

April 12, 2022 Patient Education Webinar- Oral Systemic Treatments for P/P

Amethyst: Welcome, everyone! My name is Amethyst Yale and I am the Outreach Assistant at the IPPF. Thank you all for joining us today to discuss oral systemic medicines for pemphigus and pemphigoid. This call is now being recorded. I'd like to thank you all for being on the call with us today and to our sponsors, Genentech, 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's 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 healthcare team to determine if it applies to your specific situation." Before we begin, let's take a quick poll to see what current oral systemic medications you are on for the treatment of your pemphigus or pemphigoid. And, while you're answering that, I'd like to introduce you to our speaker for today.

Amethyst: Dr. Simpson is a board certified dermatologist and Assistant Professor in the Division of Dermatology at the University of Washington. In 2012, he graduated from the Medical Scientist Training Program at Northwestern University in Chicago, earning both his Ph.D. and M.D. His thesis research focused on the cellular functions of desmoglein 1, which is targeted in pemphigus, and led him to pursue clinical training in dermatology. After an internship in internal medicine through the University of Chicago, Dr. Simpson moved to the University of Pennsylvania for dermatology residency and served as Chief Resident in his final year at Penn. Upon finishing his clinical training in 2016, he obtained grants from the National Institutes of Health and the Dermatology Foundation, allowing him to return to research, applying genetic tools and imaging techniques to a model of human skin grown in the lab. In 2021, he was recruited to the University of Washington, where he is building a lab focused on understanding how the skin is compromised in dermatologic disorders and identifying potential new treatments to promote tissue regeneration for those with rare skin diseases. Dr. Simpson's weekly clinic in Seattle focuses on both autoimmune and genetic skin diseases, including pemphigus, pemphigoid, Darier, and Hailey-Hailey disease. Thank you all for taking the poll. I will quickly close that and share results for today. It looks like a good amount of you are currently on prednisone and Cellcept or Mycophenolate. So before we begin, I would like to go over a few housekeeping slides... (Reviews Housekeeping Slides).

Amethyst: Now it is my pleasure to introduce Dr. Cory Simpson to discuss the oral systemic treatments and medications that are used for treating pemphigus and pemphigoid and answer your questions. I will hand it over to you.

Dr. Simpson: Great, Thanks very much for the opportunity to talk to such a great group today. I've been in contact with the IPPF for many years and really enjoy my interactions, especially the privilege of speaking with patients. And I got to attend the Foundation's annual meeting a

few years ago prior to the pandemic when it was held in Philadelphia and really enjoyed meeting patients, especially those who are real advocates for folks who are living with these diseases. So thanks for tuning in today and hopefully we'll get to answer most of your questions after I provide a fairly lengthy overview of the diseases and then we'll get into the treatments as well. All right, I'm going to tell you a little bit about myself. So I started my training in blistering diseases when I was doing research at Northwestern University when I studied under Dr. Kathy Green, who's a fantastic scientist and mentor and she was working on this very important cellular structure called the desmosome which, if you take a really high magnification image, this is what it looks like. And I thought these were really beautiful structures, and it turns out that these structures are really important for holding the cells of your body together. So this is the nucleus of a cell and then it has some bones to it, like a skeleton. So all the tissues in our body, including the skin, the lining of our eyes and inside of our mouth, for example are made up of billions of these cells that have to be really tightly hooked to one another. So, what these desmosomes do is they basically take the skeleton of cells in the skin or the mucous membranes, and it basically staple them together to form a really strong adhesive mechanism so that when those tissues undergo mechanical stress, like just normal activities of daily living like walking, opening jars, chewing, eating, that they don't fall apart, that they stay stuck to one another. So what Kathy's lab had done over many years was to understand, what are the different components of these sorts of spots between the cells, what are they made up of? What we've found out is that when various components at these sort of chain links and interactions, when any link in that chain is broken, it leads to diseases. When the adhesion between the cells fall apart, the cells come apart in the skin and that's what leads to them falling apart, which manifests as blistering. So, this is an example of a patient of mine who had pemphigus. You can see the erosion on the back and then there are some intact blisters as well. But these can also be targeted in a couple of genetic diseases that I also see in my clinic called Darier and Hailey Hailey disease. So, I found this to be fascinating. My lab work then inspired me to go to the University of Pennsylvania to train to become a dermatologist where I had the opportunity to train with some outstanding dermatologists who are also running research laboratories. Dr. Aimee Payne and Dr. John Stanley, they were really instrumental in being my mentors to teach me about how to treat these diseases but up to then I had only studied in the lab.

Dr. Simpson: So we'll be talking about pemphigus and pemphigoid. I know for a lot of patients, these are new words that you're learning if you're new to the diagnosis. They are similar to one another, but there are some important differences but they both come from the root word pemphix which as I understand it comes from the Greek meaning of bubble or a blister. And I think it's important to understand, how do these diseases occur? What are the existing oral treatments that we have, which is the topic of today's seminar? And then, are there potentially new things on the horizon that might be coming in from trials and other sorts of studies to help us better understand and treat these diseases? So we'll try to get to some of that at the end.

Dr. Simpson: So, it starts mostly with the biopsy. And the IPPF has had a really important campaign called Biopsies Save Lives because many patients suffer for many years with their rare disease that most doctors they will go to see may never have seen in their lifetime. So it's really challenging, sometimes just to get the diagnosis. If a patient has a blister, this is an example of a blister on the top of my hand. It all starts with a biopsy. It really is very helpful to give us a diagnosis. So it's sort of like taking a small cookie cutter and taking a little piece of the skin out and I'm showing you this because some of the diagrams that I will show later, will use this type of dimension to show you what the skin looks like if we're looking at a biopsy. So if we take a little cylinder of skin out like a little plug or a little cookie cutter piece out and look at it from the side, this is what we see. There's an outer layer of skin, called the epidermis, there is an inner layer of skin made mostly of collagen called the dermis, and then there's fat underneath that. Most of what we do in dermatology is to look at a biopsy from a side view. In a blistering disease, part of the structure is actually defective. You'll see a gap between those two different compartments in the skin and that's how we can diagnose where the blister is occurring within the skin biopsy. So if we take a blade and make a section of these things and look at a very thin piece of it and put it on a microscope slide, we get something that looks like this. We have these upper purple layers, that's the epidermis, they sit on top of what sort of like an adhesive carpet that they sort of staple down to and then they hook into the collagen and that's in the dermis. And then that's attached to the fat underneath. So the blister can occur anywhere within this structure here. So we think about the keratinocytes which are these different cells that make up the tissue which is the skin. I think of them as sort of like different pieces that have to be riveted together. So it's almost like these different pieces of metal that have these rivets in them to attach them to one another, to make them a strong sheet of metal. Desmosomes are those really strong intercellular, they sit between the cells and staple them together. That word comes from Desmos, which is a bond or a link, and Soma which means body. So the cell bodies have to be linked together, in order to make this tissue really strong to keep it from falling apart. So, this is what the cells look like. What you can see is that there are all these little spines that connect them together and that's right where the desmosomes sit. They fix these two cells together and sort of staple them together or weld them together. That's what helps us to understand why pemphigus occurs like it does. In pemphigus you have these cells that have these staples or welds that stick them together. What happens is you develop auto antibodies against those sticky proteins that make the cells stick to one another. It's really an unfortunate disease because you get antibodies which are normally helpful for us to fight infections, but instead of recognizing a virus or bacteria, these antibodies which are these Y shaped little molecules here, they recognize your own self and they recognize that glue that is stapling the cells together. When this happens, the glue that would normally hold your skin cells together falls apart so the cells can't hold on to one another. What that does, it causes a split in the skin. It falls apart. When we look at it in patients they'll oftentimes have fluid because the fluid can seep into that breach in the barrier there. Looking at a biopsy, you can see there's all of this white space where it shouldn't be there and that's where the fluid has come in, the top layers of the skin have lifted off and that's what actually the blister looks like on a biopsy.

Dr. Simpson: So there are very different manifestations of pemphigus. Some patients only have skin problems or blisters just on the skin. It's become important to us to also recognize that pemphigus can look quite different depending on the background type of pigmentation that a patient has. So here's some examples, of a patient with a little more pigment in the skin and what the blisters and the open source can look like on their skin. You can also get a vegetative form of pemphigus where you get these sort of heaped or thick crusts. This was a case that we published of someone with these really thick plate-like scales on top of their skin, that was from mounded up, dead skin that had healed. Some people only present with blisters and the mouth. The lining of the mouth is very similar to the lining of the skin, to the lining of the eye, and to the lining of the genital structures as well. So people can have erosions, open sores and blisters in any of those areas. So some patients may have skin problems, other people may only have oral findings with pemphigus. So these are some examples on the lips, on the gums, on the sides of the mouth, and then on the pallet, which is on the top of the mouth in the back. You can imagine, as many of you have experienced, this makes basic daily living activities, such as talking, swallowing, eating, and drinking, it can make them very painful and difficult. So some patients may only have these manifestations inside of the mouth. They may start off seeing a dentist or an oral surgeon, or an EMT specialist, then may eventually finally go to a dermatologist's office later on. But this is one of the reasons pemphigus can be very tricky to get a diagnosis early on.

Dr. Simpson: There's another form of pemphigus called pemphigus foliaceus which is a little more superficial. The blisters are not quite as deep. And so those can often look like more shallow blisters or crusts. It can often have this scaly red look to them and some people might mistake it for something like psoriasis for example. Some patients will get it all over the face. It can really impact their ability to feel confident going out and talking to other people because they may have many crusts, sores or blisters on the face. Sometimes it can affect very large areas of the body. This was a patient that I saw who had what we call erythroderma where basically the whole body was red and basically a giant rash where all the superficial blistering was healing.

Dr. Simpson: So when we flip over to pemphigoid, which was named because it was thought to be pretty similar to pemphigus, although we found out that they're a little bit different in the way that we treat them and diagnose them. But the problem here is that this lowest layer of keratinocytes, which are the epidermal cells, have trouble sticking down to the basement or to the carpet that they're normally attached to. So in pemphigoid, it's sort of like Velcro that normally would stick the top layer of the skin, stick it down to the basement membrane or the lower layers of the skin. We think about Velcro as all those little hooks that sort of grab into these little loops. And so that's the way that these hemidesmosomes, which are on the bottom part of the cell, that's how they work. They basically staple that bottom layer of cells down to the lower layers of the skin so that it doesn't pull off. There are a lot of different proteins like those other diagrams that I showed you, it's chainlinks that basically have to hook to one another to make sure that there's a strong adhesion, stapling the skin down to the lower layers. So again, if any of the components of this link of interactions is compromised by either an

antibody or a mutation, the skin will lift off. In this particular disease, you can get antibodies that bind to this glue, the Velcro that should stick them down to that foundation. Then the whole skin basically lifts off of its foundation, so it's almost like a house that may shift off of its foundation in an earthquake or something. The whole thing lifts off and you get a little bit of a deeper blister where the fluid comes in. And this is why the entire epidermis in the biopsy shown here, completely lifts off of its foundation. That's why the blistering in pemphigoid is often a little bit deeper and we often get larger blisters like those shown here because the top layer that's the roof of the blister stays intact. You often get these large fluid filled blisters that can look, again, very different depending on what kind of background pigmentation you have. This was an African American patient of mine who had blisters, but you can't really see much of the redness in the skin, whereas a lighter skin patient has again, a lot of redness of the skin here. It's very important that doctors are trained to recognize these types of blisters in various different types of skin tones to make sure that everybody has access to a good diagnosis, which is really important for understanding how to treat these diseases.

Dr. Simpson: Some patients with bullous pemphigoid, the blisters may pop very early on, so they may actually just have very open and painful sores on the body. So they may not see actual intact blisters with the fluid in them. Then some patients may present with something called urticarial bullous pemphigoid, where they basically have hive-like lesions and they may not even have blisters. You might get what sort of looks like insect bites or sometimes hives can look just like this. But all these patients have bullous pemphigoid as well. Again with pemphigoid it can affect both the skin and mucous membranes, which are the wet linings of tissues like the mouth, the nose, the eyes, the genital areas. So you can get very painful erosions along the gums or along the sides of the mouth and tongue. And pemphigoid is more likely to affect the eyes in certain cases. Patients can actually get problems with the lower areas of the eyelids where they can start to stick to the eyeball itself. That could be a real problem for patients and they can end up like this patient on the right that ended up having scarring of the eyeball, which then impairs the vision. So it's really important that we get a diagnosis of pemphigus or pemphigoid so that we can properly treat it early on to prevent some of these more drastic outcomes.

Dr. Simpson: In general, the goals of treatment in pemphigus and pemphigoid are fairly similar. In the short-term, we want to reduce the inflammation that's located in the skin. We want to do that quickly so the patient's skin doesn't blister or so that their mucous membranes don't have large open sores. Usually we start with oral and topical steroids, and it seems from the poll that many of you are on prednisone, which is by far the most common initial therapy. What the job of these steroids is is to really inhibit those immune cells that are attacking your own body. So an autoimmune disease means that your own body has gotten confused, and it started making an immune reaction, instead of against a bacteria or a virus, it's now turned on your own body and starts attacking your mouth, your skin, or your eyes. So it's really important that we reduce the inflammation or the immune system's reaction to prevent it from further causing damage to your tissues. In the short term, the first goal is to really stop any and all new blistering. It may take a very long time for some of the blisters or sores that you have to

eventually heal. But the first step is to stop you from getting any new blisters. Stop the process in its tracks and allow your body to do the job to heal these open sores that have resulted. In the long term, then, the main goal is to stop your body from making these antibodies that are damaging your skin or mucous membranes. That's a little trickier because it's not something that's easily done very quickly, but we wanted to do that from the beginning, start some of these longer term therapies to really get you hopefully off of prednisone individually and to get your disease into remission. Once it's into remission, meaning all of your skin has really had a chance to heal and oftentimes will see the antibody levels drop, the bad antibodies that are causing the tissue damage. That can take several months and sometimes even a year to really get you to that point. Once things seem to be stable, I often describe it to patients as sort of having your foot on the brake pedal. So if your car is sitting on a hill, and the only thing that's keeping you from running forward is the fact that you have your break, that's what we think of the medicines like in pemphigus and pemphigoid. You are on medicines that are a brake pedal on the disease and trying to prevent it from getting worse. And what we have to do is we have to gradually let our foot off the brake pedal and see, is the disease still really active? Have we gotten to a point where it's under control yet? Or do you still need a lot of medicine to keep the disease from damaging your tissue? So we do all these things very gradually, slowly reducing the medicines and then allowing your immune system to recover is the end, long term goal once you're into a remission. Remission is something that I've talked to my patients about, is not something we really can predict. Some patients can have a really quick on and off type of disease where it comes on all of a sudden, but it goes away just as quickly. And that's great for some patients, but other patients have many years where these diseases just don't seem to let up and that can be very frustrating for patients. But we have to really focus on getting the disease under control. Then, in patients who have more of a chronic disease that is not going to let up, we have to think of more of managing it like we would hypertension or diabetes, or another chronic disease where you may take a medicine every day to sort of prevent the disease from causing damage to your body.

Dr. Simpson: There are several different treatments that are available in the oral realm, meaning you take it by mouth. So there are some standard therapies like steroids, sometimes called corticosteroids, anti-inflammatory antibiotics, anti-inflammatory sulfones, which is a drug called Dapsone that we will talk about and then other non-steroid immunosuppressants that we'll talk about. These are the medicines like Azathioprine or Mycophenolate that help to be a substitute for prednisone to help you get off prednisone because of its many side effects. Then there are some emerging therapies that are also taken by mouth orally that I'll talk to you about called B-cell inhibitors. So we'll get into that a little bit toward the end of the talk.

Dr. Simpson: So I wanted to mention beforehand, before you start on any therapy, it's really a good idea to have a bunch of different lab tests. You may wonder if the phlebotomist has left you with any blood left after all these different tests that you have to get before we do treatments for pemphigus and pemphigoid but it's really important to make sure that what we're doing for treatment is safe. We want to make sure, if we're going to need to use therapies that reduce your immune system, that, first we make sure you don't have any hidden infections

that we don't know about. So everybody should really be screened for hepatitis B, hepatitis C, HIV, and TB or tuberculosis. And that can be done with either a skin test or with a blood test. It's really important because if your immune system goes down and you happen to have one of these hidden infections, it's very important that we know about that, so we can properly mitigate that risk. We can make sure that you're seeing the proper infectious disease specialists to either treat those diseases or to prevent them from coming back during your treatment for pemphigus or pemphigoid. We also have to check on basic blood tests to make sure that your blood counts are normal at the start, and to make sure that our treatments aren't affecting your blood counts too much. Then check your liver and kidney functions that can determine whether or not you're having problems with the medicine, and how you're clearing those medicines or metabolizing them or getting rid of them once they've had their effect. Then finally, you may have heard of this test ELISA before and that's really a test to understand how high are the levels of these antibodies that are bad for your body that are causing the pemphigus and pemphigoid diseases.

Dr. Simpson: The way that we test that is to take blood, spin it down so that the cells, the red blood cells settle down at the bottom of the tube. Then we can actually do a test to quantify how many of these antibodies you have and how many of them are bad antibodies that tend to cause pemphigus or pemphigoid. So that's the purpose of an ELISA test, and that can kind of be used to diagnose you, but also to monitor how well you're doing. How is your therapy handling your disease?

Dr. Simpson: So we'll talk about steroids first because that's the most common medicine that most people are on. Steroids come in a number of different formats. They can be topical, meaning you put them on top of the skin on top of the mucous membranes of the mouth or the nose. They come in a bunch of different forms: creams, ointment, gels, etcetera. There are many, many different brands and types of these. Some of the more common ones that people use are Clobetasol, betamethasone, fluocinonide, or triamcinolone. Steroids also come in pill form but they must be swallowed which can be kind of challenging, depending on how much oral involvement or erosions you might have. These are usually prednisone or prednisolone. They're typically dosed once a day or twice a day. Dexamethasone is a different type that's longer lasting, so it may be dosed less often. Sometimes it can be a lot of different pills that you have to take and it can be quite challenging. So make sure you mention this to your provider because they may have an alternative method that may be a bit easier to swallow than certain pills. Typically with steroids, we start at a really high dose and then we gradually reduce it over the course of months and this is what's called tapering, where we gradually reduce the dose little by little to make sure that we don't cause the disease to come back all of a sudden. So, it has to be done really slowly to prevent disease from coming right back to where it was before you started the steroids. Steroids can come in liquid format, so you can either switch them in your mouth and spit them out like a mouthwash or sometimes they're swallowed. So it's really important that you verify with your provider how you are supposed to take these medicines. Ask, am I supposed to be swallowing this liquid or am I supposed to rinse and spit it out? That's very different depending on whether they want your body to absorb the steroid or not.

Dexamethasone comes as a liquid. You can use it topically in the mouth to swish it around over the sores and the mouth, but if you swallow it, it essentially becomes like a liquid form of prednisone and it may actually be easier to swallow the pill so for some patients this may be a better option if you have a lot of sores in your mouth.

Dr. Simpson: Steroids have a lot of side effects so this is the reason why it's a really a godsend for patients because it can get them under really quick control. It's the fastest acting therapy that we have but it causes many different side effects. High blood sugar, high blood pressure, it can put you at risk for infections, cataracts, glaucoma, stomach ulcers, weak bones, or fractures. So it's really important that you have a primary doctor who's keeping in check all of these different things that they need to monitor. So it's really important, if you don't have a primary doctor, to get one. You may have to take a bunch of other pills to sort of offset some of the side effects of prednisone. And I think this was one of the questions that have come in. Oftentimes, we have patients take vitamin D and calcium to sort of offset the weakening of the bones that might occur. But sometimes you may need a more aggressive therapy, like alendronate or Fosamax, to help make your bones stronger while you're on the prednisone. Some people get a lot of trouble with stomach acid and might need to take something like Pepcid or Prilosec to help prevent ulcers from forming. There are certainly antibiotics that can be taken to prevent a rare type of pneumonia if you have to take a really high dose of steroids for a long time. Things like, Dapsone, Bactrim or atovaquone. Then some people will get side effects from prednisone where they get thrush in the mouth. They get this sort of white pasty lining on the top of your mouth or on the tongue that can coat it, so you may need certain lozenges or a mouth rinse or pills that can actually treat this type of fungal infection that can actually grow when you're on prednisone. So you can actually get dependent on steroids when you're on them for a long time, like multiple months or years. If you're taking them for just a couple of weeks, 2 or 3 weeks at a time, it's usually not a problem. But if you need to be on steroids for months, it's really not safe to suddenly stop them because your body has become accustomed to that dose of prednisone. Sometimes your own glands get a little bit lazy, the adrenal glands may stop making their own natural version of prednisone and that can lead to a very low level of the natural steroid which is called cortisol. It's really important that you always talk to your doctor about when you're planning on reducing the dose so that everybody's on the same page. And that when you're going to stop it, you make sure that it's safe to do that because stopping it cold turkey can actually lead to some really severe illness in patients that can make them quite sick. So be careful with those types of things. Make sure you're in contact with your doctor if you're going to change or lower the dose of the prednisone.

Dr. Simpson: We also use antibiotics and that seems strange to some patients because it's not really, truly, an infection at its root. Sometimes the sores may get infected but we use certain antibiotics that are also thought to have anti-inflammatory effects that can calm down some of the inflammation that may be contributing to the reduction of the adhesion between the cells in your skin, that happens, due to enzymes that are released by some of the inflammatory cells that come into the skin in pemphigus and pemphigoid. So there's generally three of these: tetracycline, doxycycline, and minocycline. I feel like doxycycline is probably the most

commonly used. Some doctors will combine these with a supplement called niacinamide or nicotinamide. These are thought to have antioxidant properties that may sort of help the effect of these antibiotics. These three different antibiotics are all fairly similar. They have differing side effects, but they often will cause a little bit of stomach upset or nausea, sometimes, acid reflux. They can actually cause burning of the throat or esophagus if they're not taken with a full glass of water to make sure they get all the way down into the stomach. Different versions of them can cause people to burn when they go out in the sun, so be careful with that. In some patients who take them long term it can actually lead to some changes in the skin pigmentation. We don't usually use this medication in children because it can actually lead to staining of the teeth as well. I've had some patients complain about getting vaginal yeast infections when they take antibiotics which sort of throws off the balance of different bacteria that are naturally on your skin, so that can actually lead to a yeast infection sometimes. I think that was another question people asked about, what's the long term consequences of being on antibiotics? Well, we don't really know exactly what everybody might experience but some patients do have these imbalances in some of the natural bacteria that's on their skin. And that can lead to certain problems like yeast growing too much on the skin, which can lead to infections. Some important notes about these antibiotics. It's really important that you take them with a full glass of water. You want it to go all the way down the throat. You don't want to take it with a little sip of water and how it gets stuck in the throat because it can cause burning. It's also important that you not lie down right after you take the pills, you want to make sure it has time to really go all the way down your throat into the stomach. Be cautious with sun exposure, as I mentioned, you can get more sensitive to the sun. You really shouldn't take these types of pills at the same time that you would take dairy, like milk or ice cream or calcium supplements, or other sorts of vitamins or supplements. It's not that it's dangerous, it just impairs the body's ability to absorb those antibiotics when they're in your stomach at the same time as some of these vitamins or supplements. So talk to your doctor or pharmacist about those questions as well.

Dr. Simpson: So there's an anti-inflammatory called Dapsone, which is a very different type of medication that sometimes patients get confused about why they might be taking this medicine because they look it up. It was originally a medication intended for infections, like leprosy or malaria. So that can be sort of confusing to patients. But it actually also has an inhibitory action on inflammation from certain types of immune cells that we find in the skin in pemphigus and pemphigoid and these are called neutrophils or eosinophils. These are types of cells that come into the skin and can cause problems when patients have pemphigus or pemphigoid. It tends to work best if you're known to have this specific subtype of an antibody called IgA and it's more often used for patients that have mucous membrane pemphigoid meaning pemphigoid that affects mostly the oral tissues, the eyes or a vaginal or a penile areas. There was one large study done in 2017 for bullous pemphigoid that suggested that Dapsone might actually help to reduce the dose of prednisone a little bit faster, but it was a fairly small study, so they weren't able to get totally significant results. That was sort of a challenging part of that study. With any rare disease, it's often hard to recruit enough patients into those studies to really test whether something works, convincingly, when you're doing statistics on large numbers. So it may be helpful to add on when you're taking high doses of prednisone to allow you to reduce the

prednisone, and also it can help to prevent a rare type of pneumonia that can occur when your immune system is down, something called Pneumocystis. It's usually dose around 25 to 200 milligrams a day. The dosing can vary widely depending on how severe your diseases and how dramatically you respond to the medicine. It's usually started with a low dose to make sure that you tolerate it, and then the dose is increased if needed, if your disease is not yet responded. There are a bunch of different side effects that can happen with Dapsone and I hate to present all these different side effects because many patients that really do totally fine on these medications, so I don't want to scare you off. It's just important that you're aware of these things, and then if these things happen, that you talk to your doctor about them, so that they know how the medicine is sitting with your body. In rare cases, people can get an allergy to sulfur type medicines, which Dapsone falls into that category. You can get a severe rash with a fever and you can feel really lousy. That's pretty rare, but it can happen as with any antibiotic or medication you take, you can get allergic to it. The more common thing is that people will get a little bit anemic and that is quite common, but it's usually pretty mild. But what we normally recommend is that you get a test before you start taking it, to make sure that you can take a normal dose of Dapsone. There's a blood test called G6PD, and that's something that you can just happen to inherit the deficiency of a particular enzyme that helps you to tolerate Dapsone. So if that enzyme is really low, you're not going to be able to tolerate a very high dose of Dapsone so you may have to take a very low dose of it or maybe not take it at all. People can get neuropathy or damage to the nerves, that's also a very rare outcome. It was mostly found in patients that were being treated with it for Leprosy, which also damages the nerves, but it's still something that we talk to patients about. It's very rare, but if you notice that your fingers or toes or hands and feet become more weak and you are having trouble using them, you want to let your doctor know about that. Shortness of breath, so rarely Dapsone can also affect the ability of the red blood cells to carry oxygen to your tissues, and that's something called methemoglobinemia. But you need to let your doctor know if you feel like you're short of breath, have zero energy, they need to be able to look at the blood work and determine whether you need to stop the medicine or not. It's really important that you get blood work while on these medicines to monitor your blood counts, liver, and kidney function as well. Many patients safely take these medicines without any trouble, but it's really important to get your blood work done regularly to make sure that your doctor knows whether the pill is causing problems for you.

Dr. Simpson: So there are other non-steroid immunosuppressants and the way that these work is that they inhibit immune cells. So there are two major types of specific immune cells called T cells and B cells, and these work together to help produce antibodies. Normally, that's helpful to your body, it helps to prevent infections. That's what we're hoping for when you get a vaccine like for COVID, we're hoping that your T cells will help educate your B cells and teach them how to make antibodies so that they can protect you from these types of infections. But in the case of pemphigus and pemphigoid, instead of these normal "blue type" antibodies, you've made some of these "red" antibodies which are actually harmful antibodies that go into your skin or enter into your mucous membranes and attach those "rivets" between the cells and caused the velcro to loosen up. And that's why these antibodies are actually problematic. So one way that we treat autoimmune diseases is to reduce the ability of the T cells and B cells to

make these antibodies and that'll reduce the numbers of those. The unfortunate thing is, while we saw that there were, you know, a lot fewer of these red antibodies, which are the bad antibodies, it also reduces your body's ability to produce helpful antibodies. So, that can be challenging because most of these immune suppressant drugs actually reduce your ability to fight infections. So normally that's not a problem at the doses that we use and most patients don't have major infections, but there are risks for these things. So it's important that if you start to get a sore throat or cough that's not going away or diarrhea that's not resolving, or any sort of fever it's really important that you talk to your doctor about the symptoms that you're having and that you don't wait a long time to get treatment. Many infections are very treatable but you need to get therapy right away, rather than trying to tough it out at home and fight it off on your own because you're on medicines that reduce your immune system's ability to fight off infections. These come in the form of Methotrexate, the brand name is Rheumatrex. It's a very old drug that I don't even think it's available as a brand name anymore. These can be taken as pills or it could be an injection. Mycophenolate which is also called Cellcept for the brand name. These are pills, but can also be taken in liquid format. Azathioprine or Imuran which come in pills. It's really important with any of these types of pills that are intended to reduce the production of these harmful antibodies that your body is making, it's important that you monitor blood work. All of them can reduce the blood count in the cells, they could make you anemic or have low platelets or low white blood count. They can lead to side effects in the liver or kidney. So it's really important that we have a good assessment of how your body is handling these medicines, Your doctor is not trying to torture you by all of these needle sticks to get your blood checked. They really just want to make sure that that particular medicine is working for you and then it's not causing problems. So it's very important to get your blood work done on time, make sure that your doctor's office gets a copy of it. A lot of labs have trouble making sure that that stuff gets faxed over to your doctors, so be your own advocate and make sure that that information gets into the hands of your doctors, so that he or she can make a decision as to whether the medicines causing problems or not, and whether those might need to be adjusted or the medicine could be need to stopped. We did have a question submitted about pregnancy. All of these medicines are high risk to use in pregnancy, but the one that's been studied the most in pregnancy is Azathioprine and it's generally thought to be the one of these three to be used in pregnancy. Methotrexate and Mycophenolate are just not used at all and pregnancy because they're just way too high risk to a developing embryo or fetus.

Dr. Simpson: So methotrexate is usually dosed 5 to 25 milligrams somewhere in that neighborhood. The important thing is that it's dosed usually once a week. So be sure when you leave the doctor's office and have your prescriptions, that you understand exactly how you're supposed to take these medications because this is very different from most of the other pills that you take. It is dosed once weekly and often, you start with a low dose and increase if needed. Some people ask about supplements that you might need to take. In the case of Methotrexate, folic acid is a vitamin or folate sometimes it's called, that is often taken on other days of the week. So it's not usually taken with Methotrexate, it may be taken on every other day of the week to reduce some of the side effects. Methotrexate in particular is risky to combine with alcohol, so you really should minimize or abstain from alcohol together or talk

about it with your doctor. Other certain medications may interact with it. So if you get a new prescription from somebody at urgent care, who may not have access to your medications, make sure that you carry a list of medications so that that person knows exactly what you're taking so that they can make sure that whatever prescription they give you is not going to cause a bad interaction with your other medicines. Side effects of Methotrexate are very similar to the other ones that I'll show you in the next couple of slides. Common to be fatigued when you start Methotrexate. It's usually fairly mild, and people get kind of used to it after awhile. Infections, as I mentioned, makes you have a higher susceptibility to infections that can be more severe than usual or more frequent. So if you normally only get 1 or 2 colds a year, maybe when you're on Methotrexate you get twice as many or quite a few more or they might last longer and just take your body longer to get better. You might normally fight off a cold in 2 or 3 days but maybe with Methotrexate it takes a week or two. It just reduces your body's ability to fight off infections, which is something you need to keep in touch with your doctor about. Low blood cell counts can happen, anemia is fairly common. It's more risky if you're known to have low kidney function. So, again, this is why we have to do blood work to make sure that these medicines are safe. It can cause nausea or abdominal pain, this is fairly common, but it can actually become less severe with time once your body sort of adjusts to it. Then in rare cases, people can get issues with the lungs, inflammation of the lungs, shortness of breath and trouble breathing. So, again, if you develop these symptoms while you're on the medication, it is important to keep an open dialog with your doctor so that he or she can know what's going on with you and decide that dose needs to be changed or maybe that medication needs to be stopped.

Dr. Simpson: Azathioprine is dosed differently. It's just once a day, usually 50 to 200 milligrams. Again, you usually start on a low dose and then increase it as needed. Fatigue is also a common side effect here along with infections again. Low blood counts can occur. In this case, you do need a specific test. Someone also submitted a question about other specific tests that you might need for a particular medicine. So there's an enzyme called TPMT and often your provider will check that beforehand. If you have really low activity of that enzyme, it's probably not the best therapy for you. One of the rare side effects of Azathioprine is that it can cause damage to the liver. And again, that's why we want to make sure that you get the blood tests so that in the case we start to see that your liver is getting irritated by this medicine, we might reduce the dose or stop it altogether. So, it's very important that you get the blood work done to make sure that your doctor knows how your body is handling this.

Dr. Simpson: Mycophenolate or Cellcept is also dosed daily. The dose can range quite a bit. It could be 500 milligrams. It can be up to 3000 milligrams a day. Again, it's usually a ramp up, starting a lower dose and increasing if needed. Again, side effects here are pretty similar to the others. The one that I'll call out as gastrointestinal issues are pretty common with this medication, especially at the start. You might have some bloating or cramping, abdominal pain, diarrhea that can get pretty severe. Most patients get used to it and they don't really have that problem ongoing but for some patients this can just be a deal breaker for them. They have so

much diarrhea, they just cannot take it. So they need to switch to another medication. Infections again, you're going to be at higher risk for infections while you are on these medicines. So you need to report any new symptoms to your doctor. This one particularly has restrictions around pregnancy. So if you're a person who can get pregnant, you may need to get pregnancy tests while you're taking this medication.

Dr. Simpson: So my patients often asked me, well, what's the best treatment? If you had to choose a treatment, tell me what's the best treatment. This is hard because it's quite challenging to answer this question. We don't really have huge, strong, unbiased data from big clinical trials because these are rare disorders. There are some newer studies that can help guide us. But these are hard questions to answer and there's not necessarily one best treatment for every person. Also, the answer is likely to differ, depending on whether you have pemphigus or pemphigoid and what specific type of those. So that's why it's really important. There's not a one size fits all for these types of treatments. It's really important that you talk to your doctor about what's the best treatment for me. The good news is that there's increasing interest in trials being done for blistering disease. So if you have the opportunity and you're able to participate in a clinical trial, that can be very helpful for you. You might find a new treatment that works quite well for you and it can also help the blistering disease community and other patients who come after you to know what might be effective in your disease. If you're that type of a person that wants to get into a clinical trial, these are available at different universities, most often. There are also some ongoing research studies that use existing medications that might have been approved for other diseases and people have thought, well maybe this could be helpful for pemphigus or pemphigoid so these drugs are being repurposed and studied in clinical trials. This is good news.

Dr. Simpson: So I think the better question, as I alluded to, is what's the best treatment for me? That's very individualized, every patient's unique, every person's response to medications is different. Not everybody tolerates things. Some patients seem to get every side effect. Other patients are very fortunate and don't seem to have any side effects, which is great. The treatment choice really depends on many factors, so it's hard to give a one size fits all to patients who submit a specific question about their particular disease such as what treatment should they be taking? It's very hard to answer those questions, because it depends, how severe the disease, what other risk factors might you have? How old are you? What are your other medical problems? What other medications do you take? Are you doing well on a certain medication? Do you have personal preferences as to whether you would use a needle to administer the medication or whether you would rather not get blood work regularly or whether you can't really take those by mouth? Then your social situation. If you have trouble getting to appointments, or if you have trouble filling certain prescriptions because of your insurance coverage. All of these things contribute to identifying what's the best best treatment for you as an individual. So it's really important to talk to your doctor and to provide them feedback if something's not working for you. Let them know so they have the chance to help adapt the therapy to how it's going to work better for you.

Dr. Simpson: So what do we know from the clinical trials that are out there for pemphigus in particular? There was a really early study done about 12 years ago that looked at Cellcept or Mycophenolate when combining it with prednisone. Unfortunately, it wasn't the most successful trial. They were not able to show a huge advantage on the primary endpoint, which is trying to get people off of prednisone. But they did seem to think that there was a beneficial treatment effect on the time to response and the duration of the response. So it seemed to help people get better more quickly and seemed to help them to stay better longer. So there is a role for Mycophenolate based on this placebo controlled trial that was done by Dr. Grant Anhalt at Johns Hopkins.

Dr. Simpson: Then this study came out in 2017 in the Lancet. This was sort of a famous study that really led to the approval of Rituximab, comparing it to the oral therapy prednisone. Prednisone is an oral therapy, Rituximab is an IV therapy. So the question was which is better? What they were able to show is that the number of patients able to get into remission was around 90% for patients that got Rituximab, whereas if they were just on prednisone, it was somewhere between 28 and 63%, So again, suggesting that Rituximab might actually be better than what was the standard oral therapy with prednisone. But as I mentioned before, Rituximab may not be the right treatment for everybody because it does have risks associated with it. This is just a graph showing you that on prednisone alone, patients tend to sort of bounce back later into their treatment, whereas Rituximab seemed to help keep them in our mission, which is the blue line here that stays more towards zero activity.

Dr. Simpson: Then just recently, a clinical trial was done to compare the oral therapy Mycophenolate to Rituximab. This was done by Dr. Werth's group and she was one of my mentors at Penn. This study was trying to compare these two therapies and what she found was that in this study, Rituximab seemed to be a bit better and producing a long term remission at a year out from therapy. So that was good news. It resulted in a greater reduction in the amount of steroids that patients had to take but more patients in the Rituximab group had serious side effects. So again, there's never exactly one clear best answer for everybody. So it has to be a balance of pluses and minuses for these therapies to make sure you find the best one for you, that balances risks with rewards from the therapy.

Dr. Simpson: I'll try to get through these next slides quickly so that we can get to the questions. Just a couple of notes about ongoing clinical trials on oral therapies for pemphigoid and some of the more recent data. You may have heard about some of these, this is an older study showing us that actually topical steroids, if you use them in large areas of the body, you could actually get off of prednisone. So if you have a Clobetasol ointment, a really strong steroid and you're really using it in large areas on the body, that can actually be sort of a substitute for being on an oral medication like prednisone. If your doctor has prescribed topical medication, make sure that you're using it appropriately. That may be a way for you to reduce the amount of oral steroids that you have to take. This shows that in more severe bullous

pemphigoid, using the ointment could actually be safer and more effective than even taking prednisone. So make sure if you're given a topical medicine that you are using it properly and follow the instructions with it.

Dr. Simpson: There was another trial that compared the two different oral therapies, Mycophenolate or Cellcept versus Azathioprine. This was back in 2007. They actually seem to be kind of similar in their effectiveness. They said they had similar efficacy during treatment of pemphigoid but Mycophenolate seemed to have a little lower liver toxicity than Azathioprine. Again, not a huge difference but if you tend to be somebody who has fatty liver or other sort of liver problems, I think we tend to go more towards using Mycophenolate instead of using Azathioprine more recently, based on some of this data.

Dr. Simpson: Then, one of the more recent trials done in the UK was comparing Doxycycline, the anti-inflammatory antibiotic we talked about, comparing that with something like prednisone or prednisolone in this case. Is Doxycycline potentially as effective as prednisone because maybe you could be on an antibiotic and not have to take a steroid. This was published in a really big journal called The Lancet. What they showed was that while the ability to control the disease with Doxycycline occurred in about 75% of cases, it was about 90% with prednisolone but the severe adverse events were only 18% were Doxycycline, versus about twice that with prednisolone. So the conclusion was, it's not quite as good as it seems but it's not terribly inferior to using prednisone and it might be good to use in the short term to get blisters under control, and it could be actually safer in the long term. So we often start with this in milder forms of the disease that we don't think we have to use prednisone for.

Dr. Simpson: So how do you synthesize all this data? Well it's really hard, there's a lot of data out there. How do you come up with what's the best treatment approach based on all this data? That's really going to be an individual decision with your provider to understand what's going to be the best for you. There is what we call a therapeutic ladder and everybody doesn't need the same ladder. All of us are starting at different heights and we have different levels of diseases to treat. So you have to find the ladder that's right for you. That's the most aggressive type of therapy that you need, but not more aggressive than you. It's really important to tailor the approach of your medication to your disease. That's very important.

Dr. Simpson: The last couple of slides here are just about my typical therapeutic ladder for pemphigus and pemphigoid. We can kind of go through these quickly. For mild disease, we try to use topical steroids and avoid the systemics but if it's a little bit more severe, we'll use periodic courses of Doxycycline. If it's more in the moderate range, we might add prednisone and taper for short courses. If it's recurrent, we might add something like Rituximab or Mycophenolate as a second choice. That's generally my sort of therapeutic ladder for more moderate or recurrent disease. Then for more severe disease, we have to use higher doses of prednisone that might be tapered over many months, like six months and then adding onto that,

something like Rituximab or Mycophenolate. In some cases, you may need to be admitted to get IV steroids. That's if it's very, very severe. We're not talking about IV therapies, but some patients will use something called IVIg. So, there's kind of this ladder approach based on how severe your disease is and what we might add into the treatment regimen for you.

Dr. Simpson: For bullous pemphigoid, it's pretty similar where we start off again with topical steroids if it's a very mild disease. If it's a little more severe than that, we might add Doxycycline to that and occasionally use prednisone tapers over short time courses if it's flaring up. Then we might add Dapsone if it seems to be the right category of disease for that, or if you have more oral lesions such as in mucous membrane pemphigoid. Again, if it's severe, we're going to need to use higher doses of prednisone. You may have to end up taking it for quite a few months. Sometimes people need to be admitted. Then we often will add a steroid-sparing agent like those they talked about. I often start with Methotrexate, some people will start with Mycophenolate which is fine too. Then for more resistant diseases that we just can't get under control, we may need to use Rituximab or for high risk patients or patients who fall into older age groups, you might need to use other therapies like IVIg or Dupilumab as become more of a recent drug that people are interested in, because Rituximab can actually be quite high risk if you're at a higher risk for infection group like older patients or those who have other sort of medical issues going on.

Dr. Simpson: Finally, what's in the pipeline? I'll try to get through this really quickly, but what's in the pipeline? What's out there that people are looking at? Well, there's something called Bruton tyrosine kinase inhibitors, or B cell inhibitors, these are oral medications that are dose once or twice daily. There are two of them, Ibrutinib and Ruzabrutinib. Unfortunately, the phase three clinical trial data that seems to be coming out from the pemphigus trials seem to not be that positive. We're still awaiting the kind of full publication, but unfortunately it seems like this is going to be not the best answer. But in other sort of more optimistic news, we know that there are inflammatory cells for eosinophils that are what cause pemphigoid to be particularly red and itchy. These are allergic type cells. There are a couple of molecules that sort of attract those cells into the skin. It's almost like bait for those cells. So, if you have antibodies that are in the sort of velcro here, that's sticking the cells down, they tend to secrete this sort of SOS signal that then attracts these inflammatory cells into the skin. So if we can find a therapy like these two, Bertilimumab and Dupilumab, which actually kinda block that signal, could that then cause those cells to not be attracted into the scheme and to help the disease to be treated very well? So these are still ongoing trials that are being done. Some of them have actually been given an Orphan Drug Status by the FDA. One of them is approved for atopic dermatitis or eczema. So, there's really optimism that these might be therapies that could be effective for pemphigoid like we have Rituximab for pemphigus.

Dr. Simpson: The final thing is that pemphigoid antibodies deposit in the skin, then there's a protein complex called complement that gets deposited in that basement membrane sort of carpet foundation. That again allows for certain immune cells to come in and then to destroy that sort of foundation at the skin and that's what causes the blistering. So, there's a lot of optimism around two different medications, one called Nivolumab and one called Sutimlimab and these are very difficult to say, but both of these are being investigated as inhibitors of this complement cascade, which is again allows the recruitment of immune cells and the destruction of the sort of foundation of the skin. So we are hoping that by inhibiting that complement that gets deposited in response to pemphigoid antibodies that we might actually be able to effectively treat the disease.

Dr. Simpson: With that, I hope that that leaves you with some bit of optimism, but there are ongoing really cool trials going on that could lead to brand new therapies for pemphigoid like we've gotten in recent years with Rituximab for pemphigus. With that, I'd like to thank my mentors and teachers who are mostly at the University of Pennsylvania, Aimee Payne, Victoria Werth and John Stanley. The International Pemphigus and Pemphigoid Foundation, as I mentioned, has really been a great educational resource for my patients as well. And then as mentioned in my bio, I have some funding to do research in the lab. Thank you very much for your attention, and I hope we answered most of the questions that were submitted. But I'm happy to take some now, if there are other questions.

Amethyst: Great, thank you so much doctor Simpson. We've had a lot of good feedback in the question box, and everyone was really appreciative of how well you did explaining everything at a pretty easily digestible level. So, thank you so much for going through all of that. William asked, is there a safe daily dose of prednisone, and if so, what would that be?

Dr. Simpson: Yeah. I don't think we could call anything a perfectly safe dose of prednisone but obviously the lower the dose, the better. Most people consider 10 milligrams to be a bit of a breakpoint. They're not generally as worried if you're on 10 milligrams or less per day, but that doesn't mean that you won't have side effects from it. So it's really important to try to work with your doctor and use other tools to make sure you can taper the prednisone dose so that you're only taking the minimal amount that can keep your disease under control without having the most side effects. 10 milligrams sort of becomes a little bit less worrisome when you get up into 20 and we get much more concerned about other sorts of side effects. But, I've had patients who have really severe diabetes and even being on 10 milligrams of prednisone can make their sugars go quite high. So we can't say that there is a perfectly safe dose of prednisone, but lower is better, lower than 10 is quite good, for most blistering patients.

Amethyst: Great. Thank you. Somebody stated that she's been on prednisone, and anytime she tries to stop the prednisone shift to immunosuppressant and she notices she starts having a flare. Is that common? Or, do you see that in your practice?

Dr. Simpson: Yeah. That's a very common problem and can be very frustrating for patients. So what we often need to do is to get things under control and that may be high doses of prednisone to get to where your body isn't destroying its own skin. Then while you are on that high dose of prednisone, that's when we usually start the second drug like Mycophenolate or Methotrexate or whatever it is, to eventually take the place of the prednisone. But nothing acts as fast as prednisone that we have, generally. So it's going to take a while for your body to build up enough of that secondary medicine to eventually take the place of the prednisone. And some people never are able to fully get off of prednisone, but the whole point of these other medicines is to reduce the amount of prednisone that you need to be on. So if we can use this sort of helper drug to even cut your dose of prednisone in half or in third, that's great and it will reduce the number of side effects that you have. It's really a give and take and it often takes the art of medicine. The art of medicine is based on each patient kind of doing some testing and seeing what can we cut it down by 5 milligrams? Can we try to cut it down again? You have to provide feedback to your doctor and say things like, I went from 20 to 15 milligrams of prednisone and I started breaking out again so can you do 17.5? Any little milligram that you can reduce, it is helpful. So sometimes it does take many months to figure out what's the right combination of pills to be able to escalate the dose of something like Mycophenolate or Methotrexate up to something that you can tolerate, but then it's fully active in your body to really help your disease be under control. So that process is very challenging for patients and it doesn't happen fast. It often takes many months to sort of find the right combination of pills that will allow you to be on a safe dose that's effective and to really try to get the dose of prednisone minimized as much as possible.

Amethyst: Great, very good advice. You discuss some of the side effects of each medication. One person said that they seem to be pretty drained while being on prednisone, do you have any suggestions to help with something like this? Or are there any good exercise tips or anything like that while high doses of prednisone?

Dr. Simpson: People do have this issue where oftentimes when they're reducing the dose of prednisone, when they first take it oftentimes they're very sort of alert. Sometimes they can't sleep. I've had people tell me they cleaned their whole house because they had so much energy when they started it. But then oftentimes, when you start reducing the dose, your body has become used to having that sort of jolt of steroids to give you energy. Sometimes, when you do that, you actually become drained. Some people have other reactions where they might not have the typical reaction of prednisone and maybe it just makes you feel tired for whatever reason. But it's really important that you talk to your doctor about that because there are rare

things that happen. Let's say that the prednisone on the off chance was to cause a stomach ulcer that can cause you to lose blood and become anemic in certain circumstances. It's really important that you talk to your doctor if it seems to be out of the ordinary, all of a sudden. You have to talk to your doctor about those things and make sure that they're aware of that. But it is very common as you're reducing the dose of prednisone to become quite exhausted. Some patients deal with that for many months. It can be very frustrating unfortunately. I do think exercise is important, especially for bone health. It's been shown that weight bearing exercise, where you are actually standing up or even walking, just even light walking, can help keep your bones from sort of a use it or lose. You want to make sure your bones are really remaining strong, and that your muscles don't give out if you're sort of laying in bed all the time. It's really important to try to stay active as much as you can, or to develop some exercises that work for you whether that's light walking, hiking, riding a stationary bike or something like that, that can be useful for you to make sure you keep up your exercise. So it is important to do those sorts of things. I think that if you are generally more active, it can actually sort of build on itself and actually give you more energy, although it's often hard to get started. Getting over that first hump is really important. I usually have my patients take it in the morning because some patients, they're not sleeping well when they're on prednisone. And that may be why they feel really tired during the day because they're not getting quality sleep at night. I generally try to tell people to take it in the morning but again that is something to discuss with your doctor. Some people may be on a different dosing schedule, but generally I have them take it in the morning so it's not such a high concentration when you're trying to go to bed at night.

Dr. Simpson: Great, thank you so much. Debbie asked, how long do the side effects such as the thinning of the skin and bleeding or bruising continue after prednisone treatment ends?

Dr. Simpson: That's really tricky. It can last a long time, in some cases, people don't really recover, which can be quite frustrating. Many people are just more sensitive to this for some reason. They might get stretch marks in a lot of areas or get really thin skin that seems to be fragile. I have seen some patients that seem to recover the thickness of the skin. It seems to get better when they taper their dose of prednisone but it honestly may be something that doesn't bounce back, which is unfortunate. Which is why we really try to get people on as low of a dose as possible. But I don't have a good, clear, quick and dirty answer for that. It's going to depend on each patient's reaction. I've had some patients that use tons of Clobetasol and never get skin thinning and I have other patients that use it seemingly just for a week or two and it seems like their skin reacts to it. So it's a very individual phenomenon and side effects from it. But it is unfortunate that that's one of the side effects, which is why it's important that we had these newer medications that are not steroids that shouldn't have all of those same side effects. So that's why I'm optimistic that we may get new options, so that everybody doesn't have to be on such high doses of prednisone for so long.

Amethyst: Great, thank you. Somebody said that they're currently managing their disease only through topical steroids. They don't say how bad their disease currently is, but they're asking, how do they know when it's time to move to a different treatment regimen?

Dr. Simpson: It kind of depends on the severity of the disease. I have a number of patients that have fairly mild or moderate disease and I really prefer to use the topicals because they don't want to have lots of side effects from taking something by mouth. And it can be quite effective. So there's no real rule about it or you have to move on to oral therapy. If topicals are working for you and keeping the disease at a safe level and allowing you to have good quality of life and you feel like you're able to do your normal things, and enjoy things, and not be in pain or itching then topicals are perfectly fine to stay on. Some people only use topicals, and that's okay. So it's really an individual approach and there's no rule that says you can only be on topicals for a certain amount of time. The chance of getting those side effects of having skin thinning and the problems with the topicals does go up the longer you use them. But if that risk is more palatable to you than being on a pill that requires blood work and having potential other side effects then that may be the right therapy for you. It really depends on how well your disease is controlled and how satisfied you are. So you have to give feedback to your doctor to let him or her know, how well is that therapy working for you. If it seems like your disease is not under control with topicals then yeah, it's probably time to think about either changing the topical or adding on some other therapy that might be an oral medicine.

Amethyst: Great, thank you. Natalie asked, is it normal to have bloating or a distended stomach from Azathioprine?

Dr. Simpson: That's something that people can have. You may have more GI type of symptoms on almost any of these medications, patients do have those types of side effects from it. It may be that it gets better once your body gets used to it, or it may be that it's not the right medicine for you, unfortunately. Sometimes I'll have patients stick with it for a little while if it's not completely disabling, but if it's something you can't tolerate, sometimes you have to go back and start with a fresh, clean slate and try again with something else. But it can be frustrating because there aren't endless options for patients that have pemphigus and pemphigoid which is why it's really important that the research that's going on, to provide people with more options if something doesn't work for them. Yeah, it's normal to have a little bit of GI issues when you start any of these new medications, but if it's really persisting and not working for you, I encourage you to talk to your doctor. Mention that feedback and come to a decision that this isn't the best medication for you.

Amethyst: Great. Wonderful. Vicky asked, should dexamethasone be used daily while she is in remission?

Dr. Simpson: It depends how you define remission. Some people define remission meaning, I don't have any blisters or sores right now but I'm on all of these medicines. The medicines are sort of like that brake pedal keeping me from rolling down the hill so the only reason I'm in remission is because I'm on all of these medicines. Dexamethasone may be the only thing keeping your car from rolling forward, so it's the brake pedal. If you were to stop it, it's possible that your disease would come back. Some people go into what's called a complete remission off-therapy, meaning for whatever reason their immune system has given up the fight or gone into remission like some people who have cancer therapy. They go into remission and their cancer has gone away for sometimes years or forever. That's what we hope for for patients, but not everybody gets there. So it kind of depends on what you mean. And sometimes the only way to test that out is to slowly reduce the brake pedal that you're on, so take the medicine that you're on then talk to your doctor can you reduce it. You don't have any sores and you don't have any postures and you feel great and ask, do I need to be on this medicine? Sometimes the only way to really figure that out is to slowly take your foot off the brake. You don't want to release it all the way because you don't want that car running down the hill at a huge pace. You don't want to be covered with blisters and have to start all over again with a high dose of prednisone or whatever it is that you needed or end up at the hospital. You want to do everything really gradually to make sure that you have the time to really assess, is it coming back now that I'm on a certain dose of dexamethasone. If you reduce it a little bit and suddenly you start to get itchy or you start to get more hives or you start to get little blisters in your mouth, you'll want to report back to your doctor and let them know, that must have been the magic dose that you were on. It really depends on what you mean by complete remission. The only way to know if you're in total remission is to eventually get off of therapies and see if your body's doing the same thing. That's only really the wait and see type of approach, but I encourage you to work with your doctor gradually and safely. As I mentioned in the presentation, it's not safe to just stop steroids cold turkey, that can be quite dangerous, and actually lead to very serious consequences. So make sure that you're always talking to your doctor, if you're going to make changes with your medicines.

Amethyst: Great. Good advice. I know you went through all these oral medications, are any of these treatments FDA approved specifically for the treatment of pemphigus or pemphigoid?

Dr. Simpson: Pemphigus is the only one right now that has an FDA approved therapy that I'm aware of. Rituximab got FDA approved based on that trial data that I showed you, which was sort of remarkable, that was very hard. There was a group in France that put together a trial which is very difficult if you have a rare disorder. Recruiting patients, especially if they're on another therapy that it seems to be working for them, it's hard to want to get into a clinical trial, so that depends on how you're doing. Anyway, they were able to get FDA approval for that. That's really about it because most of these trials are small or haven't shown the big effects that we had looked for to really sort of get an FDA approval. So it's hard to get FDA approval. You have to have really good data and safety data to make sure that it's safe and effective.

Rituximab is really the main one that's been approved. Pemphigoid has really sort of struggled so we're hoping in some of these newer trials with some of the two newer ones that I mentioned at the end, that either target eosinophils which are those really itchy, inflammatory cells that come into the skin or with complement, which helps to destroyed that basement membrane or the velcro that attaches the skin. If either one of those has an update on the clinical trials that are out there, that could lead to an FDA approval for pemphigoid which is really what we're hoping for. Time will tell on those but we're really sort of optimistic. Those studies are often hard to get done because patients will sometimes drop out because they do have side effects or they are just not seeing the results that they would like to see. So it can be very difficult to get FDA approval for rare diseases. That is why the IPPF really exists because they want to get everybody together because we are stronger together. If you have more patients that know about clinical studies, they might be interested in participating. That's how we move forward. To really get new data, do studies and understand what other new therapies are out there that could be safe and effective. So I'm very optimistic about some of the new ones, especially Dupilumab which is very safe and used for treating eczema. If we can repurpose that and get an FDA approval for pemphigoid, that would be really game changing. I think it would be great if it's quite safe. It's much safer than being on long-term prednisone but we really need the data to see if it's safe and effective.

Amethyst: Great. Thank you for the little plug there. So since most of these aren't FDA approved, do you see patients having difficulty getting any of these drugs approved by their insurance company in your practice?

Dr. Simpson: Absolutely, which is really frustrating for patients. It's hard to look at them and say, we know what you have, we got your diagnosis, you're suffering, and we think this thing will work for you. And I write the prescription, and they go to the pharmacy and they're told it's not covered by your plan. It's off label, meaning it's not FDA approved. When you have a disease that doesn't really have any FDA approvals, like with pemphigoid, that's very frustrating. It's like, well, what are we supposed to do? What are we supposed to use? This is where physicians often get frustrated with insurance companies. They are really tying our hands behind our back and it makes it difficult for us to be good providers to patients, because we don't have any control over what specific plan a patient has, what prescription supplement they might have or what Medicare decides to cover, or what a private insurance plan decides to cover. So I encourage you to talk to your physician about it, but also consider talking to your employer about it. If they have options to open up other insurance plans that might provide better coverage for some of the newer therapies, infusions, and other biologic therapies. It might be time to reconsider what your coverage is. If you can afford a different plan or get into a plan that might be better for you. Sometimes, it's very helpful to get that information from an infusion center or other prescription management plan. There may be something better for you that actually provides much better coverage. Even if you have to pay more upfront, it might pay off in the end, if you're able to get on a much better therapy for you. So, yes, it's a really frustrating thing and I think sometimes our doctor's offices get a lot of grief from patients, but it's

unfortunately a lot of times out of our control. We don't have any control over the pricing, which is why there's legislation right now to try to control some type of drug pricing, which has pros and cons to it. If you have a Senator or a Congressperson and you want to talk to them about prescription drug prices, let them know you have a rare disease and it can be bankrupting to patients. Let your representatives know that this is something that affects someone in their district, one of their constituents and it's going to affect the way you vote because you need medicine to be well. I think that's something where people need to advocate for themselves, and talk to the people that make the rules, which is oftentimes not the physicians. So it's very frustrating for us to have a patient who we want to treat them with something and insurance refuses to cover it. Sometimes you can do appeals or write letters, that kind of thing but many insurance companies just have policies about what they will and won't cover and that's very frustrating. Which is also why we need data to show them and say, look, there's a trial that says this is the best therapy for this disease, how can you refuse to cover this? That's what puts pressure on insurance companies often, is if there is an approved therapy to get that pressure. But the only way we get there is to do the clinical studies and the research. It's really important if you have the ability to contribute to clinical trials. If you're willing and able to do it, it's a great service to the community because it may lead to the first FDA approval for some of these medications. Think about that if you have the ability.

Amethyst: That's a good example. The IPPF works very hard. We try to advocate on Capitol Hill and reach out to our congressional representatives several times a year. So, if you guys are having any difficulties receiving certain medications, we'd like to know, and we'd like to be able to help you and give you the resources and tools to hopefully, eventually get some of that legislation passed and get those drugs approved for you.

Dr. Simpson: Absolutely. I will second that too. I've been to Capitol Hill in an advocacy group and nothing is more moving, or important, or valuable, or convincing than a patient going him or herself, taking time out of your schedule and showing the people who represent you what it looks like to live with a chronic disease and a rare disease. It could afflict anybody. Sometimes, unfortunately it's genetics or we don't know exactly the reason for that, and it can affect any of us. I think it's important to show our representatives that it's hard to live with these diseases. They can be disabling. They can be painful. They can steal our quality of life, and so it's really important to show them. There's nothing more powerful than a patient testimony for him or herself to talk about what it means to live with a disease like this. And it's hard for them not to listen. I can go there and talk all day, and they can shut me down but I've seen them, they pay attention and listen to patients, especially those who are in their district, because at the end of the day they're representing you. I think it's really important to make your voice heard and to participate in some of these rare disease days on Capitol Hill, where that's your chance to really tell them about what's important to you and what makes your life more livable. It can really be the difference between suffering and not if you can get on the right therapy. Things like step therapy, other insurance regulations, paying for medicines, orphan drug status, things

like that can all be really, really important for patients with rare diseases. I really encourage you to make your voice heard and tell your story.

Amethyst: I agree. Thank you so much for that. I know we're a little bit over the hour, we have a few more questions if you don't mind? Maire asks, is there a relationship between pemphigus and having cancer?

Dr. Simpson: So there can be. What we call paraneoplastic pemphigus, there can be a specific condition that comes up as sort of a side effect of having certain types of cancer. They are more often to be lymphoid malignancies like lymphomas or other related diseases, which oftentimes are made of those B cells that make antibodies and sometimes people will get pemphigus as sort of a side effect of having that type. It's a really, really rare subtype of pemphigus but it can happen. There are some more recent studies trying to look and see if patients who have certain types of pemphigoid might be at higher risk for certain cancers. That's being actively looked at but yes, there are certain types of pemphigus and mucous membrane pemphigoid that can be associated with malignancies or cancers. It's really important to talk to your doctor about whether you need to get additional screening or whether you're up to date on things. There are certain types of screenings you would need to do. But everybody, regardless of whether you have pemphigus or pemphigoid, you should be getting your recommended screening, which are colonoscopies, breast cancer screening with mammography. Some people do prostate screening, it depends on your provider. Then cervical cancer screening. Those are the main recommended things, then if you have a particular history of smoking or other high risk for lung cancer, there are certain patients that qualify for lung cancer screening. Regardless of whether you have a rare disease, it's really important. The other thing that I would recommend as a dermatologist is to be plugged in, if you are on certain medications, you might be at higher risk for skin cancers. Your immune system does a lot to sort of prevent skin cancers from developing. So if you're on high doses of immunosuppressant drugs, you might be at higher risk for skin cancer. You already should have a dermatologist on your team, make sure that person knows if you have a new skin growth or if there's changes on your body or skin or any new moles. That's very important as well. Make sure you're up to date on all your recommended screenings. That's why it's really important to have a good primary care doctor who's keeping track of you and who knows what you do for and that gets you those things ordered. So that's really, really important whether or not you have pemphigus or not.

Amethyst: Great, thank you. Richard asks, have you seen any sun reactions for patients that are on Rituximab?

Dr. Simpson: Certainly it's really common to have an infusion reaction. The way that Rituximab is made, it's made out of antibodies that are produced from partially human and partially mouse actually. So your body sometimes will recognize that as something foreign. Oftentimes people

will have kind of an allergic reaction the very first time they get Rituximab. That's super common. But if you go to a really good infusion center, which I recommend, they monitor you. You might need to get Benadryl or some extra dose of steroids during the treatment to keep that reaction at a minimum but it's very common to have a reaction. Other sorts of reactions would be more rare. So after you leave, like months later, could people get reactions? Possibly but the side effects of Rituximab are usually pretty mild, some patients report headaches and other sort of uncommon things. It's not common to get major side effects from Rituximab but the infection risk is what we worry about. It does reduce your B cells, which are those helpful cells that usually make helpful antibodies for you. But in this case, they're going away with the Rituximab treatment so there are risks of getting infections. That's something very important to talk about before you decide on a treatment. Most commonly, people get an allergic reaction during the actual infusion. For some people it is so severe that they can't get it again. For most, if you're at a good infusion center that has good nursing staff there, they know how to treat it, they know how to manage it, they're expecting it to happen and they're ready for it. So, it's not so scary or worrisome.

Amethyst: Great. Thank you. Gary asked, how do vaccines affect or interact with some of these oral drugs such as, getting the pneumonia shot, is recommended or a flu shot, or the COVID vaccine?

Dr. Simpson: These are really important questions, especially recently that we've had changes in guidance with vaccines. The general guideline right now, is that the only vaccines that you really have to talk to your doctor about are live vaccines, which are not that many of them. The shingles vaccine, there was a live version of that vaccine before. It's not usually the most commonly given one now but there was a version that was live. Most vaccines are not live vaccines, they're not live viruses, so you can take them but I would always ask you to talk to your doctor about it before you're going to do something. Certain vaccines do need to be avoided, that are live vaccines when you're on certain medications that reduce your immune system. The other question is, are the vaccines going to be effective if you're on some of these medicines, and that's a trickier question. It kind of depends on the dosing and it depends on the person. I've had some patients that had a great reaction and got protective antibodies that we checked in the blood despite being on something like Methotrexate and other patients who are on Rituximab and despite getting their third or fourth covid vaccine, never made antibodies to it. So it really can affect your ability to get protection from a vaccine. In those cases, I think it's really important whether you've had the vaccine or not, speaking about COVID in particular, to be careful that you still run a risk of getting more severe disease if you're on certain medications. It's very important to be cautious. I think a lot of the news coverage has been about patients that they can't necessarily get the vaccine, you might not be able to or they may not respond to it. So, it's important that all of us pitch in and we are being safe for patients with rare disorders, that may put them at higher risk for certain infections. It's a complicated question. The other half of that question is whether vaccines might affect pemphigus or pemphigoid and that's something that people are actively looking at to see if ramping up your immune system to respond to a vaccine, could that possibly lead to a flare up of your

pemphigus or pemphigoid? We just don't have enough numbers yet to make that call. I think at this point, most specialists are in agreement that the risk of getting severe COVID and having a hospitalization or even dying from it is worth having to manage your pemphigus or pemphigoid at this point, by getting that protection from the vaccination. It may require an increased dosage to get your pemphigus or pemphigoid under control but that's something we can do with additional therapies. In general, the specialist guidance right now is to still get the vaccinations and for most patients are immunosuppressed, the recent CDC guidance is to get a fourth vaccination, depending on which particular shot you got. That's something I would definitely talk to your primary doctor and your dermatologist about, to make sure that you're both on the same page about protecting yourself as best you can against some of these infections.

Amethyst: Great, thank you. We definitely went over our hour, but we really appreciate you sticking on and for everybody hanging on with us. I think this was an amazing webinar and we had a lot of questions answered.

Dr. Simpson: Great, I am happy to answer the questions and I was happy to go over a little bit. It's always a pleasure to talk to patients and to field questions. I think it's hard to get super specific answers like I mentioned, everybody has kind of a different biology and a different treatment that's best for you. Thanks for having me participate. It's really a pleasure.

Amethyst: Great, thank you again, very much. So if you didn't get your question answered, and you would still like it to be answered, please email me after the webinar. My email is amethyst@pemphigus.org and I'd be more than happy to help get your question answered. Before we go, I have a few quick announcements here. I would like to thank all of you for joining us today on the webinar and a big thank you to our sponsors. Genentech, argenx and Cabaletta Bio for making today's call possible. Our next IPPF Patient Education Webinar on May 10th with Dr. Erin Wei. Dr. Wei will discuss her published article, "Post-traumatic stress disorder in patients with autoimmune blistering diseases" and answer your questions about managing stress while living with a rare disease. Registration is open and you can register online today. Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! You can find the Natural History Study by visiting www.pemphigus.iamrare.org. The IPPF has a number of upcoming virtual support groups

across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting. Also, we are always looking to expand our support network. If you are interested in starting a support group in your region please contact Becky Strong at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients. If you are interested in continuing to help support the IPPF and allow us to continue to provide free programs and services like today's webinar, you can become a healing hero. Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small, even a \$5 or \$10 monthly donation goes a long way and continues to allow us to provide for the greater good of our community. Like I said, this call is being recorded, and the recording will be sent out to you following the call tomorrow with the survey. We hope that you all enjoyed the call today. Thank you so much Dr. Simpson, for being on the webinar with us. Have a great day, everybody.