Becky: Hi, everybody! We are sorry for the brief delay, but we are now recording. I'm Becky Strong and I will be your host for today's webinar. Thank you very much for joining us. I'd like to thank you for being on the call with us, and for the support provided by Sanofi and Regeneron for making today's call possible. It is my pleasure to introduce our speaker for today. Dr. Annette Czernik is the Medical Director of DermMedical in Wilton, CT. She has completed an Immunodermatology research fellowship under the direction of the late Jean-Claude Bystryn, MD, at NYU Medical Center. The focus of her practice and her research over the last 10 years has been investigating optimal treatments for patients with recalcitrant autoimmune blistering disease. Dr. Czernik is the recipient of several notable research awards and has authored numerous peer-reviewed publications and book chapters relating to her work in pemphigus, pemphigoid, and other autoimmune conditions. She has spoken at several national and international meetings and is a supporter of the International Pemphigus and Pemphigoid Foundation. Currently, she is the principal investigator on several clinical trials in pemphigus and pemphigoid and routinely mentors students, residents, and fellows interested in bullous disease. Now I'd like to go over a few housekeeping items… (Reviews Housekeeping Instructions).

Dr. Czernik: Hi, everyone! Good morning to the west coast and good afternoon to the east coast. I'm excited to be here to talk to you guys about prednisone and corticosteroids. I get the most issues with patients in regard to this topic, so it's good to kind of iron out some of the details. I did take a look at the questions that a lot of people had submitted ahead of time, and did my best to kind of integrate answers within the course of this talk as much as possible. So I'm going to go ahead and get started. So what are steroids? This is a good question. We use this term quite a bit to mean a lot of different things. So steroids are, of course prednisone which is the main oral steroid that we use to treat pemphigus and pemphigoid in the U.S., but it also refers to other things like topical steroids. We use topical steroids all the time, like Clobetasol is a common one, and triamcinolone and there are intralesional steroids that we inject into spots. There are also other types of steroids like the steroids that people can take if they're trying to gain weight. You know the people at the gym, you might see some people that are on steroids. So they can refer to a lot of different things. Next slide.

Dr. Czernik: There are natural and synthetic steroids. Natural steroids your body makes on its own, and those include 2 main categories like your sex hormones, testosterone, estrogen, progesteron . And there are stress hormones like cortisol. So your body produces these in order to allow you to function on a day to day basis. We can create synthetic versions of these proteins and deliver them to patients to exploit different properties that they have to get an

outcome that we're looking for. So prednisone is a synthetic version of cortisol. Cortisol is naturally produced by your adrenal glands every day. Every single morning you have a bullet of cortisol that's put into your body naturally that helps you get up in the morning and function. So a lot of times when we get up we can get up, and we feel energetic. We feel like we're ready to take on the day. We also may feel a little queasy like we're not really ready to eat yet when we first wake up very early in the morning, and that's often the result of that natural cortisol being released. When we compare the amount of cortisol that our body makes on a daily basis, it's equal to about 5 to 7 milligrams of prednisone. So every morning your body gets this kind of low dose of prednisone to get you up and running. When you're under a lot of stress, when there's a lot of stress in your environment, that will increase. You may have higher levels dependent upon what your body needs to manage that stress and the cortisol helps you manage stress. Next slide.

Dr. Czernik: What's the difference between high dose and low dose prednisone? High dose actually has the definition. A lot of clinicians agree that high dose is roughly around greater than 15 milligrams a day of the synthetic cortisol of prednisone. At high dose, prednisone has a lot of different properties. We use it to treat disease states, and it works pretty quickly. It works actually much faster than almost all other medications that we have. So we use it to treat a lot of inflammatory diseases. In conditions like asthma, pemphigus, and lupus nephritis, which is an autoimmune condition that attacks your kidneys. For drug reactions, it actually is life saving. So without the use of steroids a lot of these conditions can be very, very deadly, and so high dose prednisone can really bring down the inflammation in these conditions, and allow us to bridge over to more chronic therapies. Prednisone works really fast, which is great but it's not a cure. So if a patient has a chronic condition that requires ongoing treatment, we use prednisone to bridge them over to management with medications that will maintain them, that may not work as quickly, but will kind of keep their disease under control. What we find is if we pull back on the prednisone or the other steroid that we are using, quicking, that sometimes these chronic conditions can flare up, so we often need something else on board, so that if we pull back on the steroids the disease doesn't flare up. In some cases, in certain conditions people can actually develop a rebound where the disease is worse after we pull back on the steroids than it was before we started. So there's definitely a need for ongoing management of chronic conditions. Next slide.

Dr. Czernik: Looking at high dose prednisone, it's a very powerful drug. So we're using much higher doses than our bodies are able to make naturally. We usually say it affects every cell in

the body, and we don't really know how it's going to affect every cell. So in some patients they may have certain things happen, in other patients they have other things happen. What it does is it triggers your body to develop new proteins and changes the way that the cells behave over time. It quickly shuts down the immune system, and that's part of why we use it in medicine is to create an immunosuppression which can prevent the disease from progressing. We know that it impacts neutrophils, it impacts T-celled and B cells. So it's affecting multiple branches of the immune system. We know specifically in pemphigus that it actually reduces levels of autoantibodies as well. So it acts pretty quickly to reduce the autoantibodies that we think are triggering the disease. We also know, with a study that was done with Dr. Werth that it actually can lead to re-attachment of the skin. We don't understand how that happens but believe it or not, using these high dose steroids, short term can actually lead to the skin to re-adhere to itself when a patient has a lot of active bulla. Next slide.

Dr. Czernik: However, there are side effects, and the side effects are very common. Number one is that when you're on these medications your body's natural production of cortisol will diminish. So your adrenaline glands kind of go to sleep. They're like oh, I'm not needed anymore, the body is getting a lot of synthetic cortisol, so it's not important for me to continue to produce it. So your body stops making natural cortisol. There are short term side effects and long term side effects and I'm going to talk about that in more detail. Next slide.

Dr. Czernik: So I defined short-term side effects as side effects that are very likely to occur within the first 30 days of starting on prednisone. They may occur the first day, but typically they occur within the first 30 days. I defined long term side effects as side effects that typically would occur when you're on high dose steroids for longer than 30 days. So number one is insomnia, this is pretty common. Almost everyone who is on high dose steroids will to some degree experience difficulty getting to sleep at night. This is a stress hormone, this is again activated when your body is under a lot of stress, so you often have a lot of energy, and you're not able to wind down in the evenings. This can be associated also with anxious energy and anxiety. I will sometimes tell patients that their house will never be as clean as it is when they're on the high dose steroids, because you will find things to do throughout the course of the day. You'll be cleaning your coffee maker at 3 am. They'll be behaving in ways that are just not typical. It could also lead to mood disturbances, depression, anxiety. It can also trigger psychosis. Psychosis is very severe. It's when you have delusions, you're paranoid, you're seeing things that aren't there, you're hearing things that aren't there, you're having hallucinations. This is a very serious, albeit fairly rare consequence that can happen when you're on high dose steroids and it actually

requires hospitalization and treatment. People can feel achy. Their muscles feel not right. They can develop stomach ulcers. In the very short term use, within the first few days the appetite can diminish but then, after being on high dose steroids for longer than a few days, usually people usually have a very increase in their appetite. They're hungry all the time and they can't get enough to eat. They can develop swelling, so it causes water retention. Within a few days of starting to take medication, you might have gained 20 pounds, and that's all water. That's water weight that goes on really quickly. But again, if they're also eating, then you can also gain fat as well. In the short term, you are at an increased risk of infection as well as acne. People can break out predominantly on their trunk, but they can also break out on their face as well. Next slide.

Dr. Czernik: Long-term side effects include again, weight gain which goes hand in hand with increased appetite. However, even if you're not eating much, you may still gain weight, because this is a stress hormone that causes your body to put on more weight over time. It also reduces bone mass and increases the fragility of your bones. Your bones are more brittle and more likely to fracture. It increases your risk of cataracts and glaucoma in the eyes. Because of all that water retention, you can have an increased risk of high blood pressure, hypertension as well as diabetes, your sugar can increase. The risk of infections will continue as long as you're on high dose steroids. And then, again, that risk of adrenaline sufficiency which is where your adrenal glands are no longer functioning normally, because you've shut them down by taking prednisone. Next slide.

Dr. Czernik: So now we're going to re-shift our focus back around to talking specifically about the usage of steroids in pemphigus and pemphigoid. Next slide.

Dr. Czernik: When we're approaching a patient with pemphigus or pemphigoid there are four main steps in the management. So number one is, we want to establish a diagnosis. So does this patient have pemphigus or pemphigoid? That's typically done before they come to see me with all of the criteria needed to establish the diagnosis. Number two, is controlling the disease. We want to shut down that inflammation in the skin. We want to get their skin to heal. We typically need to do that by using systemic steroids, using high dose prednisone. Number three, is we want to manage them chronically. We're not going to use high dose steroids long term. We want to initiate a steroid sparing agent, some medication that's going to manage their disease chronically, so we can get them off of their steroids as quickly as possible and minimize the risk of needing to go back on them. And finally, we want to minimize side effects of therapy. That's the full gamut of how we approach a patient with bullous. We establish a diagnosis, we calm it

down with steroids, that's the role that steroids play. Steroids play the biggest role. Then we maintain them, and we minimize side effects along the way. Next slide.

Dr. Czernik: Looking at pemphigus. This was an article published by experts, not only nationally, but internationally, who treat patients with pemphigus They gave us a poll and said what do you guys think is the absolute necessary first line therapy for these patients, and we all agreed that in patients with moderate to severe disease, corticosteroids so prednisone, methylprednisolone, etc., were absolutely necessary to shut down the disease process. We also agreed that Rituximab was necessary as a first line therapy. So again, patients will require, at least initially, corticosteroids in order to bring down their disease as a first line agent in pemphigus and this is pretty universally agreed upon nationally and internationally. Next slide

Dr. Czernik: In pemphigus, we typically will start patients on anywhere from 0.5 to 1.5 milligram per day kilogram per day, that comes out to roughly 40 to 80 milligrams a day based on disease severity, the weight of the patient, etc. Then we wait and see how the patient responds. Then we wait and see how they have it, how the patient responds. We typically will see patients back anywhere from 7 to 14 days after starting on high dose steroids to decide whether or not we can begin a taper. We make that decision based on if we're able to control their disease. So if they have disease control, and what that means is that they're not getting any new blisters, and their existing blisters are beginning to crust over and they have a negative Nikolsky sign, meaning if they were to accidentally traumatize their skin or bump into something, they don't develop new lesions. That means the disease is starting to be controlled, and we can start tapering them. In very rare instances in patients with extremely severe pemphigus, we'll actually put patients in the hospital and give them IV steroids. We give them up to one gram a day of methylprednisolone to really shut down that disease as quickly as possible, and maximize our chance of having that skin re adhere to the blister. Next slide.

Dr. Czernik: Once the patient's disease has gained control within those first few weeks, we want to initiate tapering them slowly off of their steroids. How quickly or how slowly we taper depends a lot on how the patient is responding, how their disease is responding, I should say, and also the clinician and their comfort level. So I see patients back every 2 to 4 weeks, and I taper them by 20% every 2 to 4 weeks until I get to about 7.5 milligrams daily, and from there we go very, very slowly. That number is important, right, because that's the number where your body starts making its own natural cortisol. So at that point we're no longer treating the disease,

we're just gradually tapering off of the steroids, so your body can begin to remake its own natural cortisol. Next slide.

Dr. Czernik: So shifting to some factors relating to bullous pemphigoid and as opposed to pemphigus. So bullous pemphigoid is a disease that's diagnosed in older patients, typically over 80's is common. We know both nationally and internationally, that these patients actually have very high mortality. Not just from, of course the disease but other comorbidities. Their age is the most important factor but in addition to their age their steroid dosage that's needed plays a big role in their overall mortality. We know that when we use very high dosages of steroids in patients with bullous pemphigoid, they are much more likely to have a high mortality. So it's definitely something that is critical in how we approach and how we manage these patients. Next slide.

Dr. Czernik: I'll divide the disease severity into 3 categories in bullous pemphigoid and we'll approach treating them based upon their disease severity. Next slide.

Dr. Czernik: Initially, patients with bullous pemphigoid may actually just have some itchy areas, maybe some eczematous patches, followed by maybe some urticarial papules and plaque, just some mild sort of rashes like this, which are comfortable, but can be managed with more minimal therapy, Next slide.

Dr. Czernik: Then, as the disease progresses, we start to see bullae formation. This patient has much more significant disease than the previous patient. Next slide.

Dr. Czernik: Then, of course, this patient is completely covered. This patient has very severe disease, and it's going to require a different type of management than a patient with mild or moderate disease. Next slide.

Dr. Czernik: So again, experts agree that prednisone overall is the best initial therapy in most patients, especially patients with more significant disease. What's different in pemphigoid versus pemphigus is that we're going to use lower dosages of it. We're going to try to stay as low as possible until we're able to achieve, again control of the disease activity, meaning that they're not getting any new lesions and their existing lesions are starting to heal. A lot of it depends on the disease severity, the patient's comorbidities, their age, and other factors. The overall principle is that we really want to use the lowest possible dosage for the shortest amount of time. That's across the board, everyone is trying to do that, but we also need to treat the disease, we can't just let it go. Again lower dosages are associated with the reduced risk of

mortality. There's no optimal dosage regime. Different physicians will use different approaches but again, that overall principle is that we try to use as little as we need to. Next slide.

Dr. Czernik: This is an older study published by Pascal Joly, looking at using systemic steroids in patients with bullous pemphigoid, and they found that those patients with really extensive disease, they had severe disease, when they were treated with high dose steroids they had a greater mortality than patients with extensive disease treated with topical steroids. Okay, so clearly the systemic administration of the high dose steroids led to increased risk, and the most common causes of death were sepsis, cardiovascular disease, and stroke, which are all which are all consequences that can occur when you are on higher dosage of steroids. It's just another warning that we really need to be careful in pemphigoid specifically in using higher dosages. It doesn't look like using low dosages, which is considered in this study to be 0.5 milligram per kilogram per day, had an effect on mortality in patients with moderate disease. The steroids were utilized and utilized well, but it's just those higher dosages that we need to be careful of. Okay, next slide.

Dr. Czernik: I don't want to go into detail with treatment options, because that's not the focus of this talk. But I just wanted to briefly say that in mild disease we do try to use topical therapies and intralesional therapies and avoid systemic steroids in pemphigoid. Whereas in patients with moderate to severe disease again, we do need to use systemic steroids. Next slide.

Dr. Czernik: Let's shift, and talk about side effects. I divided side effects into 2 categories, those that can happen in the short term, and those that can happen in the long term. There are no standard protocols that are used to minimize these side effects. Different clinicians will approach them differently. A lot of dermatologists really don't feel comfortable managing some of the side effects that can happen as a consequence of systemic steroid and will ask patients to really establish a good relationship with their primary care doctor or other sub-specialists that are appropriate for managing each individual patient. Each individual patient is unique, and they have their own risk profile and past medical history that also plays a role in how we approach some of the risks and side effects associated with the use of systemic steroids. Next slide.

Dr. Czernik: We sort of talked about the short-term side effects so I will go through that more in detail on the next slide.

Dr. Czernik: Insomnia, again, most patients are going to have this. I'll recommend that patients take all of their prednisone as one daily dose in the morning. So as early as possible in the morning, they can take it with food, so that it mimics their body's natural cortisol release, which

is when it would happen. Then by the evening it's more likely to have somewhat worn off, and you'll be more likely to wind down and get to bed at night. For patients, I'll always recommend melatonin. Many patients have said that meditation does help them both with stress relief, and also with getting them to wind down in the evenings. If they need more than that, which many of them do, I will refer them to their primary care doctor to initiate additional prescription sleep aids. Mental health is a very real issue when it comes to pemphigus and pemphigoid, not only of course because of the disease itself, but also the prednisone wreaks havoc on mental health. So, having that knowledge of that number one, and also being connected to the IPPF and having a support system at home. Also having a primary care doctor that can screen you and just checking in regularly, making sure that if you're having symptoms that they get appropriately referred to a specialist. Appetite is a difficult one. I know the IPPF will routinely recommend that a patient gets referred to a nutritionist. I think that's absolutely appropriate. If a patient struggles with weight gain, in general who doesn't, then I think it's again a good option to sort of have those discussions. I will tell patients that there's going to be a period of time where they can't get satisfied with food. It doesn't happen with every patient but it happens with a lot, and no matter how much they eat, they're just still hungry. One approach that they can take is to just fill up big ziplock bags with lots of low calorie food like celery, and carrots and broccoli and rice cakes and things like that, that they can just munch on so at least they're not eating potato chips and cookies and things like that. Instead, they're eating things that generally are not going to be causing as much weight gain. Reminding them that it's a very short period of time. Hopefully just a month or 2 that they're on these higher dosages, and any weight that they've gained they can get off towards the end. Stomach ulcers can be a silent killer. Being on steroids increases your risk of a stomach ulcer which can bleed, and if they bleed it can be life threatening. So I'll recommend that patients take a stomach acid reducer first thing when they wake up. They're taking a proton pump inhibitor, which is Prilosec, which is over the counter, or an H2 blocker, which is Famotidine, which is also over the counter, 30 minutes after they wake up and after their prednisone has kicked in. They eat and they have their full dosage of prednisone for the day, which has a pretty good way of reducing the risk of developing stomach ulcers when they're on systemic steroids. If a patient has a history of stomach ulcers in the past, then they need more than just this, and I recommend that they talk with their primary care doctor or GI specialist about getting a prescription acid reducer which they may need to take throughout the course of the day. Water retention is common. You get swollen, your ankle swells, your face swells and so making sure that you're not taking excess salt can really help with that. Prednisone will also reduce your potassium levels which can kind of make people feel bad so

trying to incorporate potassium in their diet is helpful as well. Then, in terms of infections commonly, I'll have patients with really persistent lesions that just aren't healing, often on the scalp or other areas and I'll culture those and almost always they come back positive for staph, which in some ways can just be colonization lives in the community. It's quite ubiquitous, and if you have an open wound on your skin, you're going to be more likely to have it colonized or infected. So I find using doxycycline, which not only can reduce staph colonization and staph infection, but also can reduce some of the inflammation in pemphigus and pemphigoid to be really helpful. Also, Doxycycline can minimize acne so it's a two for one really, it's a kind of a win-win where we can use doxycycline, both to treat infections and also to reduce acne. I will recommend that patients of course, up to date on their vaccines. Next slide.

Dr. Czernik: Looking at side effects that can happen when patients are on steroids for a long period of time, at least 30 days, on high dose steroids. Most of these conditions we're going to really rely on a team of specialists, a primary care doctor, or other physicians that might play a role because this is really outside of the realm of what a dermatologist can do. Next slide.

Dr. Czernik: Osteoporosis is a really big issue. If I anticipate that a patient is going to need to be on systemic steroids, high dose, for longer than a month I will recommend that they talk to their primary care doctor about getting a baseline DEXA bone scan to determine what their risk level is. And if I think they're going to be on high to start for greater than 3 months, then I will initiate them on prophylactic bisphosphonate therapy. It's a very low dosage of an oral medication that helps prevent bone loss. Not many patients will fall into this category luckily, because I do try to taper patients off of the high dose steroids as quickly as possible, but some do, and they do benefit from that. Most patients will go on vitamin D supplementation to prevent bone loss. Almost everyone, even if they're not on high doses for very long, I do find it just also makes people sort of in general feel better. Due to the risk of cataracts and glaucoma, it's important to get an eye exam so I recommend an ophthalmologic evaluation. Pemphigus and pemphigoid can affect the eyes as well so it's important just to have a baseline eye exam regardless. Prednisone can increase your blood pressure, increase your glucose. These are things that your primary care doctor generally checks as part of every routine check-up. So again, establishing a relationship with your primary care doctor is important to monitor for these things. We are vigilant to make sure that we identify and appropriately treat any infections as they come up, if they come up. Pneumocystis prophylaxis is a little bit controversial. I'll talk about that in the next slide. Advocating for psychological support is important. I think the IPPF is a really great resource in many regards for this, but of course having a support system, being

able to talk to your doctors, having a primary care doctor you trust, being referred to as a therapist if you need it is important. In patients who are bed bound, which is more common in really severe patients with pemphigus or older patients with pemphigoid, I will recommend that they talk to their doctor about getting physical therapy as their disease is improving to get them back up and going. Okay next slide.

Dr. Czernik: Pneumocystis prophylaxis, pneumocystis is an infection of the lungs. It's a type of pneumonia that's very rare, very, very rare. We've seen it primarily in patients with HIV that progress to AIDS so it's extremely rare these days. When they got very, very sick and were immunocompromised they were at risk for developing this infection, and it had a very high mortality rate, a 30% mortality rate. What we know is that when patients are on immunosuppression, when they're on steroids usually in combination with other immunosuppressants, they are also at risk for the development of this type of pneumonia, although it's very, very rare. There is no agreed upon protocol in autoimmune disease on how to prophylax patients for this type of pneumonia. This is an area of a lot of disagreement, and a lot of clinicians will take into account a patient's history and their risk factors. Older patients, patients with pre-existing lung disease, are going to be at greater risk and so they might be more inclined to initiate prophylaxis. There are a couple of studies that came out, one that showed that in pemphigus and pemphigoid, patients didn't need pneumocystis prophylaxis because they didn't have a high incidence of pneumocystis pneumonia. Another study came out, there was sort of a European guideline that recommended anyone on 15 milligrams or higher a day for more than 4 weeks, sort of the definition of high dose steroids for more than a month required pneumocystis prophylaxis. Another study came out showing that the patients were really only at risk if they were on greater than 20 milligrams a day for 12 weeks. So depending upon your doctor and your risk factors, you may be recommended to start on prophylaxis. What that is, is a medication called Bactrim, although there are a few others, Bactrim is most commonly used. Taken once a day for 3 days a week, usually Monday, Wednesday, Friday. I do use new pneumocystis prophylaxis in my patients, who again are on high dose steroids for more than 3 months. I reserve it for those patients who I find are at the highest risk but again, this is based on an individual patient by patient basis, and not all clinicians find it necessary to do so. So I think it's good to have that these discussions with your primary care doctor as well as your dermatologists, to find what's the best for you individually. Next slide.

Dr. Czernik: So looking at sort of the timeline of when you're diagnosed, finally, you're initiated on therapy, and you're starting to feel better. The first initial month or two or few months when you're on high dose steroids, you're going to feel like crap. You're not going to be sleeping. Your lesions are going to be healing, which is great but you're going to start having these side effects that hopefully, we can sort of gain control over. This is sort of the dark days of these conditions where we're getting you better, but we have to sort of manage some of these side effects. Then somewhere around 12 milligrams to 7.5 milligrams, you're starting to feel more like yourself, things are getting better, you're feeling okay. Next slide.

Dr. Czernik: Then you start feeling like crap again. When you're going down below 7.5 this is when you start withdrawing. At the high dosages you have too much cortisol. You're stress hormones are so elevated, you feel awful. Then you get too low, and you don't have enough cortisol and so you feel you start feeling like crap again. This is the steroid withdrawal phase of the treatment. Next slide.

Dr. Czernik: Steroid withdrawal is when patients who are at risk again or patients who needed greater than 15 milligrams a day for over a month. So if we were to just abruptly stop steroids after one month their adrenal glands would be sleeping, and they wouldn't know how to make normal cortisol, and the patient can get very, very sick. So we want to make sure that when we are getting patients off of their steroids we do so really, really, slowly and gradually, so that they don't get sick and their bodies adrenal glands are able to regenerate that normal cortisol that's healthy for them every morning and help them get out of bed in the morning, etc. So when you're taken off too quickly, you might have some symptoms, including loss of appetite and weight loss, almost the reverse of what we're seeing when you're on the higher doses of steroids. Fatigue, you can't get out of bed in the morning, body aches, joint pains. The joint pains may be related to the fact that you may have had some arthritis that was masked by the steroids and then when you're taken off the steroids that tends to flare and you have this flare up in the arthritis. You may have dehydration, so unlike the swelling that you had when you're on high dose steroids, now your body doesn't have enough fluid and you can get dehydrated. Dehydration can be really dangerous. You can get dizzy and faint. You can be at risk for cardiac events, etc. So you really want to make sure you're taking in fluids. You can have diarrhea. So you want to not only take in fluids, but make up for the fact that you're losing fluids so that you don't get dehydrated. This can be very serious so it's important that as we're tapering down on the steroids, we do it nice and gradually so that your body has a chance to make up for being under what it needs. If a patient has emergency surgery or any sort of major stressful event on

their system during the time that they're going through their steroid taper and they're at less than 7.5 milligrams, they may need what's called the stress dose steroid. Stress dose steroids are basically an extra dose, usually given through an IV, that helps that patient during the stressful event when their body probably isn't making enough of their cortisol. Okay, next slide.

Dr. Czernik: How do we manage some of the symptoms associated with steroid withdrawal? So number one is we want to taper patients very slowly. It takes me a couple of months to get them off of high dose steroids, but it takes me sometimes 6 months to get them off of very, very low doses because I really want to see that they're not having some of these symptoms, and we're able to manage them. Patients are really eager to get off of their cortisone, so I will taper them if they're ready, but if they're not ready, we'll slow it down. Now your adrenal glands are sleeping, and they respond normally to stress. So how do we kind of wake them up? Stress actually is what wakes them up. The best way of inducing stress for your body is exercise. If you're able to exercise while you're going through that sort of tail end of the taper, it really helps your adrenal glands get back up to where they need to be. Ideally weight bearing exercises can help rebuild your bones and rebuild your muscle and help you lose weight, and all the things that at this point in your journey, you really want to start tackle because you may have gained weight when you were on the higher dose steroids, etc., but any type of exercise really helps during this phase. Patients can have some lingering symptoms of steroid withdrawal sometimes for a few months after they've stopped their cortisone completely, but it's very rare for it to linger longer than that. If it does linger, it's probably something else that's going on. And again, it's important to have that evaluated with your primary care doctor. I have had patients who were going through menopause at the same time as they're steroid withdrawal. That was really like a double whammy, because menopause itself is the abrupt withdrawal of sex hormones, so of a different type of steroid, which can linger. You can have symptoms for years, many years, and then the withdrawal of systemic steroids used in their autoimmune bullous diseases was another hit to the system. That's another thing that I just like to bring up, as sometimes an under appreciated event that can make things even more difficult. Next slide.

Dr. Czernik: Circling back, the essential steps in management, we want to identify and accurately diagnose the disease, to control the disease quickly we rely on systemic steroids, usually high dose prednisone to treat pemphigus and pemphigoid when it's moderate to severe. We try to use as little as we absolutely need to, particularly in pemphigoid, as we know that high doses can be associated with greater mortality. We want to initiate a steroid sparing agent at the same time to manage the disease chronically, as we taper patients as quickly as we can, as

safely as we can off of their systemic steroids all while minimizing the side effects of treatment. Next slide. Okay, that's it.

Becky Strong: Thank you, Dr. Czernik. You really gave us a good primer and gave us a lot of great information on pemphigus and pemphigoid and using steroids. We have had some questions come in, and some questions were pre-submitted earlier. I'm just going to jump right into them if you don't mind. Isobel wants to say thank you for talking and taking on such a huge subject. But can you tell us the difference between prednisone and prednisolone? And if so, are there big differences? She says in the UK they're prescribing prednisolone.

Dr. Czernik: I don't consider them to be big differences at all. They're just more commonly used in Europe. In fact, there's this conversion that we do here where basically the dosages can be equated to equal each other with a small conversion factor. So, if a patient isn't responding to prednisone, I will start them on prednisolone because some people have found that patients will respond better to prednisolone than prednisone and vice versa most likely. So there is that opportunity to try something different but most clinicians will use them interchangeably. It's just standard of care in the U.S. that we use prednisone and in Europe they use prednisolone. They start at that spot, and they may switch over, over time if they're not seeing the response that they want. My understanding is prednisone is eventually converted to prednisolone. Potentially, if that patient has a difficult time making that conversion they might respond better to prednisolone but everyone is different, and I don't off the bat consider one to be superior than the other.

Becky Strong: Thank you. Carolyn and a few others have mentioned, and you mentioned it in your presentation about as they come down in their prednisone that their legs are hurting, and they don't know if it's a serious thing that needs to be looked at further, or if it could be just arthritis or other normal aches and pains.

Dr. Czernik: That's a very non specific symptom. We would need to sort of tease out exactly, is it a joint, is it the muscles? Does it correlate with the exact time that you went down on your dose? Did you go from 10 to to 7.5, and within 2 days immediately you started to feel an exacerbation of the symptoms. If the timing works out where it correlates really well, it likely is a steroid withdrawal symptom and using the strategies that I sort of talked about, going a little slower on the taper, integrating exercise, trying to make sure that you're staying hydrated, managing any concurrent illnesses that might be going on like arthritis are important. If there isn't a correlation, and your symptoms are continuing to feel like they're either being maintained

or escalating over time. So if you're on, let's say 7.5, and your symptoms are not improving at all, they're continuing to worsen, then it may not be related, and it's something that I think you should have evaluated with your primary first, and then they would determine if it needs further evaluation.

Dr. Czernik: Becky, I think you kind of froze on us. Ok Becky has another question, can the biopsies be affected by being on prednisone? So yes and no. I think if somebody is on prednisone and is completely clear, they have absolutely no lesions at all then sometimes it is harder to get an H&E but that is very rarely the case that a patient is 100% clear, because it takes a while for the lesions to heal completely. So, yes and no. The steroids of course are treating the disease, and if there's no disease left to treat, then the biopsy won't be able to demonstrate the disease, but the disease doesn’t appear overnight and it doesn't clear overnight. If we're thinking about taking a biopsy and we're worried about the steroid impacting it, I think unless you're planning to delay the biopsy by a month or more, it shouldn't impact your results. There are two types of biopsies that we do in immunobullous diseases. There is the H&E biopsy, which is what I'm talking about, which is where you actually look at the skin cells, and look how they oriented to each other; and if you don't have any active lesions, you may not be able to demonstrate the sort of the classic findings that we see in pemphigus and pemphigoid. Then there are direct immunofluorescent biopsies which are actually looking at the antibodies, and how they stain on the skin. Those are actually done on normal skin so usually we don't see that being on systemic steroids will play a role in reducing the likelihood of having a positive result in those biopsies. So I guess the answer is in the short, I wouldn't delay treatment because you're concerned that it's going to impact your biopsy results because you really need relief, and a biopsy can be done within a reasonable timeframe after initiating steroids where it shouldn't have any meaningful impact on your disease. And if it does, if you clear overnight, then this may not be an immunobullous disease. Each individual case is different, so I can't speak broadly without knowing the specifics but most of the time it's not a concern.

Becky Strong - Great, thank you. Joanne says that she has diabetes and she is wondering, are steroids an option for her for safe treatment?

Dr. Czernik: Yes, so there are a lot of patients who have diabetes and who developed diabetes even during the course of their therapy, and she's absolutely still a candidate for prednisone but a lot of times this requires close oversight between her and her chronologist and her dermatologist. So what we want to do is make sure that we don't put her body at

unnecessary stress or risk if she does require systemic steroids by utilizing various treatment approaches. Some patients will even go on insulin short-term because the steroids cause a more unpredictable shift in their serum glucose levels so we want to manage that. We know that it's only going to be a couple of months, probably that we are going to need this more tightly controlled sugar level and then we can get her back to her normal functioning once our steroid levels are below that threshold of high dose to low dose. Again, we try to avoid using steroids as much as possible. If a patient can tolerate lower dosages of it, and still maintain a response with their disease we're obviously going to opt for that, but we don't go into this lightly. We don't go into this thinking, we're using this only for certain patients, and not for others, because the truth is that these are really severe diseases that require therapy and without therapy, patients can really suffer. So there are really no instances where I would say I can't treat somebody. Yes, we absolutely can use prednisone but we would require more oversight and more management between the team of doctors involved.

Becky Strong - Great, that's an excellent answer. Thank you so much. Amanda is asking if there are any pregnancy safe topical steroids for someone with a mild case of pemphigus vulgaris that can be used on the face, scalp, neck or chest?

Dr. Czernik: Yeah, I use Locoid. Locoid is a hydrocortisone butyrate so it's a stronger version of the over-the-counter hydrocortisone, and I use it because we have long term safety data on over-the-counter hydrocortisone, because it's so accessible that pregnant women have been using it for various bits and bots and things for decades. So that's my go-to for pregnant women when they're concerned about using steroids. I'll say, okay, this has been used forever, and there haven't been any known issues with it. So hydrocortisone butyrate or Locoid is the trade name for that.

Becky Strong: Great, Thank you. We've also gotten a few questions, you talked about using vitamin D when you're on prednisone or steroids. What should the dose be that people take for vitamin D?

Dr. Czernik: I will routinely recommend 2,000 international units daily, which is double the daily recommended dosage, because I think the combination of needing systemic steroids and having an autoimmune disease, they can benefit from that extra bump in vitamin D. However, if they have a baseline vitamin D level that shows their deficient, then I will increase it from there, depending upon their own individual level. So if they have severe deficiency, for instance, I will prescribe or have their primary care doctor, again this all depends upon their clinicians

comfortability with treating more internal diseases, I'll prescribe a prescription vitamin D that's a very, very high level for them to take until they're adequately replenished. Then they'll go down to 2,000 IU daily, which is what I use as my floor level for patients who have adequate serum vitamin D levels.

Becky Strong: Great. Thank you. Frank asks, what are the guidelines on how long one can safely use a corticosteroid topical, such as Clobetasol orally?

Dr. Czernik: We don't know because Clobetasol has never been tested in its oral usage. If you really look at the prescription handout, it'll say, please don't use it in your oral mucosa. We're using it off label and because it's being used off label that kind of means that there aren't a lot of clinical trials, but we do know that all of us have been using it off label for ages, and we haven't had any real issues or concerns with it. So what I would say is using topical therapies is a way of sparing your body from systemic therapies. You now know the risks of systemic therapies, and they're much greater than topical therapies. So if you're getting relief, if it's actually helping your symptoms, then that's a win in my book and I'm not going to cut that off. I'm not going to say, you can only use it for 2 weeks. You can only use it for 4 weeks. I'm going to have you use it as long as you need to, because the alternative is a much stronger medication that has a much greater risk associated with it. So as long as you need to, is the answer because again, you're treating something with a topical therapy that is much safer than a systemic therapy.

Becky Strong: Great, thank you. Eca is asking after stopping steroids and having a clear period, how often do you find that there is a bounce back of disease?

Dr. Czernik: Hopefully, never right. So it depends on what the patient is on for maintenance. If the patient is on adequate maintenance, they're getting a drug that's working well for them, then they don't rebound. The whole point is to bridge them over to maintenance therapy. Maintenance therapies often need ongoing treatments as well. For instance, we'll talk about Rituximab since that's the most common maintenance therapy we use currently for pemphigus. We see in the clinical trial data that when patients receive Rituximab, 50% of them can relapse within a year if they don't receive ongoing Rituximab therapy. There is a high relapse rate but again, if patients are getting maintenance regularly that lowers the relapse. So if a patient is not on a maintenance drug, then 100% of them should theoretically relapse when tapering off of their steroids. Again emphasizing the importance of bridging therapy over to a maintenance

drug, initially when patients start with steroids, but certainly maintaining it once they've been tapers off of steroids.

Becky Strong: Great. Thank you. Lisa asks, with topical steroids being used on open wounds and lesions, is it usual to experience similar side effects of those to that of prednisone?

Dr. Czernik: Typically not. You can get some systemic absorption, which is a risk. But you're not going to get the degree, you shouldn't get the degree of risks that you get with oral intake. In fact, the study that really looks at this is that Joly slide that I put up and they demonstrated very clearly in a randomized trial that patients who got topical clobetasol, 40 milligrams a day, that's a huge tube, every single day of the strongest topical steroid essentially that's available, all over the whole body had a a reduced risk of mortality compared to patients on 1 milligram a day of per kilogram of prednisone. So the risk was substantially lower using the topical therapy versus the oral therapy.

Becky Strong: Great. We've also gotten quite a few questions about being on a low dose steroid, either 1 or 2 milligrams, or less than 5. How long can that continue? Are there any guidelines? Then second of all, you discussed the short and long term side effects. Are they the same if you're on a low dose, such as 1 or 2 milligrams, or under 5 milligrams?

Dr. Czernik: The side effects that we see are typically when you're on higher than 15 milligrams a day, below 15 is considered very low risk for side effects. Not no risk, but considered low risk, and certainly lower than 7.5, which is your body's basal level of cortisol is also considered extremely low risk if you were to sort of fractionate it. So the question is, can you be maintained on extremely low dosages safely? That is open for interpretation, it depends who you talk to. Historically, in the United States the goal has always been to get patients completely off of steroids. Historically in Europe it's been considered sort of standard to care to maintain patients on extremely low levels of steroid safely for many years. So there's just been different approaches to it, and I don't know that I have the studies or the knowledge to really say definitively, one approach is better than the other. Some patients who have a reduction in their symptoms at very low dosages of it, I don't have an explanation for why that would be. But I can't argue if they feel better with that. We don't have the data to say for certain, and I think that it's best to talked with your doctor about it, to decide what makes the best sense for you based on how you're responding and how you feel

Becky Strong - Great. Thank you. We got another question that asks, is bleeding while on steroids much more common than, when you're not taking steroids?

Dr. Czernik: Yes. Steroids will affect everyone differently, so some people will have a greater risk than others for certain side effects. Steroids will inhibit a protein called COX. COX acts in platelets and it's also inhibited when we take things like aspirin and other medications that relieve inflammation, and also increase our risk of bleeding. So yes, we do see that you're more likely to bruise, you have thinning of the skin, you're more likely to develop those stomach ulcers that I talked about, which again are more likely to bleed. So there is an increased risk of of bleeding

Becky Strong - Great. I think this is gonna be our last question. Isabella is saying that she has a 16 year old with PF who has been treated with prednisone and who now has osteoporosis. Is there a treatment recommended for young people for osteoporosis?

Dr. Czernik: So that I would refer to both the primary care doctor and a rheumatologist because they're going to be more adept at knowing the best ways of mitigating steroid induced osteoporosis. It's different from what we see with age-related osteoporosis. The way of navigating that is going to be, to talk with a specialist that's going to be familiar with that specific condition.

Becky Strong - Great, well you have provided so much information in such a short amount of time. We really appreciate the time and the effort that you took in preparing for today's webinar. And thank you so much for being here.

Dr. Czernik: Thank you so much for having me. It was great to see you, Becky, and I hope you guys enjoyed the talk. I'm so grateful to be a part of the foundation.

Becky Strong - This was really an amazing talk. Like I said, a big thank you to you and a big thank you to our sponsors, Sanofi and Regeneron for making today's call possible. Before we go, I do have a few announcements if we can go through those. So today's webinar was wonderful and we have another webinar plan for April 19th with Dr. Donna Cuton, who is the Associate Professor of Dermatology at the University North Carolina, Chapel Hill. Dr. Culton will be discussing Rituximab treatment. Registration is now open, and you can register online today. We also want to thank all of those who participated in the Externally Led Patient Focused Drug Development meeting that we hosted on January 25th. If you didn't get a chance to speak and share your or share your story we are still looking for people to submit

written comments. Please submit your written comments to pfdd@pemphigus.org. Written comments should cover either your disease, and how it impacted your daily life or treatments for your disease, the side effects of the treatments and how to improve them. Written comments should be no longer than 500 words, and all written comments will be published in our Voice of the Patient Report and shared with the FDA and industry partners and will be used for future decision making when developing drugs for our diseases. Next, 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 those 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 U.S. Food and Drug Administration (FDA). Your information is private, and the Natural History Study follows strict government guidelines to assure that patient information is protected. Your participation and the data that you provide 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 join the registry by visiting https://pemphigus.iamrare.org/.

Next, the IPPF needs your help. Your financial support is crucial to allow us to continue to provide free programs and services like today's webinar and our Peer Coaches. Your support also allows us to continue pushing forward research and educate doctors and dentists about pemphigus and pemphigoid. If you're interested in supporting these efforts, you can become an IPPF Healing hero. Healing heroes make monthly gifts to support our mission of improving the quality of life for all of those affected by pemphigus and pemphigoid. No amount is too small, and your monthly donation goes a long way. You can scan the QR code or visit www.pemphigus.org/hero to support our community today. The IPPF has a number of upcoming virtual support groups across the country. If you're interested in attending a meeting, please check the IPPF’s event page to register for a meeting. We're also looking to expand our support network. If you're interested in starting a support group in your area or region please contact me, Becky Strong at becky@pemphigus.org. It's a lot easier than it sounds to start a support group, and you can connect and help others in your areas to learn more about pemphigus and pemphigoid. Finally, the call recording will be sent out with a survey following this call. Thank you, everyone for joining us. Goodbye.