Back to Basics: All About Pemphigoid Patient Education Series Webinar Transcription

Amethyst: Welcome everyone to the Back To Basics All about Pemphigoid webinar. This call is now being recorded. I'd like to thank everybody for being on the call with us today, and to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, argenx and Cabaletta Bio for making today's call possible. “Information is a key factor in treating and living with any condition. However, every patient situation is unique. The IPPF reminds you that any information found on the internet or during presentations should be discussed with your own doctor or health care team to determine if it applies to your specific situation.” Before I begin, I'd like to take a quick poll to see who we have on the call with us today and how long you've been diagnosed with pemphigoid. If you would just take a quick moment to answer the poll that will be popping up on your screen. And while you do that, I'd like to introduce our speaker for today. Dr. Feldman is currently an Assistant Professor of Dermatology at Emory University in Atlanta, GA. He has a subspecialty interest in treating patients with autoimmune blistering diseases. This interest began as a dermatology resident at Cleveland Clinic and continued through his fellowship in Boston at the Center for Blistering Diseases. He has been the Director of the Autoimmune Blistering Disease Clinic for the past 9 years and now manages a large number of patients from all over the Southeast with various blistering diseases including pemphigus and pemphigoid. Dr. Feldman conducts an active translational research program which includes ongoing clinical trials and collaborative efforts for biomarker analyses for advancement of novel and more targeted therapies. More recently his work has focused on the effects of autoimmune blistering diseases on patient quality of life particularly related to mechanisms of itch. I'm going to go ahead and close the poll here to see who we've got on the call with us today. So it looks like a good majority of you have been diagnosed for 1 to 3 years, but we kind of have a nice variety. So this is great. This allows us to know where everyone is on their diagnostic journey and with their disease. So thank you for taking that. And before we begin, I'd like to just go over a few housekeeping slides… (*Reviews housekeeping slides*). So it is now my pleasure to introduce Dr. Ron Feldman to answer your questions about pemphigoid.

Dr. Feldman: Ok, thank you very much. Thank you so much for inviting me and thank you to the IPPF and the various sponsors. Always a pleasure to speak with everyone out there. Hopefully, everyone's having a good night, or at least on the East Coast, here, it's 5 30pm. As Amethyst mentioned, this is all about pemphigoid, although I do have some information about pemphigus too to compare and contrast. As she mentioned, I'm here at Emory University in Atlanta, Georgia. Also I wanted to do a quick plug. We have a national NIH sponsored clinical observational trial for patients with bullous pemphigoid. If you're interested in learning more information I put the clinicaltrials.gov identifier and its for patients who have active bullous pemphigoid. We're recruiting patients to do an interesting trial where we include both face to face visits as well as remote visits by telemedicine. So it’s a unique opportunity to kind of explore new technologies for clinical trials purposes. Please write the number down at the

bottom and feel free to reach out to my research team if you want to learn more information about this.

Dr. Feldman: So autoimmune blistering diseases, many of you are interested in learning about these various conditions. I thought we'd compare and contrast what these diseases are, look at some of the basics and some pictures of patients. I'm hoping to answer most of the questions with these slides but I'm happy to take some more questions after I finish. So epidermal versus subepidermal, most dermatologists when they treat you or at least diagnose you, they're trying to figure out which one you fall under in terms of categories. So epidermal, those are the pemphigus type diseases, pemphigus foliaceus and pemphigus vulgaris, the most common. The subepidermal ones are the ones we're focusing today, the pemphigoid type diseases. There's a fair number of them, the main ones are bullous pemphigoid and mucous membrane pemphigoid, although some other ones too. Many of you out there may be you may also have been diagnosed with a little more rarer than the two which are most common ones, bullous pemphigoid especially.

Dr. Feldman: So when we talk about that, what is the epidermis? So this is the part of the skin, and you can actually see. If you look at the very top, that's the part of the skin that's exposed to the environment. Your skin is actually several layers thick. It's the epidermis which is made of skin cells called keratinocytes. Keratinocytes produce keratin and those are the main cells of the epidermis. The epidermis is held down very tightly to something called the dermis, which is below the epidermis. That's the part you cannot see. And if you look between the cells, these are the keratinocytes which look like little blocks and then between them is what I call the glue. This is what holds the skin cells together. There's a lot of adhesion proteins that are super important. The main one is this hamburger looking protein called desmosome. This is where there's a lot of proteins that cross between the cells that hold the cells together very tightly. If you go down to the bottom this is called the basal layer of the epidermis. Here you have half a desmosome, this "half a hamburger", that's a hemidesmosome and that's what attaches your skin down to the dermis. This is a very tight bond incredibly important for holding the skin down. If you lose that, the skin can easily blister and peel off. So that's the simple structure, a cartoon of the epidermis.

Dr. Feldman: So with pemphigus, pemphigus foliaceus is where the skin is involved for the most part and then pemphigus vulgaris patients can have both oral lesions or mouth lesions as well as skin lesions. So that is the pemphigus type of epidermal disease. For example, these are some pictures of patients with pemphigus vulgaris. You can see widespread erosions throughout the mouth and it can involve the gums, the top of the mouth which we call the palette or the roof of the mouth. You have a tongue, or under the tongue, or the floor of the mouth, the sides of the cheeks. It can be anywhere and patients obviously can suffer from difficulty talking, swallowing, eating. It's very painful, right? Then it can involve the skin as well. So widespread erosions on the skin. This is showing some examples on the trunk, chest, back,

buttocks areas. These painful skin erosions, resulting from loss of adhesion, so the skin is no longer able to hold onto itself.

Amethyst: Many dermatologists do biopsies when you first probably got diagnosed, the dermatologist took a biopsy as shown here. This picture on the left is what we'd like to see in normal skin. You have this upper layer of the epidermis, as I just mentioned. So this is what we see under histology. So you take the biopsy and you process it, you put it on one of those microscope slides, and you look under the microscope and what you're gonna see is this picture. So the epidermis is that purple area and then it's attached to the dermis which is this whole pink area. So that's what normal skin is supposed to look like. If you biopsy a patient with pemphigus you can see on the right, it doesn't look very normal at all. The skin cells are falling apart as shown here. They typically leave a small layer at the bottom still attached to the dermis, but the upper layer is falling apart, so we call this acantholysis meaning the skin cells no longer have the ability to hold onto each other and they fall apart.

Dr. Feldman: If you look at this cartoon here, again this is the epidermis held onto the dermis, and we blow up the image between the two cells. What I mentioned earlier, here's those proteins that are crossing over between the cell here, this cell over here, and this cell here and this is at the desmosome. This is a very important structure that's important for holding skin cells together. The main protein for pemphigus are desmoglein proteins you may have heard about or read about. Desmoglein proteins go from one cell to another cell and they hold the cells together. In pemphigus patients produce antibodies that bind to these desmoglein proteins and disrupt that normal function. So the skin cells are no longer able to hold on to each other. So what we're looking for diagnostically, I think one of the questions was about direct immunofluorescence. So for pemphigus, we're looking for deposition or presence of those antibodies between the skin cells because they are binding to the desmosomes. That's this pattern here, these are the skin cells in black and this sort of chicken wire patterns see this fence pattern which is where the antibodies are being deposited against the desmogleins. This is classic for pemphigus in a direct immunofluorescence. In pemphigoid in contrast, the two most common we'll talk about is bullous pemphigoid which, for the most part involves skin but they can sometimes have oral lesions versus mucous membrane pemphigoid, which is predominantly mucosal involvement. So that's the mouth and or eyes, skin, or nose as well. Then some of those patients only have eye involvement so we call that ocular cicatricial pemphigoid.

Dr. Feldman: So these are some cases of bullous pemphigoid. You can see blisters on really any area of the body. It can be localized or it could be more widespread involvement. It tends to be very itchy but obviously, as the blisters peel off, that can be very painful too, similar to pemphigus. Mucous membrane pemphigoid, obviously we're going to see mostly involvement of the mucosa and can also look very similar to pemphigus, which is why you really need a biopsy to diagnose this. Patients can have oral erosions in the gums or the gingiva is what we

call it. You can intact blisters as shown in this patient here on the gums. You also get involvement with the palate as I mentioned earlier. You can get blisters that are rupturing in the gums so that the skin kind of sloughs off and it can evolve the cheeks as well, what we call the buccal mucosa. You can have these erosions or peeling of the skin and that's very common. Again, the same concept and it's very painful and can be difficult talking and difficult eating. Sometimes patients can have difficulty swallowing too if it involves the back of the throat.

Dr. Feldman: The ocular version of this, the ocular cicatricial pemphigoid has the same process but involves scarring of what's called the conjunctiva. This is the piece of tissue that connects the eyelid to the eyeball and for some reason when it involves this area, it can result in scar tissue formation. So it could be very, very devastating and it has to be obviously taken care of as quickly as possible because the scar bands can eventually form onto the cornea shown here, then the patients can potentially go blind. So the sooner we catch this the better in terms of being able to treat this disease. So this is ocular cicatricial pemphigoid, it's the eye involvement version of the mucous membrane pemphigoid.

Dr. Feldman: So, we've talked about pemphigus earlier. So let's compare and contrast what you would see with a biopsy of pemphigoid versus pemphigus. So again, on the top is what you should normally see under the microscope when you look at the normal skin. The pemphigus patient we saw already. Now here on the left is your pemphigoid, it looks quite different from pemphigus. Instead of the epidermis falling apart, the epidermis is being completely lifted off the dermis. So the cells are still alive, these cells are not falling apart like pemphigus but they're completely being lifted off from their base, which is the dermis. And there's a lot of inflammation. So a lot of cells, the immune cells that are coming in here and causing lots of damage which results in the blister. So this essentially would clinically be a blister here. This is where the fluid has formed and it's pushing the upper layer of the skin, the epidermis up. So clinically, it looks like a big blister or tense blister. And if we look again at the similar cartoon and we go down to the bottom of the epidermis, this is the area of the hemidesmosome.The other name you might hear dermatologists talk about is the basement membrane zone. This is the connection between the epidermis and the dermis. There's a lot of proteins in this area shown on the right in the cartoon. The main ones for the purposes of today we'll talk about are BP 180, this is the protein or collagen 17 is the other name for it. This is that very important protein that runs between the basal cell of the epidermis down into the dermis area and it holds the epidermis down. It's very important and acts essentially like an anchor, if you will, to the epidermis, and if you lose that or it's disrupted by antibodies the patients are producing, then you lose an anchor and your epidermis becomes very fragile and can potentially blister up. So this is the mechanism of pemphigoid versus pemphigus. So, hopefully that makes sense for everybody and feel free, obviously, to send me questions later, if there is stuff that I said, you don't understand.

Dr. Feldman: Then we diagnosis this by direct immunofluorescence which is essentially the same concept as pemphigus. We're trying to find auto antibodies that are being deposited or

present in the skin. So in contrast to pemphigus we saw this sort of chicken wire pattern at the epidermis. Now what you're going to see is the antibodies are being deposited lower, they're being deposited at the junction of the epidermis and the dermis or the basement membrane zone. And we'd see this linear or the line of this green staining which demonstrates that there's presence of antibodies that are binding to the proteins at the basement membrane zone. That's classic diagnostics or what we call the gold standard, if you will, for diagnosing pemphigoid. That's all I have for the slides. I've covered most of the questions, I think in general but I'm happy to take some more questions.

Amethyst: Great, thank you. Thank you for that great explanation of the difference between the two diseases. I think that was wonderful. Like Dr. Feldman said, please, If you guys have any questions, feel free to type those into the question box. And I'm going to start going through some of the questions that we received beforehand as well. I know you're talking about the difference between how you diagnose. Is the direct immunofluorescence test the gold standard as well, for how to diagnose the disease?

Dr. Feldman: It's, for the most part but we use all the tools we can to diagnose these diseases because sometimes one of the tools comes back, potentially negative. Again, it's not always clear why that is. The most common tools would be, the biopsy for the H and E and that's the one where I show the purple staining. That gives you a general pattern of what's happening at the level of the skin. It doesn't tell you there's antibodies present so that's why you really need the direct immunofluorescence biopsy that way you can look and see, in fact, there are antibodies being deposited. But then you have to figure out what type of antibodies are being deposited. So that gives you a pattern of pemphigus in general versus pemphigoid. But you kind of want to know, what antibodies are the protein binding to? And that's when we talk about the ELISA test where we can do more studies where we're trying to figure out what did the antibodies actually bind to. So for example for pemphigus the antibodies bind to the desmoglein proteins, so we can look for desmoglein specific antibodies in the blood by ELISA technique. Or for pemphigoid we can look for antibodies against the collagen 17, or BP 180, or the related BP 230. Those are the most common with bullous pemphigoid and or a mucous membrane pemphigoid.

Amethyst: Great. Thank you. Somebody asked what is the average age that somebody is diagnosed with pemphigoid?

Dr. Feldman: So in bullous pemphigoid, it tends to occur more in our elderly patients, so 70 to 80 is the average age. Mucous Membrane pemphigoid, a little younger, usually in the 60's average age and then pemphigus tends to be a little younger than that 40's to 50's age range.

Amethyst: Great, thank you. Sandra wrote in and asked specifically, Do you need to see a dermatologist to treat this disease? Or can your primary care just treat you?

Dr. Feldman: The short answer is I would recommend a dermatologist just because most dermatologists are much more experienced at diagnosing and treating these diseases. Whereas most primary care doctors have rarely ever seen these diseases. They may have seen one in medical school, or potentially one later on in residency if they trained at a large academic center. But, most primary care doctors are not familiar with these diseases. So, my recommendation is that the dermatologist should be treating this. You may find sometimes, also, if there is not a dermatologist, a rheumatologist sometimes may assume the care of these patients with blistering diseases just because they're comfortable with using the immunosuppressive medications that are generally required to treat these diseases. But for the most part, they have not had much training either in these diseases so they're sort of treating with the drugs they're comfortable treating with but they really don't necessarily know how to manage the same way that a dermatologist does. A dermatologist is very skilled in skin diseases and treating different diseases of the skin. So I recommend, almost always, especially for these diseases, it's very important to see a dermatologist.

Amethyst: Great, thank you. And another question about finding the right doctor when looking for a doctor to treat their disease. Is there anything they should be looking for besides a dermatologist or any questions they should be asking? Almost like an interview with their doctor?

Dr. Feldman: Again, it depends. Obviously, a new patient is not sure what the diagnosis is. I think it's important to get sent to somebody who is familiar with these diseases. And I think the IPPF should be one of the first stops on your journey as I say. To go to folks who are very familiar or it can at least get you in the right direction to find somebody who is. So I think when you first start your journey, there are simple questions that you can ask such as: “How many patients with this disease have you seen and treated?” Very simple questions you can ask. If the answer is only a few or I've seen this a long time ago, then you may want to look elsewhere to get another opinion, potentially. I think you'll find, for the most part, at most larger universities there's typically an academic dermatology center. They're a good reference place to at least start or if not, I again recommend talking to the IPPF. They have a list of dermatologists across the world, actually.

Amethyst: Great. Thank you for that, we definitely do. And then we also have a Patient Checklist too. So if you are unsure about what to ask your doctor, this might be like a nice guide for when you go in to keep your mind in track because those appointments can go really fast and there’s a lot of information. So feel free, you can email us afterwards and we can send that over to you guys as well. Dr. Mason wrote in and asked if you could explain why linear IgA disease has been renamed and how frequently do remissions occur?

Dr. Feldman: Renamed? Not sure what that refers to. Essentially we talked earlier with the direct immunosuppressants where we typically look for IgG, IgA, and IgM. So most patients with pemphigoid will have IgG, which is a very common protein which most of us produce. That's important for fighting off infection to provide immunity, for example, against a vaccine response. You are producing IgG against that element for whatever you vaccinate against. For IgA, there are instances where for some reason patients just produce IgA against the basement membrane zone. They don't produce IgG so we tend to call that linear IgA and that protein is really just the breakdown product of the collagen17. So I'm not sure what he refers to by the new name. It's just a different pattern we see in direct immunofluorescence.

Amethyst: Okay great. Somebody wrote in and asked, does pemphigoid leave any permanent scarring and if it does, if there's anything that you could use to help reduce scarring?

Dr. Feldman: That's a good question. For both forms of pemphigoid, it doesn't normally leave significant scarring. Again it also depends on the color of the skin. Patients with darker skin color tend to have more of what we call post inflammatory or hyper pigmentation. So as the lesions heal, it tends to leave a dark area and unfortunately the darker skin is the longer it takes to go away. We don't exactly know why that is, but for the most part it doesn't leave scarring per se. However, if the antibodies tend to attack lower down into the dermis, that does tend to result in processes that lead to scarring. So for example, patients with EPA, epidermolysis bullosa, tend to have collagen 7 antibodies and those patients tend to have more scarring than patients with bullous pemphigoid. Now when you talk about mucous membrane pemphigoid, that was a little different scenario. Like I mentioned earlier for some reason the mucosal tissue when it's attacked and there's a lot of inflammation from autoantibodies, it can result in scarring. We don't quite know the difference between why that is versus normal skin. So normal skin or cutaneous skin we call it, versus mucosal skin especially the ocular conjunctiva can result in scarring compared to other areas of the body. So it's a combination of whether it's bullous pemphigoid versus the mucosal pemphigoid versus scarring and also a combination of, like I said, post inflammatory, hyper pigmentation, which can result in the darker skin involvement.

Amethyst: Great, thank you. Nancy said that she's had pemphigoid since 2008 and for the last 4 years has been seeing a doctor for some annoying, loose, white skin in her mouth. She had a biopsy and one of the doctors said that it's just the buccal mucosa but no matter what, she cannot get rid of it. Are there any suggestions for some of those oral lesions?

Dr. Feldman: It's hard to say. That's something that you might have to have a conversation with your trading dermatologists about. The buccal mucosa is the part I talked about which is the inside of the cheek where you can have these erosions. The white, you're referring to could potentially be the part that is peeling off. Or there's some patients who have what's called lichen planus which is a related condition where you get these white streaks. So I'm not sure in her

case, what she's referring to. If it's still active, in other words, the skin is still peeling off you have multiple options whether you can go from topical options. That's topical steroid gels for example or non steroid gels to rinses. Again, steroid rinses are very commonly used for this such as Dexamethasone rise. Sometimes we even do injections. You can inject a liquid steroid, Kenalog, into the area of the buccal mucosa and that helps the skin to heal. If those things do not work, then we usually have to go to systemic medicine. So either pills or other aggressive medications like infusion. So I'm not sure exactly what she's referring to, but I think that those are conversations that need to be held with her treating dermatologist to figure out what's the right treatment plan for you.

Amethyst: Great. Thank you. Talking about those rinses, Sandra wrote in right before the call and said that she has cicatricial pemphigoid and was told to rinse with the dexamethasone twice a day and to take nicotinamide once a day. She's asking if you think that's beneficial. She says she's been using steroids and antibiotics but has had no relief.

Dr. Feldman: Yeah, again, this also seems to be a conversation that needs to be held between her and her treating physician. So like I said, Dexamethasone rinse is a type of steroid rinse that can have some efficacy in terms of helping to calm down the inflammation of the mouth and helping the sores to heal faster. You can also use steroids gels for example, very commonly Clobetasol gel is commonly used and it can be put directly onto the lesions. Without hearing your full case or the extent of your disease, I'm not sure but there's a lot of different options if that doesn't work or if you feel that nicotinamide is not effective with the rinse there's always other treatment options too.

Amethyst: Great, thank you. Karen asked, is this disease brought on by any types of medications or any environmental factors?

Dr. Feldman: That's a good question and it's funny because it's somewhat of a moving target. Every few years we learn about these new potential triggers. So classically, one of the triggers we talked about is a diuretic called furosemide or Lasix you may have heard of. That was a possible, or a well described trigger that was found many years ago. And then more recently, some of these new diabetes medicines, there's been a potential link between D4 inhibitors, or the class of drugs called Liptons which may, in fact, also play a role in inducing bullous pemphigoid. Some patients who are on newer immunotherapies, so patients who have some cancers for example metastatic cancer, are being put on some new immunotherapies, which essentially induces the immune system to go after the cancer, if you will. And doing so sometimes also turns on autoimmunity. So we also have a fair number of these patients who are starting to come to us, who have been put on these PD1 PD-L1 inhibitors, then they develop these autoimmune blistering diseases, most commonly bullous pemphigoid or lichenoid diseases and especially pemphigoid types of diseases. So those are the two newest ones that have come out more recently in terms of medication induced bullous pemphigoid.

Environmental triggers, we're not quite sure that's a good question. We don't have any clear link between environmental triggers other than in terms of personal triggers such as stress. We consider stress and environmental trigger, especially in this past year there has been a tremendous amount of stress. So that definitely plays a role with somehow causing the immune system to go haywire and pemphigoid can develop. So medications yes, environmental not quite clear in terms of the other relationship there as well as diet. I think that some of your questions are about diet. We don't know much about the role of diet and autoimmunity either.

Amethyst: Speaking of diet, we get so many questions from patients wanting to do the autoimmune diet or take out gluten and is there any study specifically about that or any foods they should avoid?

Dr. Feldman: My usual answer is, go for it. But we don't know in terms of the autoimmune diet, paleo diet, etc. it's not quite clear the role of foods in terms of these autoimmune diseases. The one link I would be cautious with is that, especially when they have what's called dermatitis herpetiformis, this is a disease that can be linked with celiac disease and patients can get itchy blisters particularly on the sites like elbows, knees and buttocks. That's been well described in terms of a link with gluten so that is a gluten sensitive skin disease. So for those patients, we do tend to recommend a gluten free diet as gluten does seem to aggravate. Outside that, we don't really know the link between foods like gluten or sugar rich foods. For overall health, of course, we recommend always limiting sugary ,processed foods but does that affect autoimmunity, we don't really know yet. There's no good studies that I'm aware of, anyways. So my short answer is usually if you want to try a particular diet, by all means if it helps your overall health, then of course.

Amethyst: Great, thank you. Along those same lines, are there any natural or holistic treatments? We get a lot of people talking about wanting to try vitamins. Are there any good suggestions or steer clear from those types of holistic treatments?

Dr. Feldman: I don't know. That's my short answer to that one. I don't know, in terms of the holistic treatments. I know there's a lot of them out there in terms of culturally different practices. I don't know the role of those, in terms of the relationship with pemphigoid.

Amethyst: Thank you. Karen just wrote, and she says, is it common to be fatigued when you have MMP?

Dr. Feldman: Not necessarily fatigue from the disease itself but from the medication sometimes it is true. You can get fatigued, some of the side effects are fatigue. Although, anecdotally, I will say some patients when they first present and their disease is really active, it does seem that they don't necessarily feel well either. It's almost like you have the flu. So you

feel kind of crummy, fatigued, feverish sometimes. So that is a common description of patients who have new, active disease but short of that I'm not really aware necessarily of any fatigue specifically with MMP.

Amethyst: Great, thank you. I'm going to combine these two questions in one. Mei Ling and Sandra wrote about oral pemphigoid. Mei Ling asks, if you have BP do you need to see a dentist who knows how to treat these diseases or can you see a regular dentist? And Sandra also said that her gums are receding. Could it be possible that she's losing her teeth and should she be seeing a specific dentist for this?

Dr. Felman: That's a great question. Not an easy answer either. I know the IPPF has done a lot of work in educating dentists. Sometimes it's hard to find a dentist who has seen this disease before. Again, they may remember back in dental school or may have seen one case over their lifetime of the practice. So part of it is just education, many dentists are just not aware of these diseases and not so comfortable, necessarily treating these diseases. I think most people don't necessarily realize either that most dentists don't do biopsies. So your dentist may say, yeah, you clearly have something but I'm not sure exactly what it is. It looks to be probably really inflammatory but they don't necessarily do biopsies. So it's important then to say, who can the dentists refer you to? I think that in most cases, the dentist may identify you first on the journey but it's important to figure out, with the help of the IPPF, where should you go next? And you want to go somewhere next where you can get a biopsy done. So that's going to be, typically periodontist, oral surgeon, or an oral pathologist if you have one that is perfect, or oral maxillofacial surgery. Those are the folks who typically do a biopsy or a dermatologist obviously. If it's easily accessible a dermatologist can do it too. So at least in the beginning of the journey it's important to find somebody who can diagnose your disease, and then once you're diagnosed, it is kind of tricky to find someone who's comfortable treating you. My usual advice is that, although others may have different opinions, my usual advice is if the disease is really active you may want to wait until things calm down before you have an aggressive cleaning because with an aggressive cleaning the gums can get really inflamed and that can cause a lot of bleeding and discomfort and sometimes can activate the disease too if it's not under good control. So that's my general advice. In terms of gum recession, it is possible both from the disease itself and the inflammation, you can get some gum recession. There's even some evidence that some bone resorbing can occur too with chronic inflammation, especially with mucus membrane pemphigoid. So it's kind of a conundrum, right? So you want to do the best you can to keep the teeth clean, the gums clean, and to remove the plaque but you also don't do too much to reactivate your disease and you're uncomfortable. So it's kind of a fine line to walk. The best thing we can do is kind of calm down as fast as we can and then get you to your dentist for regular hygiene care. I do recommend every 4 to 6 month once things calm down. You want to make sure the gums stay as healthy as possible. But it's important to have a conversation if other procedures need to be done, say surgical procedures, to help with the gum recession, it's important to talk with the Periodontist as well as a general treating Dermatologist to make sure that everyone's on the same page.

Amethyst: Great, thank you. Good advice. I know you touched a little bit on the various types of medications. Is there a usual order of medications that you typically try with a new patient?

Dr. Feldman: It really depends on the context. So if we consider the patient to have mild disease then we tend to go with more conservative type treatments, like topical treatments. So for example, topical steroids, topical gels, and I mentioned rinses for the mouth or local injections with Kenalog or injection of steroids. That may be all you need for a mild patient, but if the patient has more moderate to severe disease and it's more widespread, for the most part, most of us, at least in the United States, we tend to go with oral agents. So pills, for example, or other therapies like infusion medicines. This is when you have to treat the disease from the inside. You have to slow down the immune system so it stops attacking the skin and the mouth. In other words, there's no no magic formula. I think it really depends on the context of the severity of the disease, and where the disease is affecting. If it affects the eyes, for example, we tend to get more aggressive quickly. So, we tend to go to more systemic therapies faster, but if it involves more local areas of the skin or are small areas of the mouth or a localized area of the mouth, we can get away with assertive treatments.

Amethyst: Great. Yes, I wish that there was a magic, “cure all formula”.

Dr. Feldman: Yes, I wish there was a magic formula where you could just plug in but also you have to take into account the age of the patient and other comorbidities that the patient has, which are other diseases that may affect the use of therapies. So if they have severe diabetes or bad kidney disease or liver disease and sometimes you can't use some of these medicines you would like to normally use and you have to go with more conservative. So it all depends really on the context of the severity of the disease, the patient, their age and other comorbidities we call them in terms of making a decision, what's the best treatment for this patient. So it's really honestly a case by case basis with some general guidelines based on disease severity.

Amethyst: Great. Thank you. Sally wrote in and said that her sister is 59 and was recently diagnosed with bullous pemphigoid. She seems to have a very aggressive form of it, and she's been treated with 50 milligrams of prednisone and immunosuppressants. How long would it take for remission and what is the ongoing treatment?

Dr. Feldman: Well, it's hard to say without knowing the full detail of your sister's case, but sorry to hear she's got an aggressive case. It is true, sometimes younger patients with bullous pemphigoid can have more aggressive cases anecdotally, it seems to me anyways. So, again, I don't know exactly what immunosuppressant agents she is on, but in general, if things are going well, we expect to see improvement within 3 to 6 months. So things should get much better and we'd like to see patients wean down on the prednisone or off of their steroids if possible. Typically if it's that aggressive, we have to use what's called a steroid sparing

medicine and that comes and what I call “many different flavors”. The pills that we talk about as steroids sparing agents, the common ones would be Methotrexate, Azathioprine, Mycophenolate or Dapsone are very common oral agents we use as steroid sparing agents. That means we want to try to lower the prednisone without the disease becoming active. Then sometimes if those don't work, we use in conjunction or in place of those, we use medications that are infusion medicine. That can be either IVIg or intravenous immunoglobulin or Rituximab is very commonly used now to treat both pemphigus and pemphigoid diseases. So that's sort of just a general guideline for treatment options for patients with severe or what we call refractory disease. It’s important to have a conversation with the treating dermatologist to go over what are all the options? And if one of the options isn't working, what to do next? Whether you want to switch to something else or add on? It really depends on the case.

Amethyst: Great, thank you. Rhonda asked, is Cellcept a medication that an otherwise healthy person can be on for extended periods of time?

Dr. Feldman: Cellcept is a brand name for Mycophenolate which is the generic name. Patients can be on Mycophenolate for years. There is no exact timeframe. Again, it really depends on the goals of the treatments. If my goals are, we use Mycophenolate as a steroid sparing medicine in order to avoid keeping patients on long term, high doses of steroids because steroids have too many side effects. So the goal of Mycophenolate or Cellcept is to help wean patients off to limit those side effects and keep the disease quiet as you come off the steroids. So we have patients on it for months and more commonly we have patients on it for years. So there is no necessarily magic time point you need to be on Mycophenolate or Cellcept, it really depends on a case by case basis. And of course if things are going well and you're in remission as we call it, then our goal also is to eventually wean you off everything. That depends on the comfort level of the treating dermatologists, that's a conversation you need to have in terms of what is the actual goal and are there well defined endpoints? What's the end game here? When can we start weaning medications and when can we potentially come off everything? That's a conversation that has to be held between the treating physician and the patient.

Amethyst: Great, thank you. That kind of leads in, and I think it kind of answered this question, but I'm going to just repeat it. Barbara asked, if a patient is stable, do you ever take them off medication or do you just always keep them on a low dose of meds?

Dr. Feldman: That's a great question and there is not necessarily an easy answer, it depends. The best case scenario for those of us who treat autoimmune diseases is you have a well defined diagnosis. You can select what's the right therapy for this patient. You check that box. This patient needs this drug and this drug is going to work for one year and then we're going to check the next box. Then we look for the clues or biomarkers as we call them that says this patient is in remission, stop medicine. Unfortunately, we don't have that nowadays. That's going

to be a few years now to have those tools. So we really rely on all the clues we can use to determine remission. So I usually say there is clinical remission, that is, you have no new lesions and all the old lesions have healed. That's the simple definition that we for remission and that's complete remission. So either your in complete remission, hopefully, off all your medicines or a complete remission, still on medicines and hopefully a lower dose. How to define that? Like I said, if you come to me and you have no more lesions and all the old lesions have healed, the disease is in what we call complete remission. So then we have to decide whether or not it's safe to wean off everything and there is no easy answer like I said. It really depends on the goals and what's the end point? Most dermatologists who treat these diseases are trying to wean patients down to the lowest amount of medications as possible to limit overall side effects. But of course, if the patient is in complete remission and is doing very well, I tend to try to wean off. That's my particular style. You'll find different styles with different folks who treat these diseases. But I'm using clues too. I'm using the clues that I mentioned but sometimes we can look at antibody levels in the blood, for example, I mentioned the ELISA in my talk. For bullous pemphigoid, you can look for and follow the antibodies present in the blood with the ELISA against BP 180 or BP 230. Ideally, it's very high at diagnosis and then as you treat, the patient doesn't remission and it goes down to zero or negative. That's somewhat reassuring and what I would call a biomarker, that you're doing well and I can consider weaning off completely. So we use all the clues we can to try to figure out how to wean off. Now, some folks may say, I want to keep on them a little longer just to be on the safe side. Not unrealistic and maybe totally reasonable, on a case by case basis. But for most of us who are treat the disease, I think the goal is ultimately to try to lean down as soon as we can, then try to wean off, assuming the patient is in remission.

Amethyst: Great. Thank you. Sally asks, does MMP with eye involvement ever go into remission or is it always chronic? And should they keep up with an eye doctor to continue watching any eye involvement?

Dr. Feldman: Yeah, I usually do recommend continuing follow-up. Again, it's a difficult thing because what's the markers for disease activity with the eye? We don't really have good blood markers so we rely really heavily on the eye doctor to tell us if the disease is still active or is the disease quiet? I typically have patients, if their disease is still active, follow more closely with opthamology on a regular basis along with me and we come together as a team and figure out what's the right treatment goals here and if we need to adjust as we go along. But as the patients do much better and the eye doctor says, the patients is in remission and the eyes are quiet, again, we try to wean medications down as low as possible. I still keep patients going to the eye doctor at least once a year if they are in remission. Again, a case by case basis. If there's other clues and something else is changing, sometimes they go less or sometimes more depending on the comfort level of the eye doctor. It's also important, if you do find a dermatologist who's treating the ocular pemphigoid, you want to find a corresponding colleague in ophthalmology who's comfortable seeing these patients. Remember, most ophthalmologists have never seen that disease either, believe it or not even though it's an eye disease. They may have heard about it in med school or residency but many ophthalmologist have never

seen ocular pemphigoid before. I think it's the same sort of discussion you should have when you find that right person who's going to treat the disease, who's the person who's going to follow the eyes? I usually talk about how I am the quarterback if you will. I'm the one managing the systemic medicines and my eye doctors are the ones that are telling me, things look good or things don't look good, you need to adjust them. So we worked as a team and that's really important. The IPPF, can be also helpful in helping you find that treating eye doctor and where you can go potentially. So it's really important and it's a multi-disciplinary effort as we call it. It takes multiple physicians sometimes to treat these diseases. It really depends on where the inflammation is, whether it's the eyes and it's going to be an eye doctor with the dermatologist. If it's the mouth you might need a dentist or a Periodontist or the ENT. Or even the GI doctor if it affects the swallowing. That's going to be conversations held with the team. So, I have my team here at my university. Hopefully, the other dermatologists treating these diseases also have their teams that they can go to if they have questions or concerns about different body parts. Then if it involves the genitals, sometimes the disease can involve the genital area, that's going to be in females a GYN doctor and in males urology. And also the genital-anal area can be involved too, so sometimes we have colorectal surgery, sometimes we have to get involved. There's areas there that we're concerned about as well as GI. So it really depends on the context of where is the involvement of the antibodies? What part of the body are they attacking, that somewhat dictates, who's going to be the team of physicians who are going to treat you? Sorry a long answer to a short question. It's so important just to open the communication channels.That's the most important thing. Just, talk to your dermatologist. If you don't feel like you're getting the right answers you need, of course you can go to the IPPF. You can always get a second opinion too from another specialist who may have seen more cases and has a team of folks that are able to help you.

Amethyst: That's great, we like to get the team involved. Speaking of remission, we get a lot of questions about this. If a patient goes into remission, are they ever cured? Do you ever use the word cured?

Dr. Feldman: We don't really use the word "cured" too much in autoimmune diseases. We use the word remission. Our goal is remission, that is the disease is, as far as we can tell quiet. Everything's healed, you're not getting any new lesions. My goal is to get you back to your normal life. I want this disease to not bother you anymore. It's a combination of goals of getting the disease biologically quiet, but also quality of life. I want you to get your quality of life back, somewhat to what you had before this crazy disease came on. My goal is to get the disease to where it's not bothering anymore or minimally bothering you and it's not disrupting you like it was when it first flared. So that's my two prong approach. Yes, remission means as far as we can tell, totally quiet. Now, if you want to use the five year remission or ten year remission like cancer doctors use as a measure for "cure" it's up to you but for the most part, I never say the "c" word because we just don't understand what that means yet in autoimmunity.

Amethyst: Great, thank you. Elizabeth asked, have you ever heard of cases of MMP being associated with other autoimmune diseases? Are there instances where MMP goes away after a period on its own?

Dr. Feldman: Yeah, so definitely. Any of the autoimmune blistering diseases can be associated with other autoimmune diseases, that is very true, MMP included. I just had some cases today in the clinic. The patients had rheumatoid arthritis and pemphigoid, psoriasis and pemphigoid. Autoimmune thyroid disease sometimes comes with pemphigoid. I will say bullous pemphigoid in particular seems to have a propensity of having other autoimmune conditions that are more neurological in nature, such as multiple sclerosis or a condition called neuromyelitis optica which is a form of multiple sclerosis which can form with bullous pemphigoid.So the short answer is yes, patients can have more than one autoimmune disease at the same time. So sometimes what I try to do is find treatments that potentially treat both diseases so I'll kill two birds with one stone. A scenario where sometimes you can use it to your advantage, so we can use something to treat both rheumatoid arthritis and pemphigoid. Sorry, what was the second part of the question?

Amethyst: Does it ever go away on its own, without any treatment?

Dr. Feldman: That's a good question. There have been some studies that have shown the ten year rates of some of the blistering diseases, the rates of remission are about 75%. So, yes some diseases can, what we call “burnout” on their own. I tend to say the longer it goes on, the more chances that it's going to potentially burnout, even potentially without therapy. But again, it's hard to find those cases because most people get therapy. But if you had a mild case of pemphigoid for example and it wasn't aggressively treated, the longer you go, the more likely it's going to potentially burn out and go quiet on its own. That is true.

Amethyst: That seems like a long time, though to be in pain and not on treatment.

Dr. Feldman: You are right, it is.

Amethyst: Great, thank you. Sarah asked, is there any data around regional diagnosis? Is it more common in the US or Europe or Africa or Asia?

Dr. Feldman: Not that I'm aware of in terms of bullous pemphigoid. It's the most common autoimmune blistering disease in the world. I don't think that there are necessarily geographic hotspots for bullous pemphigoid as compared to some of the other autoimmune blistering diseases. In other words, most dermatologists around the world have treated patients with bullous pemphigoid.

Amethyst: Great. Thank you. Robert asked, is it okay to get the shingles vaccine if you have pemphigoid either active, or maybe even in remission?

Dr. Feldman: That's a good question. So, the new shingles vaccine we tend to think is okay because it's a killed vaccine, as opposed to the live vaccine, the previous one. So, the short answer is yes. But, again, it's a conversation that needs to be had between the dermatologist and the primary care physician who is going to be potentially administering it whether it's appropriate and depending on the context, whether the patient's on immune suppression. But in general, we consider the new shingles vaccine okay for the most part.

Amethyst: Great, thank you. Deb wrote in and she said, have you heard of bad reactions to increased doses of doxycycline? Recently, her doctor increased her dose from 40 milligrams to 200 milligrams. And she had very bad side effects including blurry vision and being tired so she stopped. The doctor then reduced it down to 100 milligrams, but now she seems to be okay.

Dr. Feldman: With a lot of medications there is definitely a dose dependent profile in terms of toxicity or side effects. So yes, she may have had a reaction to the higher doses. I would say the more common side effects with Doxycycline would be GI upset, stomach upset is very common in higher doses of doxycycline. The side effects she is describing, I am not sure. I would have a conversation with the treating dermatologist in terms of those unusual side effects.

Amethyst: Wonderful. Armine wrote in and said she was recently diagnosed with BP and she's 36. Her daughter is now 11 months old. Her IgE was very high during her pregnancy, what could be the cause of that and how can she reduce that high IgE?

Dr. Feldman: I just wonder if this was a case of gestational pemphigoid. In terms of bullous pemphigoid, it’s very common to see very high IgE. It seems to be that pathway that is activated with bullous pemphigoid. We tend to think of the IgE pathway involved with allergy type symptoms. So it's very common to see a very high IgE and there is also evidence that the IgE may actually be binding to that BP 180. There are a fair number of studies suggesting that it may play a bigger role than we think it does. What was your question?

Amethyst: I think she was asking, is there a way to get her IgE down? And do you think it was mostly from the pregnancy?

Dr. Feldman: I'm not sure. I would have to hear more about her case. In terms of following patients, do patients do better when the IgE comes down? I'd say we don't really know and I would say for the most part, it tends to trend down as patients get better, but not always some patients can still maintain a very high IgE and still be doing well. But I'm just wondering, given her age and profile, she might have had the pemphigoid during pregnancy and that is what we call gestational pemphigoid and that can act just like bullous pemphigoid, very similar.

Amethyst: Rhonda said she suspended her Mycophenolate for two weeks on the advice of her dermatologists, when she got her first COVID vaccine. Within a week, she was experiencing mouth and scalp lesions. Would you recommend suspending the Mycophenolate again for the second COVID vaccine?

Dr. Feldman: That's a great question, and we don't have good answers on these questions yet. Still an active area of research to try to figure out what's the best way to administer the COVID vaccine for patients with immune suppression. A couple of issues, one is the terms of the efficacy. Does Mycophenolate for example, affect the efficacy of vaccination if you're on it? And if you stop it, does that potentially help in terms of mounting a response? We don't know, actually. In theory, yes. That's why most physicians do recommend stopping it but you run the risk. Its a risk benefit ratio and you have that discussion with your dermatologist. So there benefit, of course, getting the COVID vaccine, you have to weigh against the risk of the disease getting active or flaring. So that is something we have to consider. Then it's the same caveat if you have the shots that require boosting, same issue with the second second dosing. So, we don't know the answer and what the best way to do this is yet, to be honest with you. You may require another boost potentially on immune suppression, if you didn't get a good effective vaccination response.

Amethyst: Great, thank you. Renee also asked, do you recommend the MMP patients get tested for antibodies after receiving the COVID vaccine, especially if they're on immunosuppressants? Are there any specific antibody tests that you recommend?

Dr. Feldman: No specific tests, you can get tested for the COVID antibodies, the spike protein antibodies, you can get tested for that. That's totally reasonable. I think that the trouble is what do you do with the results? So this is something important to have a conversation with the dermatologist about. Let's say, it's negative, you didn't seem to mount a response although the time frame is not quite clear when should we look, how soon after the vaccine? If it's positive then of course you wanna assume the patient's immune, but you really don't know necessarily, in terms of the quality of the immune response against the vaccination. So I think we still don't know enough yet, so I can't answer those questions easily. It's not so black and white as we'd like to make it out. But yes, you can request to have the antibodies tested. Some patients have

called me and said, look I got my antibodies tested and I am positive then we would just have to assume that is probably a good thing. They are probably, potentially protected. But I think we need to wait for further research to come out and there's some ongoing studies. We're actually even involved and the NIH is very interested in trying to figure out these questions because we may need more boostings or yearly boostings potentially for COVID. We don't quite know yet, so if that's the case, then we have to make sure all of our patients who have autoimmune diseases and on immune suppression, we have some well defined general guidelines for all of us to follow. So stay tuned, still research in progress.

Amethyst: Great, thank you. Dana also wrote about that. She said she did receive the Pfizer vaccine, but then she didn't show any response. Have you heard of any patients getting a third booster shot yet?

Dr. Feldman: Yes, I just had one last week. Third, maybe fourth, we don't know. So yes, we do have that. Again, another NIH sponsored trial to potentially evaluate whether or not a booster would be something that's appropriate for certain groups of patients including our groups of patients who have autoimmune diseases and are on immune suppression. So the answer is yes, that is a possibility, but again, the discussion needs to be had between the treating physician and the patient.

Amethyst: Great, thank you. You may have said this already, Elizabeth asked, if you're immunocompromised with Rtixuimab how does the COVID vaccine seem to be responding to the Rituximab patients?

Dr. Feldman: Wonderful question. Don't know the answer yet. That's something we're actually currently studying. I could tell you that we published an article a few years ago looking at the response to influenza or the flu vaccine. If you had Rituximab and got the flu vaccine within three or four months, the vaccine response was very poor, actually. So it takes a few months for the B cells, particularly the circulating B cells to recover to get a vaccine response. Again, I'm extrapolating that to COVID. We don't know but if we extrapolate that, our general guidelines will be either you should definitely get the COVID vaccine before your Rituximab if possible, and allow at least a few weeks for your vaccine response to occur before you get the Rituximab. Or if you had the infusions already, you may want to consider waiting at least up to 3 or 4 months after infusions to get the vaccine, if you can. Obviously, if not and it needs to be given, then get it. I think the benefit of getting it outweighs the potential risk of anything. But we don't know yet if you're going to be completely protected, although some protection may be better than no protection, right? So, my answer is, just get it when you can get it, the COVID vaccine. But it may be that within the next few years we may find that patients who use

Rituximab, there may be a more appropriate window we need to give it when we can maximize the efficacy of the vaccine.

Amethyst: Well, that was a very quick hour. We're already past the hour, so thank you so much for being on the call with us today. Thank you all for joining us, and a huge thank you to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, argenx and Cabaletta Bio for making today's call possible. I know that we had many questions that did not get answered today on the call so if you would like to email me after the call, we can go ahead and try to get your questions answered. My email is amethyst@pemphigus.org and we'll definitely try to get all your guys' questions answered. Before we go, I do have a few quick announcements. Our next webinar will be next Tuesday, May 18th to discuss the ADDRESS Study, a Phase 3 pemphigus trial, with Dr. John Holtz, Associate Medical Affairs Director for Dermatology and Kathrine Perez, Head of Global Patient Advocacy & Policy at argenx. Please join us and registration will be opening tomorrow. Also, the IPPF has several upcoming virtual patient support groups around the country that will be meeting in the next few months. To find a virtual support group visit our website www.pemphigus.org and click on the news and events tab. This is a great way to connect with other patients in your area and have more support so we encourage you to do so. The IPPF is looking for patient advocates to represent the pemphigus and pemphigoid community during the Virtual Rare Disease Week in July. This is a great opportunity to share your story with your representatives as well as make a difference and advocate for legislation that will help pemphigus and pemphigoid patients have better access to treatments and increase funding to advance medical research for rare disease. To find out more please email Marc Yale, the IPPF's Research and Advocacy Coordinator at marc@pemphigus.org. The IPPF and RDLA will provide training to prepare you for this event. We hope that you will consider joining us as we the more pemphigus and pemphigoid voices that are heard the more of a difference we can make, together we are strong.

Amethyst: The IPPF has been looking towards the future and how we can continue to help you and our community. We need your help to grow our community of Healing Heroes. Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small, even a $5 or $10 monthly donation goes a long way and continues to allow us to provide for the greater good of our community. If you have not registered for the IPPF's natural history study we encourage you to do so. The IPPF Natural History study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). You can register today at www.pemphigus.iamrare.org. This online data system collects, stores, and retrieves patient data for analysis in research studies. The more data we can collect, the better the information we can give to researchers, the sooner they can find better treatments, earlier diagnosis, and one day – A CURE! Lastly, If you have a question that didn't get answered on the call, or have additional questions please contact one of the IPPF's Peer Health Coaches on our website by visiting: www.pemphigus.org/peer-health-coaches/ or you can call (916) 922-1298, and we would be

more than happy to help. This call recording will be sent out with the survey following this call. Thank you all so much for joining us. Thank you so much Dr. Feldman for being such a great resource to our community. We appreciate it.

Dr. Feldman: Thank you everybody. Great questions.

Amethyst: Wonderful night, everyone. Thank you so much for joining us. Bye.