Becky: Great, thank you. Darryl says he has had severe case of bullous pemphigoid for about seven months. He has been on heavy doses of prednisone of about 60 mg per day for several months but has been tapered to 20 mg now but is still taking 4000 mg cellcept daily. He had two infusions of rituxan but did not see results. But it seems that the steroids have finally worked to stop the blister formation. His doctor intends to gradually reduce the steroids but keep the high dosage of cellcept for a long time up to a year. Why is that?

Dr. Marinkovich: Well both cellcept as well steroids have their side effects. High dose steroids, 60 milligrams or 40 milligrams, anything above 20 milligrams can be considered high dose, a day. Those side effects are going to be higher than those of mycophenolate, also known as cellcept. When you get below 20 milligrams a day the side effects of prednisone are less and then it is debatable which one is more toxic. What I like to do when I am working with patients, I like to try to first start off on high doses of prednisone and mycophenolate. I think that is a good steroid sparing regime. Its side effects are less than some of the other ones and toxicity is less. So what I do is start off on high dose prednisone, use the mycophenolate. I don't normally go up about 4 milligrams a day, I like to use 3 milligrams a day however you can push it a little further. Then you get the mycophenolate on board, you start with the 60 milligrams of prednisone and then I gradually taper the prednisone. I taper it 10 milligrams a day each week, then go down to 50 milligrams a day for a week, then 40 for a week. Then at that point I start tapering at a milligram at a time. For example, Monday 40, Tuesday 39, Wednesday 40, Thursday 38, Friday 40, Saturday 37, dropping it every other day until you get to 40 zero, 39 zero, 38 zero, 37 zero, 36 zero, like that. So it is this gradual but steady tapering. If you taper any faster than that then the disease can rebound and then you are just back to square one. You have to go back up high on the prednisone. So that is a tapering regimen that works for me, every doctor has a slightly different regimen but you want a nice slow but steady taper. And then you want to see how low you can go before the disease starts to try and come back. So what I do then with this tapering regimen, as the disease gradually starts to become more stable, you are able to get to a lower dose of prednisone, once I get to the equivalent of 20 milligrams of prednisone every other day or 10 milligrams of prednisone a day. At that point I consider that the cellcept is higher toxicity than the very low dose of prednisone and then I will shift gears. I will have the patient

hold the prednisone steady at a low dose, 20 milligrams every other day or 15 every other day and then start tapering down the mycophenolate or the cellcept. Drop it down by 500 milligrams a day, each month. Once the mycophenolate is tapered off then I go back and work with the patient to taper off the last bit of the prednisone. The reason I like having a small amount of prednisone on board when you are tapering is because if you are just trying to manage the disease with mycophenolate alone without the prednisone, see the thing is with mycophenolate when you make a change in dosage, and this is true with all the other steroid-sparing agents, like azathioprine, cyclophosphamide, and methotrexate, it takes month or at least 3-4 weeks to see the effects of the change of the dose. So if I am trying to manage you with mycophenolate alone and I have got you down to maybe 2 milligrams a day, if you flare and I am just trying to work with mycophenolate alone and I put you back up to 3 grams a day you are not going to see the effects for 3-4 weeks and you are going to be suffering with all the blistering in the interim. Whereas with prednisone, if I was managing you with low-dose prednisone after the mycophenolate tapers off and you flare and then I put you a little bit higher up from 15 a day to 25 a day, you will get that flare quelled within a few days. So managing pemphigus with something like mycophenolate alone is like driving an ocean liner, you make a turn and then maybe about 3 miles down the coast you finally start to see the bow start to shift a little. Whereas managing pemphigus with low-dose prednisone or pemphigoid with low-dose prednisone it is like driving a sports car, you make a turn and then you immediately get a response. So that is my philosophy on the pros and cons of tapering the mycophenolate first or tapering the prednisone first.

Becky: Great, thank you. I am going to ask a couple of question because they are related. And you kind of eluded to it already but, what is the effect that diet can have on managing PV and are there any foods that tend to make pemphigus or pemphigoid worse?

Dr. Marinkovich: So I am not so savvy on social media but my impression is that this is a topic that is talked about among patients. I've had patients inquire about foods. I mean sometimes it's hard you eat a certain amount of foods or a certain type of food and then a day or 2 later you get a flare and then you think, oh gosh it must of been the food. But you can never know for sure unless repeatedly eat that food and repeatedly get a reproducible flare. I mean I don't think that there is a lot that diet plays in the activity of pemphigoid. You want to eat a healthy, balanced diet. As far as certain food that really frequent causes the disease, I don't think that the diet plays a huge role. There may be some instances where the diet can exacerbate the disease, possibly in some people. Like for example I would probably say that the best example of something that has gone beyond the level of anecdotal experiences to something that is a least somewhat reproducible in a small proportion of people is onions and garlic. So if people really want to try dietary modifications you can try omitting onions and garlic from your diet for a couple of months and see if it makes a difference. I would have a hard time doing that because I really like onions and garlic. So that is one thing you can try. And obviously if you have pemphigus in the mouth or pemphigoid for that matter and you have open sores, acidic foods like tomatoes and citrus, that is going to make the pemphigus sting. It is like putting acid in a wound or vinegar on a wound. It is going to sting. So if you have sores in your mouth, of course

you want to eat more bland foods so it won't irritate the open sores. As far as causing new blistering and increasing the activity of pemphigus, I don't think that there is enough evidence out there to convince me that it is playing a major role in the disease but I am very open to any new data that might come out.

Becky: Great, thank you. There are a couple questions and they are kind of related. Is there a role of gut health in managing symptoms and is there any connection with leaky gut or poor stomach health that would trigger the pemphigus or would high levels of MCH be a trigger or a treatment consideration?

Dr. Marinkovich: What does MCH stand for?

Becky: I don't know. That was just a question that was asked.

Dr. Marinkovich: Well as far as a skin connection, there is definitely some overlap between the gut and the skin. Like for example patients with epidermolysis bullosa acquisita, one of the less common blistering autoimmune diseases, about 20-30% of patients with this particular disease also have inflammatory bowel disease, Crohn's disease, or ulcerative colitis. Also there are patients that have the autoimmune disease dermatitis herpetiformis and those patients overlap, it is thought that celiac disease is a member of the same family as dermatitis herpetiformis. So people with dermatitis herpetiformis have mostly skin but a little bit of GI disease and people with celiac disease that is mainly causing GI symptoms can sometimes have skin disease too. So it is an interesting overlap between the gut and the skin in couple of some of these less common autoimmune bullous diseases. As far as pemphigus is concerned, there is nothing that has been clearly demonstrated as a connection between the gut, the GI, and the skin. But there a lot we still don't understand about biology and medicine in general. So just because it hasn't been proven at this point doesn't mean that it is not possible to be proven at a later date. I know it is an area of intense research right now, they call it the microbiome, the bacteria that live in your gut. People are studying them very intently right now and they are also studying the microbiome of the skin, the bacteria that live on the skin as two different ways that they could potentially influence disease. So it is possible that all of us may learn more about interactions between the gut and the skin in the future.

Becky: Great, thank you. David says that he has suffered with pemphigus vulgaris since 2007. He said he wasn't diagnosed properly until 2010 with the help of a dermatologist. He was on huge amounts of Prednisone and finally was put on Methotrexate and he has been taking Methotrexate for almost 8 years due to outbreaks. He is currently taking 12 - 2.5 mg tablets of Methotrexate once a week and have been for 2 years now. He is still under the care of a dermatologist and will be seeing a gastroenterologist to make sure his liver is still good. Would he be a candidate for Rituxan or is there a better treatment recommended?

Dr. Marinkovich: What was the diagnosis again? I did not hear it.

Becky: Pemphigus Vulgaris in 2007

Dr. Marinkovich: Candidate for Rituximab, yeah definitely. It used to be that people were very hesitant about using Rituximab when we didn't know as much about it and sometimes people are still hesitant about using it. But you have got to be able to reduce the cumulative toxic effect of different drugs. Certainly ongoing significant quantities of prednisone. If you can't get the prednisone down that is a good indication for use of the Rituximab. You have to give a trial of conventional therapy. The prednisone plus a steroid-sparing agent like methotrexate would be one, cellcept would be another one. So currently what I do is I will go the conventional route with steroids and a steroid-sparing agent. I don't usually use Methotrexate so much I like mycophenolate or cellcept. That would be an adequate example of a steroid-sparing agent, the methotrexate with prednisone. If you can't get the patient off methotrexate and the prednisone and you give it a good try for a few months, at that point nobody even insurance companies you can make a very good argument that is patient has failed conventional therapy. So then the next standard of care would be to use Rituximab. You could make a very good argument to the insurance companies. Sometimes doctors will have to write a letter or get on the phone with the peer-reviewed doctors that work for the insurance companies. But if the doctor does the research and can document the effective use of the Rituximab in clinical trials and articles out there then you can readily overcome the objections from the insurance companies. But yes, I think that if you have been on methotrexate for a long time and taking 20 milligrams a day is a decent dose, you can make an argument that the disease activity is still too high and you can't get these medicines tapered down and you are getting cumulative toxicity. So you should be able to petition to try Rituximab. Of course I don't know all the details of your case. If you have some coexisting medical conditions that would make Rituximab contraindicating then of course you can't use it. But if you don't have any contraindications to it then certainly you can make a case of using it. There was a french study that came out last year, it is in the british medical journal called the *Lancet* and that study was done by a researcher in France, Pascal Joly, and his study very convincingly showed that Rituximab used as a frontline along with prednisone was actually quite effective in reducing the total steroid dose in pemphigus patients. The thought is among these specialists the earlier you use Rituximab the better the results will be. The idea is that you can build up memory cells, memory immune cells over time that then require you to use Rituximab more frequently. If you use the Rituximab early then you don't get build up of these memory cells and you could end up using fewer courses of Rituximab. So I think that that is the trend of where autoimmune bullous disease treatment is going in the future is earlier use of Rituximab when it's not contraindicated.

Becky: Great thank you. Bobbie says her husband is in remission from Bullous Pemphigoid; however, he still suffers from constant mouth burning. Have you heard of any treatments for that? He curren used Magic Mouthwash and Nystatin Oral Suspension, but it didn't really help much. They had some leftover Prednisone so he took 5 mg for 5 days and now he's tapering off. It seems to help the most, but they really hate to use Prednisone. Any suggestions on what to do about the burning?

Dr. Marinkovich: You know I think that this is probably unrelated. That the burning mouth syndrome can be a very significant problem. I had a couple of patients who had this situation, they get over their bullous disease but they still have consistent burning in their mouth and what I do is I refer them to an oral medicine specialist. I really believe in the idea of treating patients in a multidisciplinary fashion and having a network of allied non-dermatology specialists that I can call upon for help in patient care. I have a some good oral medicine specialists that I work with and I respect and they do a great job. And this is exactly the type of disease that an oral medicine specialist would be the best person to try and tackle. So I would recommend that if your dermatologist is having a rough time dealing with this. I would say that I am not the expert on something like this, I am very ready to defer to an oral medicine specialist. I think it might be worthwhile to consider a consult from an oral medicine specialist.

Becky: Great, along the same topic we have had quite a few questions that refer to the itching associated pemphigus and specifically with pemphigoid. What do you recommend to help with the itching that is just kind of mind-blowing and keeping people awake at night and to the point that they are making their skin bleed from itching. What do you recommend for that?

Dr. Marinkovich: Well first off, pemphigus does not itch so much it may be a little itchy but it should not be terribly or debilitatingly itchy. If you have pemphigus and you have really terrible itching it may be worthwhile having your dermatologist to not automatically attribute it to the pemphigus but explore other things that are causing the itching, like for example dry skin can itch significantly. For people one thing that may be common is that somebody has eczema and pemphigus at the same time so it could be the eczema that is contributing to some of the itching. So with pemphigus I would say look around for another cause and try and treat some of the more common causing proactively. Use a good moisturizer to moisturize the skin and if all those other sources are negative and you really think the pemphigus is causing the itch try and correlate the antibody titus with the itch symptoms and see if there is a correlation then it makes sense to treat the pemphigus more aggressively to help the itching. Pemphigoid is totally the opposite. Pemphigoid does itch and that is part of the disease process. In that case you need to treat the itch as part of the disease until proven otherwise. So treating the itch in pemphigoid, one good way to do it is try to avoid high dose prednisone, you can use high dose prednisone but you want to try and avoid it if you can. One way to avoid using high dose prednisone is strong topical steroid. Again the same Pascal Joly, he did a study in France with pemphigoid patients and found that if you use total body clobetasol or a widespread application of strong topical steroids which is clobetasol on large areas of the skin this is just as effective as say 60 milligrams a day of prednisone. You get a little systemic absorption from topical steroids but not so much as using the oral steroids. It's about half the side effects so especially in bullous pemphigoid patients a lot of them are elderly so you want to be careful about side effects and comorbidities and immune suppressing them too much because they might get an infection. So the topical steroids can be quite useful. I recommend one way to treat the itching is to maybe rely a little more on the topical steroids and to use them aggressively.

Becky: Great, thank you.

Dr. Marinkovich: Sorry, and that would be with pemphigoid only. I don't feel that topical steroids work that well in pemphigus. So specifically in pemphigoid that is where topical steroids will be helpful. Sorry Becky, I didn't mean to interrupt.

Becky: No, that is fine. All the information we can get only helps our community. Venus says that in the past she mostly in her mouth but now she is getting them on her labia minora. Would you recommend a Fluocinonide ointment? She is wondering if her pemphigus will ever go away?

Dr. Marinkovich: Like I said I am a big advocate of topical steroids in pemphigoid but unfortunately in pemphigus they don't work so great. They may help a little bit, they are equivalent to Dapsone they are a weak agent you can use on the disease, if you substitute for 10 milligrams of prednisone or less. So I wouldn't consider topical steroids, I mean if topical steroids work then great then that means that the disease is really mild but if they don't work, I think it is okay to try them in the labia but if they don't work then you maybe you have to use something systemic.

Becky: Okay, Christine says after almost two years I finally received the diagnosis of pemphigus vulgaris. I want to try the rituxan. I am 58 years old and when I was 19 I was diagnosed with hepatitis B. She doesn't remember how it was treated and she hasn't had any issues since then. She is also a type two diabetic for almost 20 year but she is very compliant i gets her a1c tested every three months and her liver is tested, and there no problems. Her doctor wants me to receive the hepatitis B vaccines which will take over six months to get all three. Her most recent labs for hepatitis B are hep B core an is reactive, her hep B core antibody is non reactive and her hep B surface antibody is borderline She wants to know if you think the hep B vaccine is necessary and would it help her not to get hep B while doing the rituxan infusions?

Dr. Marinkovich: They want her to get treatment for the hep B before?

Becky: They want her to get the vaccine series, correct, before she gets the Rituxan.

Dr. Marinkovich: But she already has a history of hep B infection.

Becky: Yes

Dr. Marinkovich: She has a chronic hep B infection, okay. But I thought the vaccinations are supposed to prevent the infection. Does she already have an infection?

Becky: Yes, she says she was diagnosed about 30 years ago with hep B.

Dr. Marinkovich: Okay, well I would infere to either the infectious disease doctor or the liver doctor on their recommendations with how to treat the hepatitis. And whether she could be a

candidate for the Rituximab, just like I was saying before the dermatologists need to have good communications with these outside non-skin specialists in caring for the patient. So I think the dermatologist treating the patient needs to have a nice one-to-one conversation with the person who is treating the hepatitis and then be able to decide whether the Rituximab can be used. I have done this before with other specialists and I believe by monitoring the serology carefully and being able to follow it closely with the PCR results and at the same time using an antiviral agent for easily infectious diseases the hepatologists recommendation that you can cautiously use Rituximab. But I think it requires really good communication between the different specialists with the dermatologist.

Becky: Great, thank you. There are some questions that are together and maybe you can discuss the pros and the cons of using Rituxan and how it compares to using other treatments and give a brief of what it is usually given or a dosed out and how does the medicine get into the patient?

Dr. Marinkovich: So you are talking about Rituximab? Well there are a couple of different ways to use it, there are 2 standard ways. One is the oncology way and one is the rheumatology way. So the oncology way, you have to measure the body surface area and then you give 375 milligrams per 1 unit of body surface area each week, for 4 consecutive weeks. So the patient has to come in 4 times for the infusion. The rheumatology method is a lot simpler and easier on the patient. You just get 1,000 milligrams and you give 2 doses, spaced 2 weeks apart. So the patient only has to come in 2 visits for 1,000 milligrams and then 2 weeks later for another 1,000 milligrams. So I like the rheumatology method because it is easier and it is actually less expensive too taking into account how expensive it is for these infusion centers. If I was administering I would give the 2 doses but sometimes dermatologists have to work with outside providers either the insurance company says, "You can't do it at your institution you have to go to another place" or the patient lives far away and the only person in town is an oncologist. So if an oncologist is the person that ends up administering the Rituximab I think it is better to have the patient have the person who is administering the drug use the method that the specialist feels most comfortable with. Either the 4 visits the oncology, or the 2 visits the rheumatology, you are still going to get the same results. The results are going to be equivalent that has been shown be clinical trials. But the convenience is a little easier with the rheumatology method but if your provider is more comfortable with the 4 visits then you have to go along with what your provider wants.

Becky: Great, thank you. Wendy asks a question. She is newly diagnosed with Bullous Pemphigoid and is concerned about long term use of steroids. Could you advise on taking prednisone and doxycycline?

Dr. Marinkovich: Yeah, I think that doxycycline is great. It has an anti inflammatory activity on the skin and it is far far less toxic than the prednisone. I am very much in favor of using doxycycline. One of the drawbacks though is that it is weak. Doxycycline is only going to at best would be the equivalent of 5-8 milligrams a day of prednisone. So if you are having a major

flare, doxycycline is not going to arrest your flare, you need prednisone. But the goal is as you are tapering the prednisone down use all the tricks you can to get the prednisone down, use the Rituximab use IVIG, use the topical steroids, use the steroid-sparing agents like the mycophenolate acid and keep pushing down to low levels. And then at that point then maybe you can use doxycycline as the way to get you off that last amount of prednisone. Or maybe even before you get to that level, when you are still on that higher dose of prednisone you can use the doxycycline as a way to reduce the prednisone a little bit. So it's a weak medicine, it doesn't work for pemphigus by the way. Although a lot of people use doxycycline for pemphigus it doesn't work in the same way as it does for pemphigoid. For pemphigoid it does work but it is weak. But it definitely is a good thing to use because it is less toxic than prednisone. It is especially effective when your disease is a little bit more under control. The goal is when you are trying to get the patient off systemic medicine to get them on to doxycycline and topical steroids. In addition there is another anti inflammatory medicine called niacinamide and it is a vitamin. It is vitamin B-6 and it also has an anti inflammatory action on the skin and it works very nicely with doxycycline. It is like the dynamic duo, Batman and Robin, and they work well together. So if you are going to use doxycycline it makes sense to also use niacinamide. There is another oral anti inflammatory agent of the skin that I also like to use is curcumin and the active in the indian spice turmeric. So if you really want to maximize your less toxic anti inflammatory agents in addition to doxycycline and niacinamide you can also try curcumin. Niacinamide is really cheap. You can get it for like \$10 a month on Amazon but curcumin is going to cost you around \$30 a month or so. You can get it a places like Whole Foods and I like to use 3 grams a day of the curcumin. But if you get the niacinamide and the curcumin, it helps and it is over the counter. But the doxycycline is a prescription. So sorry about the long answer but I just want to let you know that doxycycline does work for pemphigoid but it is weak so you have to realize that it is limited in its activity. And it works good with these other anti inflammatories and topical steroids.

Becky: Great. The next question comes from Sally and she asks, "Is it typical for patients with mucosal pemphigoid to develop skin lesions as well?" She is also wondering if she can build up a tolerance for steroids like prednisone?

Dr. Marinkovich: Yeah, sometimes pemphigoid can just be mucus membrane, we call it mucous membrane pemphigoid or cicatricial pemphigoid. Very often you can get both skin and mouth lesions. Like in bullous pemphigoid maybe about 20-30 percent of patients can get some lesions in their mouth and it is usually less problematic in the skin. But on the other hand, patients with cicatricial pemphigoid or mucous membrane pemphigoid, they can sometimes get skin lesions. So they do overlap and the therapy for the skin is the same therapy for the mouth basically.

Becky: Okay, Lori is asking, "Is there a problem with being in the sun with sunscreen for somebody who is having an outbreak or even in remission?"

Dr. Marinkovich: Well when you are talking to a dermatologist about sunscreen and being in the sun we have been trained ever since we were an intern that the sun is going to damage your

skin, especially when you have a light colored skin, a type 1 or type 2 skin, if you burn easily from the sun. It is going to cause skin cancer and it is going to cause aging too. Like for example, have you ever gone to the gym and you see someone like an old person or for me I see some old guys there in the shower or the dressing room and I look at their face and it's all wrinkled. But their areas that don't get a lot of sun, like their buttock or other areas, like if they wear a shirt all of their life and I look at their chest and back, it looks pretty good. It is the areas that get a lot of exposure to the sun get a lot of photoaging. The sun is really destructive in going that in lightly colored skin. Also skin cancer, you hear a lot about melanoma, squamous cell carcinoma, and basal cell carcinoma. The sun is just going to, it is not going to do it immediately, but it is going to catch up with you over years and years of exposure. So for that reason alone, it is really good to, you don't have to be a hermit you can go out and enjoy your outdoor activities but protect yourself. Wear a hat, wear protective clothing, wear sunscreen. As far as whether it exacerbates autoimmune bullous disease, there is really no good evidence that it is going to do that. But if you get a bad sunburn it is possible that can precipitate a flare in pemphigoid and pemphigus. But there are lots of good reasons to protect yourself from the sun. A lot of people try to make the argument, well if I use the sunscreen it is going to prevent my vitamin D absorption and isn't that bad? Well, if you want you can use sunscreen and protect yourself from the sun and then get a vitamin D level. If your vitamin D level is low just take some vitamin D supplements, they are not expensive. So it is not an excuse not to use sunscreen. I don't mean to sound so opinionated but that is my view on the subject.

Becky: Great, thank you. Rodger says that he has pemphigus foliaceus. He completed a series of IVIG followed by a four week treatment of Rituxan about 3-4 months ago and he has been blessed with no symptoms other than an occasional episode that lasts for a day or so with little damage. He currently is taking no medications. Even though I appear to be in remission, should he be seeking some kind of booster in the near future like a one time treatment of Rituxan?

Dr. Marinkovich: No, I am not a big advocate of preventative therapy. I think that all the different therapies we use have different degrees of toxicity and if you are lucky enough to get off all medicine and be in remission I think that is great. I would not try to have some sort of preventative maintenance dose or some kind of Rituximab to prevent some theoretical future flare. I would just wait and be vigilant to see whether you are getting any disease activity and if you are, be in good communication with your doctor. Don't let it get out of hand if it starts to creep back. But I would say that the name of the game is to use the least amount of the these medicines as possible, least amount of prednisone or Rituximab or immunosuppressive agents. They all have cumulative toxicity so if you can get away with not using them and you have no disease there is no reason to use them.

Becky: Great, thank you. Sandy says, "Rituxan was recently approved by FDA for treatment of Pemphigus. How effective is Rituxan for remission? What are the potential side effects, what are the most common side effects?"

Dr. Marinkovich: It is approved from pemphigus but us dermatologists or disease specialists, we are very open to using off-label, non-indicated uses of different medicines. Given before the approval, Rituximab is a standard medical care for patients with pemphigus but with the approval it just makes it a little bit easier to battle with the insurance companies. Now, there is no excuse not to use it if you need it. Basically you have to start with using a steroid-sparing agent with prednisone first and give that a first try. But if that doesn't work than Rituximab would be the treatment of choice if there are no contraindications. It is possible with the results from the treatment in France with that *Lancet* article that I mentioned earlier that Rituxan may evolve into being used as a first time agent along with prednisone. But despite that, it is not like a super safe medicine like doxycycline. You have to be careful with the Rituximab and you have to talk to patients about the possible side effects and you have to look to see if patients, for example the hepatitis discussion earlier. If a patient has a chronic infection you have to be careful about reactivating it. The main thing that I tell patients when I am discussing the side effects of Rituximab, number 1 is the infection. If you are going to be taking Rituximab you want to take a preventative medicine to prevent certain forms of pneumonia like Pneumocystis pneumonia also called PCP pneumonia. For most people just a simple antibiotic pill, Bactrim, 2 times a week is sufficient to prevent that. Even though you are preventing that pneumonia you still you are still susceptible to other infections. It could be anything, it could be urinary tract, cough, sore throat. I usually tell patients, take your temperature once a day and if your temperature get elevated or if you get a cough or sore throat or urinary symptom. You want to tell your primary care doctor if you can before you start the Rituximab that you are going to be getting the Rituximab. By the way it you get a sore throat or a cough or urinary tract infection if you aren't taking the Rituximab, wait a few days before calling the doctor and see if it goes away. Versus if you took the Rituximab you want to not wait a couple of days if you notice these symptoms, just talk to your doctor right away. The response from your doctor will probably be that they will be more ready to prescribe antibiotics and that is a way to try and prevent a bacterial infection. So that is the main precaution I give as far as infections, is just be vigilant and have good communications with your primary care doctor. Most people if they follow that advice they will do well. It is okay to travel but you don't want to travel to really remote locations, like Nepal or backpacking through the Himalayas. You want to go to a place where you know where the major medical center is and write the address down beforehand. Do a little research, check out if you are going to go to some city, check out where the address is of the major medical centers and where they are so just in case you get a fever or something like that you can go in and get it taken care of. So all of these precautions you just want to do it. You only have to follow these precautions for about 6 months after you get the Rituximab. After that your immune system will have recovered and you can consider that you don't have that same immunosuppression problem. So those are the main cautions that I give to patients that are taking Rituximab. There is a theoretical list but if you constantly suppress the immune system over long periods of time you could actually promote the cancers such as lymphoma and things like that. It has been proven for other immunosuppressants medicines. It is not known for sure for Rituximab because we have not used it long enough but there is a theoretical possibility that you could have a slightly increased chance at some kind of a cancer over time.

Becky: Great thank you. Are you aware of any studies that corroborate the idea of an implant in the body such as a mesh can trigger an autoimmune disease such as pemphigus or pemphigoid?

Dr. Marinkovich: No, I am not aware of that. Again, we don't know everything in medicine so I can't say that it can't happen but I am not aware of that being a well recognized cause of pemphigus. For the most part we don't know what does cause pemphigus. It is what we call idiopathic it means that we just don't know what is the cause. And this is a major challenge in the field of medicine right now, autoimmune diseases. That is a major research question right now, we are still trying to figure out what is causing autoimmune disease and so some people are looking at genetics, like Ani Sinha at the University of Buffalo. Looking at genetics we know that sometimes pemphigus can run in the family. There is a group of patients in Brazil they have what is known as endemic pemphigus where everyone that lives in that area has a higher risk of getting pemphigus. It is thought that there is a black fly that lives in that area that there is a protein in the fly that is thought to have an antibody response that cross-reacts with pemphigus and the desmoglein. So that Brazilian population they are having, what looks like an environmental they call molecular mimicry cause of pemphigus. And there is the situation with pemphigus running in certain families like Ashkenazi, eastern European Jewish populations are the best example of a genetic predisposition. People who are studying autoimmunity are looking at both of these things, the environment versus the genes as the cause. The foreign body reaction would fall more into the environment but still I am not aware of a foreign body being a major area of focus or a major precipitator of autoimmune disease right now. But who is to say that somebody might come up with new findings in the future.

Becky: Great, one last question. Karen says her 89 year old father was recently diagnosed with Bullous Pemphigoid. He is in pretty good health but has been on Warfarin and Amiodarone for afib. He was conservatively treated with 40 mg of steroids but the symptoms remained until he was placed on a decreasing dose beginning with 70 mg per day. This is expected to taper off in a month. She has got him home care to check his blood pressure and he is regularly having repeat INRs. The dermatologist has indicated that they can not tell us what the progression will be because he has only had one flare-up. Is there anything that we should be considering to help with the goal of keeping his skin free of these blisters and how long can he safely take steroids, since this dose seems to have helped dry up the skin and relieve all the itching and swelling.

Dr. Marinkovich: So this is pemphigoid?

Becky: Yes.

Dr. Marinkovich: So in the question it was suggested that he was on 70 milligrams of prednisone but they were going to taper it off. I would say don't taper it that fast if you can help it because tapering it that fast is going to cause him to rebound and come back. I mean the patient will do well and then you will get him off prednisone but then a week later there is a chance that the

disease can just come roaring back and be just as bad as it was and then he would have to go back up on the prednisone again. So the best way to ensure that the disease won't come back is to be more slow in the prednisone taper. It sounds paradoxical, tapering it more slowly is actually going to result in a lower long term use of prednisone than tapering it fast. A lot of people who I see are referred to from another dermatologist, they say this patient has pemphigoid or pemphigus, it is out of control. And then I find out that they are getting tapered way too fast. So what happens is they get tapered fast, the disease comes roaring back then they go back up on high dose steroids and then the disease goes down and then when they taper fast the disease goes back up and it is sort of like this roller coaster ride they are on. Once you stabilize the prednisone and tapering it more slowly than the disease activity settles down. So having a more stable, slow but steady taper of prednisone is a better way to go is the first pointer. The second pointer is using the appropriate additional medicine to be able to help reduce the total amount of prednisone. Topical steroids like I mentioned before, topical steroids is something that should be used even when the disease is still severe. And using topical steroids aggressively over large body areas might be a good way to reduce the total amount of steroids. For an 85 year old with the heart conditions and all the other stuff you want to be careful about using all the systemic immunosuppressive agents so I would hold off on things like Rituximab, try to avoid using the Cellcept and other immunosuppressive agents if you can get away with it. But you might need to use a little bit of Cellcept or methotrexate or something along those lines in order to help get the prednisone dose down. I like to use IVIG in elderly, kind of frail patients with BP. I think it is helpful and the nice part of the IVIG is, we didn't talk about it very much, but it doesn't immuno suppress the patient. So the side effect profile is pretty low with IVIG. One problem though with this case is heart disease and if there has been heart failure the extra fluid from the IVIG can exacerbate the heart failure. So that would be potentially an issue. I would say try and lean more on the milder, less toxic medicines in order to get the prednisone down. Taper the prednisone more slowly because of the rebound and then use some of the milder agents like the topical steroids. Do the IVIG only if the cardiologist is okay with it. Then also using doxycycline, niacinamide and curcumin as well. They are not going to add a ton but every little bit helps to this combined therapy. So that is what I would do in that kind of situation. A slow tapering of prednisone and those other mild agents.

Becky: Well Dr. Marinkovich that was a very quick hour. In closing I just want to thank you so much for being on the call with us today! You have provided a lot of great information and it was extremely educational having you on our call.

Dr. Marinkovich: I was glad I was able to try and help. I am sorry if some of my answers went kind of long. I wanted to try and be as helpful as I could.

Becky: Oh we certainly appreciate it. And I would like to thank all of our listeners for being on the call today as well. I also wanted to let everybody know that the IPPF has kick-off our third quarter fundraising. Funds raised this quarter are used to support Patient Services such as this call today. Other patient services include our Peer Health Coach Program and Local and Regional Support groups. Please consider visiting our website today to make a tax-free

donation to support the valuable programs and assistance the IPPF provides to pemphigus and pemphigoid patients.

Becky: As a reminder, the IPPF Annual Patient Meeting is right around the corner! 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 hope to see you there! This year we will also be having an extra field trip. With your conference registration 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 all attendees. Our next webinar is scheduled for August 29th to discuss Prednisone and its side effects, with Dr. Ron Feldman, Director of the Autoimmune Blistering Disease Clinic and Assistant Professor at Emory University. Registration will open shortly for this call. Also 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. Lastly, we got a lot of questions and I know we did not get to answer them all. If you have a question that didn't get answered on the call, or have additional questions related to the call today, 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 for being on our call today!

Dr. Marinkovich: Thanks.

Becky: Bye.

