

January 31, 2022 Patient Education Webinar- “Ask The Experts- A Q&A with Dermatology and Dentistry”

Becky: Hello everyone. Welcome and thank you for joining us tonight on our Patient Education Webinar, “Ask the Experts a question and answer with Dermatology and Dentistry.” This call is now being recorded. I'd like to thank you for being on the call with us and a big thank you to our sponsors, Genentech, argenx, and Cabaletta Bio for making today's call possible. “Information is a key factor in being able to treat and live with any condition, however, everyone's situation is unique. The IPPF reminds you that any information found on the internet or during tonight's presentation should be discussed with your own doctor or health care team to determine if it applies to your specific situation.” Before we begin, I would like to take a quick poll and we'll be launching that now. We want to know, who was the first person or doctor that you saw when you started having symptoms? While you answer that, let me introduce you to our guest speakers for today's webinar.

Becky: Dr. Neil Korman, is a Professor of Dermatology at Case Western Reserve University in Cleveland, Ohio. He is also the director of the Dermatology Clinical Trials Unit in the Department of Dermatology at University Hospitals of Cleveland. In addition, he serves as the clinical director of the Murdough Family Center for Psoriasis, a comprehensive psoriasis research, education, and treatment program. Dr. Korman holds subspecialty board certification in dermatological immunology/diagnostic and laboratory immunology. He is a member of the American Dermatologic Association, the Psoriasis Expert Resource Group of the American Academy of Dermatology, an Emeritus Member of the Medical Advisory Board of the National Psoriasis Foundation and is an Emeritus member of the International Pemphigus and Pemphigoid Foundation Medical Board. Dr. Korman is the founding Director of the Regional Center for Immunobullous Diseases.

Becky: Dr. Aimee Payne is a Professor of Dermatology and Director of the Penn Clinical Autoimmunity Center of Excellence at the University of Pennsylvania in Philadelphia. Dr. Payne's clinical practice specializes in the diagnosis and treatment of patients with autoimmune blistering diseases.

Becky: Dr. Said-Al-Naief is currently a Professor of Oral and Maxillofacial Pathology at the Department of Integrated Biomedical and Diagnostic Sciences at OHSU, School of Dentistry and School of Medicine and most recently served as a Professor & Chair,

Department of Pathology and Radiology at OHSU and as a director of the maxillofacial diagnostic pathology laboratory. He received several awards in his field, has been also invited to present numerous lectures, seminars, and continuing education courses nationally and internationally. He did and continues to actively participate in a wide range of basic and translational research related to head and neck pathology.

Becky: Quickly, I'd just like to share the poll results. It looks like a lot of us went to oral medicine, dermatology, and then our primary care physicians. Some even went to ENT. So thank you for answering that poll. Now, before we begin, I'd like to go over some housekeeping items... (Reviews Housekeeping slides).

Becky: Now, it is my pleasure to introduce Dr. Korman, Dr. Payne, and Dr. Said-Al-Naief to answer your questions about pemphigus and pemphigoid and dermatology and oral and dentistry. Welcome, Thank you for joining us on the call.

Dr. Payne: Dr. Korman, Dr. Said-Al-Naief and I had the pleasure of receiving some of the pre questions that came in before the seminar started. We organized them into a few topics. So this is basically how your questions clustered and we're going to try to address as many as we can here on the call today. So if we go forward to the next slide.

Dr. Payne: A lot of the questions that came in surrounded diagnosis and disease associations and one of the biggest clusters of questions dealt with disease triggers. For example, what triggers pemphigus? Can an inoculation later in life trigger it if I didn't have it for the first 60 years of my life? Eileen also asks, can bullous pemphigoid be triggered by a prescription medication or radiation after breast surgery? Janice was wondering whether or not MMP can be drug induced? Linda was asking whether or not there were associations with Parkinson's disease? Dorothy was asking about associations with primary sclerosing cholangitis of the liver or Niacinamide? Ultimately, there's never been a systematic cause and effect, for example, where this drug always causes bullous pemphigoid or this particular condition always causes pemphigus. But in response to some of these questions, neurologic disease is one of the strongest associations with bullous pemphigoid. So for example, Parkinson's, stroke, Alzheimer's, Dementia there is actually a very strong association with bullous pemphigoid. The neurologic disease can either appear before the bullous pemphigoid or shortly thereafter. There's some hypotheses that the bullous pemphigoid antigens are expressed in your brain so that if there is some kind of neurologic issue in your brain and your immune system is basically noticing that something's wrong there, that it

might make a mistake and start attacking that protein ultimately in your skin. In general, there has been a good amount of research in pemphigus showing that you can generate cross-reactive antibodies to a whole host of borne pathogens. So for example, there was a study done on endemic pemphigus foliaceus in Brazil where they noticed that the incidence of leishmaniasis was actually higher in this particular area of Brazil and they did studies in mice where they showed that if you inoculated mice with leishmaniasis, they tended to make antibodies against leishmaniasis and some of those antibodies actually cross-reacted with desmoglein 1 which is what the antigen that's targeted in pemphigus foliaceus. So in that particular model, the idea is that your body's infected with leishmaniasis, it does the appropriate thing and tries to fight it off but in a subset of people, you may make an unfortunate mistake and some of those antibodies start cross-reacting with a protein in your skin and then triggers pemphigus. But clearly leishmaniasis is not the cause of pemphigus in the vast majority of pemphigus patients. The general idea is that with both pemphigus and pemphigoid, it's just an unfortunate mistake that your immune system makes in the process of trying to do something good for your body. In general, every single day we're inhaling, eating, coming into contact with a whole variety of foreign pathogens and any one of these triggers can potentially cause autoimmunity. So, this is sort of a general theory of why autoimmune disease occurs. I'll pass it off to Dr. Korman.

Dr. Korman: One other point I would add to Dr. Payne's statement about autoimmunity is just that autoimmunity is more common as people get older and we know that pemphigoid is a disease of the elderly. Pemphigus may be a little more middle aged. I think everything you said Dr. Payne is totally on target. I'm not sure that it always answers everybody's questions, because I think they're very specific questions. Really the best short answer is, we don't know. Why did you get this? Because you're special, that's why you got it. One statement that I make to my patients a lot when patients ask me why, I said, I don't do why, I do what? Patients want to know did this happen and I say doctors are not often good enough in why but we're pretty good at what. What is it and what are we going to do about it and how are we going to take care of it? So, I think that's an important way to try to think about your condition. The last question about Maureen, she was diagnosed with MMP and then she had a biopsy and the dermatologist said it was BP. So the pemphigoid, pemphigoid not otherwise specified is what I would say. Generally speaking I think that most of us would agree that bullous pemphigoid is a disease primarily involving skin and not involving mucous membranes and that mucous membrane pemphigoid is the exact inverse. There's obviously other subtleties, but that's the simplest way to look at it. I think a lot of times, it's not critical to give a name, and to separate a name and sometimes the answer is when I'm a little confused and somebody has a little more skin disease than I would have expected with

MMP or a little more oral or other mucosal disease with BP, I will say you have pemphigoid and often, that will allow us to go forward with an approach, in terms of taking care of them. Why don't we jump to the next slide, please?

Becky: Thank you. Before we go to the next slide, do you mind if we do a poll question real quick?

Dr. Korman: Sure. Go for it.

Becky: This one wants to know, since we asked who you came to first. Now, we want to know which doctor, which specialty diagnosed your pemphigus or pemphigoid? If you could just take a couple seconds and answer the question. I think the answers that you guys gave were phenomenal. I think as a patient, we always want to know why but I think Dr. Korman you're spot on that we need to focus on not necessarily why but what we're going to do about it. So thank you for bringing that point up.

Dr. Payne: While we're waiting for some of the poll results, there are some medications that are more strongly associated with bullous pemphigoid and diabetes are the gliptin class of diabetes medications. There is a reasonably strong association with bullous pemphigoid if you're on a gliptin medication, it ends in gliptin. It's reasonable to actually stop that medication, switch to another bullous pemphigoid medications and see if that helps. That's just one example but there's also plenty of examples where individuals who have had a drug induced form of bullous pemphigoid or mucous membrane pemphigoid may stop the medication and the disease doesn't get better. Some people say it's kind of like closing the barn door after the horse has gotten out. It's just too late and even though you've stopped it, it won't actually reverse the disease process. To go back to Dorothy's question, to my knowledge Niacinamide does not cause the disease, if anything it treats it.

Becky: Great. We're going to show the results now of our poll and it looks like your two specialties lead the pack, dermatology at 63% and oral medicine at 35%. So thank you everybody for participating in the poll, we'll go back to answering the questions now. So Dr. Said-Al-Naief it looks like we're going to put you on the spot now. A whole bunch of questions came in prior to the webinar about oral care, if you do want to start answering some of these questions?

Dr. Said-Al-Naief: Sure. The first question is, if pemphigus vulgaris in the mouth is left untreated, will it get worse? Pemphigus affects the mouth at different rates. It could be severe, it could be mild. In general, eventually you will be having difficulty eating. The general functions including speaking or swallowing will be affected, depending if the throat is involved or not. So, I would say at least you should get a diagnosis first, confirm it's pemphigus or another vesicular bullous disease and then have a mild treatment just to make sure the tissue is stable. Tissue breaks down gradually with pemphigus if it's not treated, so it can get worse, yes, again, depending on the severity. The second question is, when should I seek an oral specialist? Immediately, at the same time. Not only an oral specialist, this covers another question that I read as far as team approach to the diagnosis. When I have a pemphigus patient or a pemphigoid patient, I will immediately involve an OBGYN, I will involve an ophthalmologist for the eye to make sure there are no eye lesions with pemphigoid and treat it immediately. Also depending on how difficult it is swallowing and if the trachea is involved I'll go to a pulmonologist. Whether it's a rheumatologist or a dermatologist, all of this is an important team from the beginning just to prevent exacerbation of disease manifestations as they come through. So immediate involvement of all the care team is important. The third question is, Rob says, my pemphigus vulgaris has been in remission for about a year and he had Rituxan this month. Is it safe to get a graft? It is safe as long as the disease is controlled. Actually, the best time to get extractions, deep cleanings around the teeth and deeper in the gingival junction going down to the roots, extractions, grafts, even implants, the best time is when you have a controlled disease, either with high dose steroid or Rituximab. Not when the disease is exacerbated, that's not the time to do it. There are mixed reports and feelings about how steady and how good these are long term whether they be grafts or implants. As long as you have good bacterial care and control, you don't want to have epithelial breakdown, you don't want to have bacteria accumulation, you don't want to have dental disease because eventually those can lead to bone loss and bone loss will lead to tooth loss and infection. And that's all against the control of the disease of the pemphigus and pemphigoid. As long as you're in control and in good shape as far as your mouth, the tissues are not breaking down, not sloughing, you can do the procedures. There are again, mixed feelings and mixed reports about long term success. In general it's in the 40th percentile or so.

Becky: You're doing great, but I just have one question. Once the disease gets under control, while the disease is active and a patient is experiencing gum recession, will the gums recover after the disease gets under control?

Dr. Said-Al-Naief: They can, not fully optimum. As long as you are controlling disease with the medications, you can have the recession stop. A periodontist is very important in the management of oral vesicular disease. You will have a very strict regimen on the oral hygiene index, with chlorhexidine in addition to maintain the bacterial levels to the lowest. We will maintain the gingival level to the maximum to prevent bone loss. So yes, they can recover again, depending on how controlled that disease is and what do you use to control it? And at what cost, how high are the steroid doses? You want to move off higher doses of steroids and replace them with other medications that are steroids sparing. So that all of this is really a case by case success level. But in general, yes, you can. Great question. Thank you.

Dr. Said-Al-Naief: Felix asked, what are the topical treatments for tongue, lip and gum lesions? It depends on how widespread these are. If you have 1 lesion, 1 blister, let's say on the tongue or floor of the mouth or the lower parts of the gingiva, I usually use topical steroids, either Temovate or lidex gel. These are potent steroids but they're localized so you don't have to go all over the mouth with rinses. Otherwise you can use the Clobetasol or decadron rinse and that's a steroid rinse. When you use an oral rinse you are going to shift the oral flora and there is a potential for having Candida yeast in their mouth. That is one question that also came up lower in our list, what damage can an oral steroid rinse do? It's really not a damage, but that's part of the treatment. If I treat with steroids, I'm going to shift the flora, good and bad flora. The steroid rinses make the yeast flourish and if this shows up, we'll treat with a slight acidity in the decadron rinse, benzoic acid. The benzoic acid is not as damaging to the teeth as people make it sound but you have to be diligent in the rinse and taking care of your mouth afterwards. But the decadron is not as harmful, except for the potential of having Candidiasis in the mouth appearing as it changes the flora. Vince asked, what are the options and potential risk of triggering a flare with a tooth extraction? Anytime there's trauma, anytime there's deep cleaning, there's always a chance of a flare up of pemphigus or pemphigoid. And that's why the recommendation is to do the procedures, deep cleanings, extractions, periodontal surgery, grafts, during the period of control, especially in pemphigus where the patient has had Rituximab or high dose steroids, not when you start weaning the patient down. When the patient is controlled, that's when there is the best chance of doing all these dental procedures to make sure that you don't have sloughing and the separation of the tissue, which is really painful, not only painful, but it's really harmful to the overall periodontal bone and tooth loss. A lot of tooth loss occurs as a result of negligence of the gingiva because you cannot brush, it's painful. So you just leave it alone and then you end up losing your teeth as one of the patients here mentioned she preferred to extract all her teeth due to pain. There's another question about Dexamethasone rinse and mood swings. Tacrolimus is it better

from that aspect? Yes. Decadron causes mood swings because steroids can cause emotional changes and that is known. Tacrolimus is a great medication and it does not cause mood swings but Tacrolimus is also a stronger medication than just a topical steroid. By the way, depending on the severity of the disease, I never treat my patients with a solution that they swallow. I usually tell them to swish and expectorate, which means they swish and then they throw the Decadron out, not swallow it. There are periods when the diseases severe, especially when there is skin involvement at the same time, then you do swallow for a certain period during the treatment, but the more you swallow the steroids, the more chance of adrenal suppression and the lungs and immune suppression and the side effects that come from it as far as mood swings and moon face and other side effects. Joyce asked about the difficulty in removing all her teeth because it was painful and decided to extract her teeth. Implants are a choice, I know it's a costly choice as you mentioned over the dentures. They are a better choice over the dentures because dentures rub the gingiva, the floor mouth or the vestibules close to the floor of the mouth which leads to sloughing in an uncontrolled patient. If at all possible, if you even do one implant on each side of the canine area which is here in the corner, you can stabilize a good denture on an implant which is totally stable to eating and will function and you only have 2 implants instead of all-over implants. These implants, you can hook prosthetics to them and they're really very stable prostheses for eating, function, et cetera. So if it's all possible, try to explore that option. Otherwise, for dentures you have to maintain a really, really good control of the disease because they will rub the tissue and they will slough the tissues. And if I missed anything or any points, please let me know I tried to do them as fast as I can.

Becky: Thank you if we can move on to the next slide.

Dr. Korman: So I'm going to take these. Liz has mucous membrane pemphigoid, not involving her eyes, and she had an intraocular lens inserted for cataracts, and then she had inflammation and eye pain. She's now having another cataract removed. The question is, what should she do? Should she have pre-op medication to decrease inflammation? First of all, I'm glad she doesn't have ocular involvement of her mucus membrane pemphigoid but is she seeing an ophthalmologist who has experience with that? It's very, very important with all of these diseases. These are rare diseases and Dr. Said-Al-Naief mentioned the need for multiple specialists, but they have to be ones that can actually pronounce these diseases and have actually heard of them and seen them. And there are not that many specialists in other fields that have so I do want to address that because many patients, Dr. Said-Al-Naief don't even have oral medicine specialists in their city who knows anything about these diseases. I'm in Cleveland and

I'm lucky that I have a colleague who was very, very involved in this. I'm sure Dr. Payne has colleagues in Philadelphia that do, and I know that you are that colleague in Portland. It's important but lots of people don't have those opportunities. So back to this question. Yes, if there's ocular inflammation, maybe the pre-op medication would be indicated, but I would be that would be a discussion between myself and the treating ophthalmologist who knows something about this disease and knows enough to be able to make a recommendation and any other recommendations would come from that ophthalmologist or from the ophthalmologist and I as a team. A lot of times neither of us know the answer for sure but we both take a stab at it and say: here's probably what seems to be the best answer but we're not sure. And that kind of holds for The next question: How is pemphigus in the rectal area treated? Well, the good news is that pemphigus in the rectal area is very uncommon. The most common place of pemphigus is in the oral mucous membranes but certainly this person mentioned the nose. I see a fair amount of nasal disease as well with pemphigus. Those are probably the two most common areas but in theory, any of the mucous membranes can be involved in either pemphigus or pemphigoid. The answer is you treat the pemphigus the way you would treat it with aggressive treatment. If it's pemphigus vulgaris which is undoubtedly going to be or maybe pemphigus vegetans, a super rare variant, it's going to be treated with Rituximab. That's the drug treatment of choice in the year 2022. It's very challenging if that's a stubborn site, there is nothing magical. I would get involved with a colorectal. I would get them involved and have them help me see what tricks they might have to to manage such a person. Again, these are the systemic diseases, they need to be treated systemically an awful lot of the time. And so, rectal pemphigus that was stubborn, I would be thinking about stepping up my systemic therapy. Maybe my colleagues in colorectal surgery might have some tricks up their sleeves for what else to do for topical approaches that might be of value. I'm ready for the next slide?

Dr. Korman: Derek wants to know if it's possible to get paraneoplastic pemphigus into remission and what can we do to prevent flare ups? So paraneoplastic pemphigus, thankfully, is a very rare variant of pemphigus vulgaris I would say, where patients get this very, very difficult disease in association with cancers typically. The large majority of the cases are with cancers. Times that the disease can go into remission or even get cured is when the patient has a benign disease. There are a couple of benign conditions where, for example, thymomas. If the patient has a resectable, meaning a type of thymoma that can be surgically removed, we can get paraneoplastic pemphigus into remission. We just had a case just recently, but unfortunately the thymoma was not resectable, it couldn't be cut out, and actually the patient died from complications of immunosuppression and treatment of their paraneoplastic pemphigus. So it's a very, very tough disease to treat. How do you prevent flare ups? The same story over and

over again, a good systemic approach. Rituximab and steroids are often used. There are patients that sometimes need Rituximab and other immunosuppressive agents at the same time, which we don't love to do, especially right now in the midst of the COVID crisis which will come to. There are a lot of questions about COVID if only we can all talk really fast, and get there. Rejeev wants to know, how long do you take these immunosuppressive medicines? So what I do is, let's talk about a patient who has pemphigus vulgaris and when treating them, right away I make a diagnosis and I put them on prednisone when I see them and I suspect it's pemphigus vulgaris because they are miserable and they have bad disease. Then when I prove that they have a positive ELISA for desmoglein then I do a direct immunofluorescence biopsy and a positive ELISA, I can go to insurance and try to get Rituximab approved and get them on Rituximab and try to taper them off prednisone relatively quickly. Then they're getting a course of Rituximab, everybody has different opinions whether to give Rituximab continuously or on an every six month basis or on an every year basis. There's lots of different approaches and opinions about this but if they're on Rituximab and you're able to successfully taper them off prednisone, which I'm able to do with a lot of patients, I would say we might actually have somebody that's in remission. Clinical remission means no disease, then immunologic remission which is another step up means no antibodies. No antibodies in their blood. They don't have antibodies that are directed against desmoglein anymore and even no antibodies in their tissue. So, those would be the different levels of remission. That's when you are going to take away immunosuppressive medicines, is when the patient is fully in remission. If they were not on Rituximab and they have pemphigoid and you weren't using Rituximab you were using prednisone and Cellcept or mycophenolate mofetil, we would taper the prednisone all the way down and then we slowly taper the mycophenolate down. Usually what I do is I get them to a very low dose, and then I check their antibody status and see if they are in immunologic remission. Again, if they're in clinical remission, then, how long does it take? Everybody's different. A few years typically, unfortunately, is the really the honest answer. Anyone who tells you that you can get it there in a few months, I think they're dreaming unless you have super mild disease. Kim wants to know when the sores appear, how long to wait before contacting the doctor? Call me right now. There is no reason to wait. Helena wants to know if flare ups heal using only topical meds? So there are rare cases of pemphigoid where you can get localized bullous pemphigoid to the skin and the lower extremities, where you might be able to get by with super potent topical steroids. For pemphigus, rare cases of pemphigus foliaceus, limited to a small area like on the face or something where you can rarely get away with topical medicines, but pemphigus vulgaris always requires a systemic approach and a large majority of the time pemphigoid and pemphigus foliaceus require a systemic approach. A systemic approach almost always means prednisone along with something else, with a steroid sparing or an immunosuppressive

medicine. Steroids sparing is a little broader phrasing. It doesn't have to be immunosuppressant whereas the immunosuppressive medicines are a little more potent and tend to give us a better and more prolonged response. Sam wants to know if treatment is the same for PV and PnP? As I said, PnP paraneoplastic pemphigus is a much more aggressive disease so we are much more aggressive systemically. And we will combine multiple immunosuppressive agents in an attempt to treat the disease successfully. In PnP, it's really about being able to successfully treat the underlying cancer, usually, it's chronic lymphocytic leukemia or Non-Hodgkin's lymphoma. Those are the two main causes of PnP. Most of these patients, unfortunately, don't do well when those are the underlying diseases.

Dr. Korman: Okay let's jump into a bunch of questions about Cellcept. Marteen wants to know, how does it work for patients with BP? Very well. Normal dosage is recommended, if you read the literature they usually say about 40 milligrams per kilogram. I know all of you on this call listening patients know exactly what that means, right? Let's say you weigh 150 or 160 pounds, that typically means about 1500 milligrams twice a day. They come in 500 milligram tablets so we usually build people up to three pills, twice a day for sort of an average hundred 160 pound person. How long are you on this medicine? As long as it takes to get your disease under control, everybody's different. Cellcept is usually pretty well tolerated in my experience. It can suppress your blood counts. It can cause kidney or liver issues but is really uncommon. I actually, for the first time, had somebody who had elevated liver functions with Cellcept Sept. Their answer was, my Hepatologist said they've never seen it before. So that's the same with me, I've never seen it. How long can you take steroids and mycophenolate before asking about Rituximab? A lot of times Rituximab access is about insurance issues. For pemphigus vulgaris, I'll say I can almost always get it approved in Cleveland. Amy, can you always get approved in Philly?

Dr. Payne: It's FDA approved for pemphigus so really everybody who has pemphigus vulgaris should be about to get it insurance approved because it is FDA approved.

Dr. Korman: Yeah. I like the word should, I agree with that. But if somebody has bullous pemphigoid, that's a tougher question. I was just on the phone with a colleague about this an hour and a half ago. She wanted to know when is the time to pull the trigger and, quote, give up on steroids and mycophenolate? My answer would be, if I'm unable to successfully taper the person's prednisone down. Off, really, that's what I want. I don't just want it down, I want them off. I always want my patients to be off steroids. I don't even like keeping people on a small dose of prednisone. I want the

mycophenolate to successfully be able to get them down to zero prednisone. But the challenge is that Rituximab is not approved for pemphigoid so a lot of times insurance blocks our way. Years ago, I used to have real problems getting Rituximab approved for pemphigoid. Since it's been FDA approved for pemphigus, I have found that it's an easier task to get pemphigoid patients approved to treat with Rituximab. It depends on what their insurance carrier is, that's what it's all about. Someone heard of a study of low dose Rituximab to keep RA low in responders. Are there any studies in pemphigus or pemphigoid of lower doses? I'm not aware of any. Dr. Payne, do you know of any?

Dr. Payne: Yes, there have been some studies actually internationally that have been done in the Netherlands as well as Korea where they looked at just 500 milligrams and Dr. Said-Al-Naief was mentioning plus or minus methotrexate in some cases. In general, just to give you an idea, the FDA approved dose of Rituximab in pemphigus vulgaris is 2,000 milligrams. So 1,000 milligrams separated by two weeks. A lot of these studies looked at a variety of different regimens, including 500 milligrams separated by two weeks, or just 500 milligrams one time. In general, the lower of a dose you go, the less likely patients are to go into complete remission meaning, having their pemphigus sores heal, as well as less likely to actually get into complete remission off therapy. If they do actually achieve complete remission off therapy, the length of that complete remission is usually much shorter than you observe with the FDA approved dose. In general, there's really no need to use it here in the United States. I actually don't like using baby doses of Rituximab because Rituximab itself is a monoclonal antibody. There are examples where you can develop anti-drug antibodies which, I think potentially may be more likely when you're using these tiny doses that don't actually deplete all of your B cells. So, I just like using the FDA approved dose.

Dr. Korman: One other thing that I that I would add to that though, Dr. Payne, is your retrospective study demonstrating the better results with the oncology dosing of Rituximab, where those patients get a certain amount based on their body surface area four weeks in a row. But that does add up in the end, for almost all patients to more than a 1,000 milligrams on two separate occasions.

Dr. Payne. That's correct. So, before Rituximab was FDA approved, we actually always used the oncology dose, the cancer dose of Rituximab. The study that Dr. Korman is referring to, there was an analysis where we showed that patients that were treated with the cancer dose actually had a much higher rate of complete remission off steroids and a much longer duration of complete remission off steroids. So, that is actually what I always used to use. Interestingly enough, after Rituximab became FDA approved, I've had a harder time getting that dose approved because sometimes the insurance

companies will come back and say you have to use the FDA approved dose and if that doesn't work, then maybe we can use the cancer dose. So I think it again comes back to insurance. I mean clearly the strongest data from a clinical trials standpoint is supporting the currently approved dose, which is 1,000 milligram separated by two weeks.

Dr. Korman: One trick that I've found is that sometimes we have a patient with pemphigus who happens to have a history of some kind of cancer and then I hand them off to oncology and I say, please get me that four dose regimen and they're able to get it in about half an hour.

Dr. Payne: That's true. Yes, the oncologists have a much easier time getting cancer dose approved. The flip side is, in general the more effective a drug is, the more immunosuppressive it. So during COVID, I've been perfectly happy sticking with the Rituximab, 1,000 milligrams separated by two weeks. If the duration of that remission lasts shorter, I feel like that's an okay trade off because the concern is Rituximab increases your risk of serious outcomes from infections. Maybe you're balancing the dose a little bit so that you're getting good control of the disease and you're also sort of limiting the immune suppression that you get from the Rituximab... (Inaudible). And you would expect your B cells to recover sooner.

Dr. Said-Al-Naief: I just want to add to what you beautifully mentioned, Dr. Payne and Dr. Korman about the diet. The importance of diet when people are taking Tacrolimus or mycophenolate. They have to be careful with grapefruit, pomegranate, and potassium containing potatoes. They should be very prudent on how they consult with their diets because some of those medications interact with some of the food products. So I think patients should be very careful in what they eat and what they drink as well.

Becky: I just have one question. Have you found that Rituximab is more effective if it's used earlier to treat either PV or pemphigoid? Or is it better to wait and do other drugs first and then use the Rituximab?

Dr. Payne: So basically, early Rituximab therapy is associated with better clinical response. There were a number of studies that showed that people who are treated within the first 2.5 years of their diagnosis had a much higher chance of getting into complete remission, than people who are treated greater than 2.5 years into their disease course. I think that the best example of that is that there have been two clinical trials that have been run, for pemphigus and Rituximab so far. The first one was

actually using Rituximab as first line therapy, so you didn't even have to fail any other therapies. You got diagnosed with pemphigus, then you got steroids and Rituximab right away. 90% of those patients got into complete remission of steroids as long as they received continuous Rituximab infusions every six months. A subsequent study was done where they took patients who had relapse or refractory pemphigus. So they might have been on other therapies, maybe they were on mycophenolate or various different things and then they randomized them to actually getting either Rituximab and steroids or mycophenolate and steroids. In that particular study, only 40% pemphigus patients treated with Rituximab and steroids actually went to complete remission off steroids by the end of the study. So I think that it sort of makes sense in the very beginning. You may have fewer misbehaving B cells if you will, then the longer the disease goes, the thought is, perhaps the more retractable they get.

Becky: Great, thank you.

Dr. Korman: Okay, the last question on this slide is what do I think about Thalidomide? I don't know, does anybody have any experience with it? I can't remember there might be a little small study somewhere. Do you remember Dr. Payne?

Dr. Payne: There are case reports on Thalidomide. In general, Thalidomide is used for diseases where we think that a particular cytokine called TNF is important. TNF is not thought to be a major driver of pemphigus. For example, there was actually a clinical trial that was run, looking at infliximab or Enbrel for pemphigus and it was a negative study. The thought is, it could possibly work, but it's not within our standard care or first line therapies for these diseases.

Dr. Said-Al-Naief: Can I just add one thing before we flip to the next slide. There was a question on the oral slide that talked about the throat and potentially tracheal involvement. We use tetracycline products. Tetracycline products in mucous membrane pemphigoid work beautifully in controlling the gingivitis or the bulk of pemphigus, pemphigoid, and lichen planus. It works really very nice as an anti-inflammatory controlling disease in pemphigoid rather than pemphigus. That's one thing that periodontists and oral specialists like to add, Tetracycline with certain oral diagnosis of pemphigoid. Thalidomide, Dapsone, Imuran I have tried all of those for my patients. They are not the best tolerated, they are not the first line, but they are used and they are still used in clinics and literature.

Dr. Payne: Then we can go on to the next slide. We had a lot of questions on additional treatments, future clinical trials, COVID-19 which we definitely want to get to, so maybe we can cover those quickly in the next 12 minutes. For current treatments and side effects there are two questions about scalp and hair. So one of them was how to treat scalp lesions that are open or scabbed. Are there prescription shampoos or oils that reduce the thickness or hardness of the scabs? That can be very, very challenging. As Dr. Korman was mentioning in regard to pemphigus that was affecting special sites, in general the best treatment is to treat the underlying disease because essentially, there can be erosive lesions that are underneath. A thick crust will form but you don't want to pull off the crust because what you're doing is you're basically sort of ripping that off and then restarting the process, which can then lead to festering. There are topical steroids and oils that can help to address the crust, but in and of themselves these probably are not going to do the job. You basically have to treat the disease with systemic therapy at that point. I found that topicals alone will not actually get rid of that. A Synalar solution or Derma-Smoothie oil can help in part, but they usually don't cure it on their own, Clobetasol mousse, foam, et cetera. About losing hair, that can actually be a pemphigus specific effect, because pemphigus can actually affect the hair follicle and it can make it more likely for the hairs to fall out but it can also just be due to illness. So there's something called telogen effluvium, which can happen to your scalp whenever you undergo a severely stressful event and that can be emotional or physical. So for example, if you undergo general surgery with anesthesia, if you have a high fever, if you start heavy medication all at once, this can actually cause your hair to start falling out usually about three months after the insult. You'll start noticing clumps falling now. It should peak after about a week or two and then start to subside after about 1 to 2 months but it could take up to 12 to 18 months for your hair to actually get back to a normal thickness. I would just talk to your dermatologist about that. About bullous pemphigoid and Xolair, this person asks about 150 milligram injections. The typical course is 300 milligrams every two weeks, or 375 milligrams every two weeks or not. So, I don't know if 600 milligrams every month, if that's what you're actually referring to. The one advantage I like with Xolair and the way I usually describe Xolair is that it works for about 25% of people. But in the 25% of people that it works for, it works really fast. So one of the advantages, you will know within 2 to 4 weeks whether or not it's working for you and that's assuming that you're getting the every two week dose. The clinical trials on Xolair were actually stopped. There was Xolair itself that went into clinical trials and then, there was a cousin of Xolair that went in and ultimately both of those trials were stopped because of lack of efficacy. But I think the 25% probably holds true when you average across a lot of patients. I will say the 25% that do go into complete remission are thrilled. So, I always feel it's worth trying if your insurance can improve it. Janice notes that her doctor prescribed IVIg with steroids, should she do such an aggressive treatment if her condition is mild and under control?

I guess the question is what do you mean by mild? Because with MMP, there are certain things that make me very worried. For example, one blister in the eye can be enough to cause blindness. So, I don't consider one blister in the eye to be mild. One blister on the gums could be mild and in that case, using topical steroids, trying doxycycline or Dapson, these are things that you could consider trying in place of that. So it sort of depends on the site of involvement and really what the risk is for progression. What blood pressure medication is the best to use if you're on steroids and IVIg? That actually depends on your comorbidities so I would ask your primary care doctor about that. If you have diabetes or high blood pressure, a lot of doctors like an ace inhibitor like Lisinopril or Losartan for example. I would definitely talk to your primary care doctor about that because that's driven more by your other comorbidities, rather than the pemphigus or pemphigoid. Then about diet, there's really no proven data to suggest specific diets for these diseases. Individual people might mention that tomatoes always flare their disease or they always notice that X, Y, or Z flairs their disease. If that's the case, it's perfectly reasonable to avoid those items but there's been no systematic data to suggest a particular diet can actually reverse it. Okay, maybe we can go onto future treatments.

Dr. Payne: I'll quickly hit the pemphigus clinical trials. What we ended up doing was we went into clinicaltrials.gov and we took all of active NIH sponsored clinical trials that are ongoing. So the pemphigus clinical trials are shown here. Efgartigimod is an antibody that blocks the Fc receptor. But essentially what it does is it drops your pemphigus specific antibodies as well as your total antibodies. That's actually in a Phase III trial that's ongoing right now. DSG3-CAART is actually a targeted cellular therapy that is designed to target only your anti desmoglein 3 B cells, leaving your overall lymphocytes alone. So in response to Seth's question, this is a targeted pemphigus vulgaris treatment that is currently in clinical trials to determine whether or not it is safe and effective and I'll turn it over to Dr. Korman to discuss pemphigoid clinical trials.

Dr. Korman: So the first one is Dupilumab, this is a biologic drug, meaning it's an injectable drug like the other two pemphigus trials are. It's a drug that's already on the market and approved for a few things including a dermatology indication for patients with bad eczema, atopic dermatitis. There were a bunch of case reports and case series that suggested this looks promising so they've actually taken it into clinical trials and it's in the so-called pivotal Phase III trials. A lot of patients have been enrolled so I think we're going to find out how valuable this therapy is. I have not had any experience with it because I can't get drugs like this that are off label so I don't even try. Nomacopan, that's an antibody directed against a compliment. Maybe it's not an antibody, maybe it's a small molecule. If I'm not mistaken, is that right? Yes, good. So

complement is a protein in your bloodstream that plays a pivotal role in the pathophysiology of bullous pemphigoid. When thy antibodies directed against bullous pemphigoid bind to the place in the skin where they are, they immediately bring in this complement and that triggers all the inflammation that leads to blister formation. So, if you can block complement, that's the theory here that you will be able to minimize disease. Then the last one is called Benralizumab and that's also a drug that's currently on the market that's already approved to treat asthma. It blocks a molecule called IL-5, receptor antagonists and IL-5 is a molecule that helps to move cells around in our bodies and it particularly moves a very important cell called the eosinophil. The eosinophil just so happens to be the cell that really is pivotal in bullous pemphigoid. So the question is, if you can block eosinophils from getting into the lesions with Benralizumab, will we be able to shut down pemphigoid? So, those are the main three trials that are on. And I believe that's also in Phase III trial. So Dupilumab and Benralizumab are enrolling a lot of patients. So, I think we're going to have some real data in those areas. I think the Nomacopan is in a smaller earlier phase, if I'm not mistaken.

Dr. Payne: Great, and in regard to Arthur's question, there was a case series where 12 or 13 patients I believe, had a very good response to Dupixient. I think the key is, it's not fast. The thought is that there's a lot of these syncs for cytokines and it takes a while to actually soften them all up. I think that if you start it, it's going to take about 2 to 3 months to know whether or not it's working for you. Okay but we can go on. The next slide is about COVID-19.

Dr. Payne: Let's see if we can get through this in the next three minutes.

Dr. Korman: Maybe a little more.

Dr. Payne: I had to Google neti pot. That's actually something that you used to flush out your nose. Will using a neti pot or drinking fluids help to flush out or decrease the amount of viral particles in your nose and throat? I would say, not to the point that it would make a difference. In general, the strain that's circulating right now is Omicron. It's incredibly tight in regard to binding to your nose and mouth. So I think for example, if somebody were to sneeze on you or you were to inhale it and even if you immediately flushed out your nose or drank a lot of fluids, I'm not sure that that would be enough to actually prevent you from getting infected in a significant way. So I guess

the answer is no. Is there any relationship to getting the vaccine or having had COVID-19 and getting pemphigus or pemphigoid? I've heard that the vaccine is acidic which could predispose, is there any truth to this? So basically, the jury is out. I think the only way to answer this question, and basically nobody can answer this question until we get long term epidemiologic data knowing whether or not pemphigus and pemphigoid actually became more common from 2020 to 2022 compared to the prior years. And the reason I say that is because whenever anybody gets a rare disease like pemphigus or pemphigoid you're always searching for the trigger, as we talked about in the first slide. Pemphigoid is actually relatively common. It occurs in 1 out of every 25,000 patients. So every single month in the United States, there's over 1,000 people who are being diagnosed with bullous pemphigoid. With the rate of people being vaccinated between 2020 and 2022, that means maybe 1,000 people per month might develop bullous pemphigoid after having their COVID vaccine. And there's probably no way you're going to convince the person who just developed bullous pemphigoid that the vaccine didn't cause their bullous pemphigoid but statistically speaking, that may have happened anyway. So that's why it's really, really difficult to tell on a person by person basis. We can only tell, on a population basis once we have that data and the studies are probably ongoing. Is there a preferred COVID vaccine? The answer to that is, no. Other than the fact that the CDC has now come out saying that, if you're getting your primary vaccination series, that they do recommend the m.R.N.A. vaccines either, Moderna or Pfizer over the Janssen vaccine. I have not heard of autoimmune side effects with Pfizer more so than any of the other vaccines. By the way, the CDC has also come out to say that even though they do recommend the M.R.N.A. vaccines over the Janssen vaccine, there's a number of reasons why people would get the Janssen vaccine. Number one, people who are allergic to polyethylene glycol. So, it is possible to become allergic to components of the m.R.N.A. vaccines and in that case, you should get the Janssen vaccine. It may be for some people out there just because of supply chain issues, Janssen may be the only vaccine that's available to you. So, in that case, certainly getting the Janssen vaccine is preferred to getting no vaccine.

Dr. Korman: Dr. Payne, can I interrupt you for one second? It's Johnson and Johnson to clarify for everybody, not Janssen.

Dr. Payne: J&J, yes. What do you think of Evushield for patients who are on immunosuppressive medications who did not make a response to the COVID vaccine? Evushield is an antibody that you can get that's received as an injection or infusion. Then that would protect you for roughly six months after that injection. So basically that is actually very difficult to get. So it's very limited here in Philadelphia. I don't know

about other parts of the country, but there are strict guidelines as to who they are prioritizing for that. The number one category of people who are moderately to severely immunocompromised and who have not made an adequate response to the COVID-19 vaccination. So, that includes people who've been treated with Rituximab in the last year and more so, people who got Rituximab before they got vaccinated. If you got the vaccine before Rituximab chances are you may have a decent response and the Rituximab won't completely erase the vaccine. Then the second question was, can you take it if you're on monthly IVIg? So, actually that would not be a good idea because how IVIg works is it actually lowers the level of serum antibodies. So, if you get Evushield and then get IVIg, that will actually cancel out Evushield that you just got so I wouldn't actually combine those medications. Regarding fourth shots, Rebecca asks, is there any discussion of people with autoimmune disease needing a fourth vaccine? Currently, the fourth vaccine guidelines are not for people with just autoimmune diseases, it's actually specifically for people who are immunosuppressed. So, having pemphigus and pemphigoid in and of itself does not make you immunosuppressed, unless you are taking a medicine like Prednisone greater than 20 milligrams, Mycophenolate, Azathioprine, or Rituximab as an example. Basically, the guidelines are, if you are at least five months out from your booster shot and you are on one of those immunosuppressant medications, you are eligible for a fourth shot. If I've been vaccinated and boosted for COVID and I get a Rituximab infusion, do I need to get another COVID vaccine? Not necessarily. So, again, if you got your booster or your COVID vaccine at least two months before Rituximab, chances are the Rituximab will not totally erase the vaccination that you just got. Then, the same rules would apply to your fourth shot, which is to wait at least five months after your prior booster to get the fourth shot. Then, finally, for immunocompromised patients who are now getting their fourth shot, do you recommend you get the same brand you already had? Or do you recommend that you mix and match? So, this is actually a clinical trial that is ongoing right now through the NIH. It's going on at multiple sites around the country, and they're actually doing a Phase II study where they're actually comparing mix and match to getting the same shot. In my opinion, obviously, we have to basically wait for the results to see what studies show. I think that there is a rationale that if you've got a J&J as your first vaccine and you didn't make a good response, there's a strong rationale to go to either Pfizer or Moderna. The J&J vaccine is made from an adeno-associated virus vector and some people have pre existing antibodies against that particular vector which may contribute to why they don't respond to the J&J vaccine. In that case, the m.R.N.A., LMP vaccine would bypass all that and shouldn't have any problems. I can't really come up readily with a reason why somebody who got Moderna would go to J&J. Pfizer actually has a lower dose than Moderna. There's potentially some reason to go from Pfizer to Moderna, especially a higher dose. I'm not so sure there's a super strong

rationale to go the other direction. I don't know if you want to add anything to that, Dr. Korman or Dr. Said-Al-Naief?

Dr. Korman: Nope.

Dr. Payne: Okay so we can skip to billing.

Dr. Said-Al-Naief: I can briefly discuss billings and oral care. We don't use dental codes, we use medical codes. If I'm not mistaken, dentists do general billing for degenerative gingivitis which includes pemphigus, pemphigoid, and lichen planus as a clinical code. With pathology, we have codes that we follow mainly the dermatology when we code the pemphigus and pemphigoid. For gingivitis I've here the dentists use and general dental codes.

Dr. Payne: The final question was on financial assistance for treatments. So I put two resources here. Number one, talk to your doctor because your doctor may have connections with social work or various different things and it's an insurance issue. Just getting insurance to begin with. But then there's also this website for Rituximab which gives you options for finding financial support, specifically for Rituximab treatments. And again, that's largely only going to apply to pemphigus vulgaris because that's the disease that Rituximab is approved for. Then GoodRx is also a company, you can go to [GoodRx.com](https://www.goodrx.com). You can type in the medicine of interest and then that can actually show you coupons or other discounts or compare pharmacies near you in regard to the cost and that's always worth visiting as well.

Becky: Can I add something on to that? Usually, not all the time, but in many cases, whatever treatment you are on, the manufacturer may have a coupon program or some kind of discount program. So it's always good to find out who the manufacturer of your medication is and contact them, whether it is an IVIg or Rituximab or a tablet or a cream. Always try to reach out to the manufacturer themselves. There may be a foundation associated with that manufacturer.

Dr. Said-Al-Naief: There's a lot of links to different sites where patients can find links.

Becky: You were talking about the Evushield., I know you said it's not widely available, but have patients with PV gotten that? And has there been an effect on their disease since it is a monoclonal antibody?

Dr. Payne: I don't have experience with it yet. Penn received some Evushield but there's actually a lottery system that's ongoing right now because we will see very few doses. The CDC published guidelines on how they list out tier one, tier two, tier three. So just to give you an example, somebody who will be bumped to the top tier one is somebody who is moderately to severely immunocompromised, meaning received Rituximab within the last year and has a proven non-response to the vaccine and also is over the age of 75. What they do is a cutoff by age. So over 75 is the top tier, 65 to 75 with clinical risk factors is the next tier. Less than 65 with clinical risk factors is the third tier, so these are just some of the examples of how they prioritize people for it.

Becky: Great. Thank you. Just to recap, it looks like this link is covered up. Somebody is asking about the website for Rituximab assistance?

Dr. Korman: www.rituxan.com/ra/financial-support.html

Becky: Well, thank you all for hanging out with us. I know we went over a little bit, but you guys were champs in getting through all of those questions and I really appreciate that and all that you do for our communities. A big thank you to you. Thank you to everybody who is hanging with us a little bit late, and of course a giant thank you to our sponsors, Genentech, argenx, and Cabaletta for making today's call possible.

Becky: Our next patient education webinar will be on February 9th to discuss "An Overview of AstraZeneca FJORD Trial for Bullous Pemphigoid" with Dr. Janet Fairley-Chair, John S. Strauss Professor and Chair of the Department of Dermatology, University of Iowa and Skylar Sever- Registered Nurse and Clinical Trial Educator at IQVIA. We hope that you will join us to learn more about this trial. Are you ready to share your story and help make changes in real legislation that will impact our community's access to medications, access to high quality health care for patients, and increase federal funding for advances in medical research? If so, the IPPF is participating in Rare Disease Week 2022 and we need your help! If you are interested in sharing your story with your Congressional Representatives please register for Rare Disease Week at www.everylifefoundation.org. This is a great way to not only get

involved but really have your voice heard. If you have any questions or are interested please contact Marc Yale at marc@pemphigus.org. The IPPF has a number of upcoming virtual support groups across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting. Also, we are always looking to expand our support network, if you are interested in starting a support group in your region please contact me at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients. If you are interested in continuing to help support the IPPF you can become a healing hero. Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small, even a \$5 or \$10 monthly donation goes a long way and continues to allow us to provide for the greater good of our community. Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! You can find the Natural History Study by visiting www.pemphigus.iamrare.org. This call recording will be sent out with the survey following this call. Thank you all for joining us.