Immunosuppressants Patient Education Webinar- June 10th, 2024

Becky Strong: Welcome everybody. This webinar is now being recorded. I'm Becky Strong, IPPF Outreach Director. I'd like to thank each of you for being here today, and before we begin, I want to remind everybody that “Information is a key factor in living and treating any condition. However, everybody's situation is unique and the IPPF reminds you that the information found on the internet or during presentations like today's webinars should be discussed with your doctor or healthcare team to determine if it applies to your specific situation”. Today we are excited to have Dr. Rachel Lipman with us to discuss Immunosuppressive treatment for Pemphigus and Pemphigoid. Before we begin, I'd like to introduce you to her. Dr. Rachel Lipman is a dermatologist and internist at Northwestern Memorial Hospital in Chicago, Illinois. She completed her undergraduate training at the University of Pennsylvania. While in medical school at Emory University, she was inspired to help patients with immunobullous disease under the clinical mentorship of Ron Feldman. She subsequently completed a combined residency in internal medicine and dermatology at Northwestern University where she served as the chief resident of the Med Derm program, as well as Chief Resident of Community Engagement. She was the recipient of the Medical Dermatology Society Mentorship Award enabling her to work alongside Dr. Daniela Kroshinsky to gain further expertise in inpatient dermatologic disease. Dr. Lipman sees patients with autoimmune blistering disorders in her weekly complex medical dermatology clinic. She serves as a core faculty member of the inpatient dermatology consult team, caring for those hospitalized with dermatologic diseases. She continues to practice internal medicine as a member of the Hospitalist Division of Internal Medicine. She enjoys using her dual training on a daily basis to provide holistic care to her patients and collaborate with colleagues. Now I would like to go over a few housekeeping items… (Reviews Housekeeping items and slides). Please join me in welcoming Dr. Lipman.

Dr. Lipman: Hi there. Thank you for the wonderful introduction and I'm so grateful to be joining you all. Let me go ahead and share my screen. Okay, tell me how is this looking? Can you see everything okay?

Becky Strong: Yes, we can see it.

Dr. Lipman: Okay. Well thank you for everyone who's submitted such wonderful questions ahead of time. I've done my best to incorporate them into the talk, but I have so much to discuss in such little time. So let's get started. As Becky mentioned, I'm an Internist and Dermatologist over at Northwestern and caring for patients with pemphigus and pemphigoid family disorders is among the highlights of my work.

Dr. Lipman: It is always important to think about the source of your information whenever you're receiving any sort of medical information, so I want to let you know that I'm no different. And so to start with, I'll let you know that I have no financial disclosures. I receive no funding from pharmaceutical companies, and these opinions that I'm sharing with you are my own. They don't necessarily represent Northwestern University and I'm hoping to answer your questions to the best of my ability, but there's something very specific to your situation I always recommend connecting with your individual physician who knows you the best. There's a ton of information

out there about pemphigus and pemphigoid and I know I'm talking to a very diverse audience who have varied experiences. Some of the information I'll be presenting to you might be old news to some, but brand new to others. So while I think about interpreting information, I always like to present this as a way of thinking about what's the source and what's the quality of the data that I'm getting. Part of treating rare diseases is acknowledging that there's a lot that they're still left to know and still left to study. The highest quality research is something called randomized control trials or blinded studies. They have strict guidelines for inclusion and standardization and they're are gold standard. You may see reports of emerging therapies or promising laboratory studies. However, this is not as high of a standard as these randomized control trials. This can be difficult to achieve for rare diseases like pemphigus and pemphigus. Pemphigus and pemphigoid are not diabetes, and many of my patients will express that their family, their friends, or even their physicians has never met anyone with this condition before. So when you're thinking about treatments, it's good to ask, what evidence is there to support the use of this medication for my disease? And I'll do my best to present some of that information here and give you a sense of how strong is the evidence.

Dr. Lipman: In order to discuss immune-suppressive medications, I'm also going to touch briefly on the role of the immune system in pemphigus and pemphigoid. It's important to know that we're lumping a lot of conditions together today. These are families of diseases, not one single condition, and pemphigus and pemphigoid are quite different from each other as well. Another disclaimer, not all immune suppression is equal. Changing the dose of a medication can really alter how much your immune system is suppressed. Different medications have different mechanisms of action and they don't all affect the immune system in the same way.

Dr. Lipman: So to talk about immune suppression, we first need to understand, what's the immune system? So the immune system is a complex system of tissues, organs and blood cells. Everything from the skin that protects us from the outside world to our tonsils, to the bone marrow that produces blood cells, to the immune islands in our gut. There is a large complex system and the functions primarily are to defend us from infection, to recognize harmful foreign objects, and to surveil our body to detect early cancer cells. So the immune system does a lot of important things for us.

Dr. Lipman: What is immune-suppression? Well, immune suppression is any time when there's decreased or malfunction of the expectations of the immune system. This could be due to a disease state such as HIV, diabetes or immune deficiency that some children are born with, but it can also be induced due to certain states, such as patients who've had organ transplantation or use of immunosuppressive medications like for pemphigus or pemphigoid that we're going to discuss today.

Dr. Lipman: And for your reference, here's an underlying diagram of the skin that is going to help us point out a few areas that we're talking about today. The two major areas that we're going to talk about are the epidermis or this top layer of the skin and the dermis, the lower area of the skin. Those are the areas that are going to be affected by these disease processes.

Dr. Lipman: So like we said before, pemphigus and pemphigoid are families of autoimmune blistering diseases. And while I don't need to tell this community what blisters are, autoimmune means that the body is under the attack from self. The immune system has complex mechanisms to defend ourselves against viruses, bacteria, fungus, and the outside world. But one way it knows to defend is through protein signals that are called antibodies. And here we can see a little cartoon of a B cell that becomes a plasma cell that then sends out these antibody signals. And generally these can be produced after vaccination or after illness to help your body know foreign from self. But in the case of autoimmune disease, the body fails to recognize self and creates antibodies against yourself. So you can almost think about it as if you're becoming allergic to yourself and your body is starting to attack yourself. And so in the case of pemphigus, it's to a certain protein called desmoglein. And in the case of pemphigoid, it's to certain antigens, part of the hemidesmosome complex, which we'll go into in a little more detail.

Dr. Lipman: So getting back to pemphigus, which again is a family of diseases, I'll be showing you a lot about pemphigus vulgaris today. But we could also talk about pemphigus foliaceus, paraneoplastic pemphigus, or IgA pemphigus. Under the microscope we can see that the top layer of the skin, that epidermis that we were talking about before is having trouble sticking together, or the adhesion is having difficulty. Neighboring cells are falling apart and that's because that desmoglein, that protein that holds the two cells together is being attacked by autoantibodies. Antibodies made by the body that are attacking these desmoglein. Here you can see that highlighted on a special stain called a direct immunofluorescence. And what this results in, for patients is blistering of the skin and the mucus membranes depending on the type of pemphigus they have.

Dr. Lipman: There's lots of interesting science going on, which this is not an immunology talk, so we won't be getting into all of the nitty details, but it's not just the auto antibodies, the immune system has an interlocking complex way of creating signals and there's lots of targets to address in pemphigus.

Dr. Lipman: Another disease that we're going to touch upon today is bullous pemphigoid and mucous membrane pemphigoid or the pemphigoid family of disorders. In this autoimmune disease, these autoantibodies are targeting a different part of the cell. Here we can see, looking back at the skin that epidermis or that top layer is relatively well intact, but the bottom layer is now having difficulty holding together. And that's because we're attacking this protein over here called BP 180 or BP 230 or sometimes other proteins within this complex. And I like to think of this as kind of the anchor between the dermis and the epidermis at this dermal epidermal junction. And so it's both the antibodies and a lot of other inflammatory cells that are acting here. For the patient, this results in incredibly itchy and tense blisters on the skin and occasionally mucus membranes.

Dr. Lipman: So as we said, this is not an immunology talk, but there are a lot of complex immuno-pathways and signals going on right now. So even bullous pemphigoid can vary dramatically between individuals. So everyone really needs to be treated like an individual when we approach their individual disease.

Dr. Lipman: One question I received was is there blood work or monitoring I will need or is there anyone who shouldn't be on immune suppression? And when we talk about immune suppression so far we've covered that it's going to change your immune system in order to address that some parts of it are not working as we want it to be. So the biggest thing that we are at risk of is putting you at risk for infection. Before you start treatment, your doctors should be screening you for any latent infections, meaning any hidden infections. The common ones we screen for are hepatitis B, hepatitis C,HIV, and tuberculosis, but there are others depending on your individual circumstances. Then you want to ask, are you protected against future infections? This is where your doctor might be asking you, are you up to date with all of your vaccines? For example, have you received your newest covid vaccine, your flu vaccine? Are you up to date on your pneumonia vaccine if you're eligible? Have you received the shingles shot? And in some areas of the country, including Chicago, I'm now thinking more and more about measles and are my patients adequately protected against measles?

Dr. Lipman: The other thing that we know that our immune system does is, it surveys our body for cancer. I always like to ask my patients, are you up to date with your primary care health screenings for cancer? Have you received your colonoscopy or FIP test? If you're a smoker, have you been screened for lung cancer? Are you appropriately screened for prostate, cervical and breast cancer? These are all things that you should talk about with your doctor before starting immune-suppressive medications. And then for some of our medications, they can affect other parts of your health. So you always want to think, is my general health optimized? Have I thought about my cholesterol, my diabetes, my bone health, my eye health? And do I have any risks for blood clots? These are all things that we should address before starting any medications.

Dr. Lipman: The major medication, which is the basis of all other immune suppression is prednisone. And many of you may be familiar with prednisone. The important thing about prednisone is that it works incredibly quickly. Steroids are fast and steroids are made by the body, by the adrenal gland. So steroids work fast and in a broad way of inflammatory pathways, which is great because no matter the cause of the inflammation, it can calm it down quickly but it's not targeted, which can be a downside because it can have a lot of unintended side effects. Now I like to describe prednisone to my patients as our best, worst drug. And first I want to start with the best portion of it. So this is a quote from Dr. Lever who treated pemphigus in the era before prednisone. He said, “Prior to 1950 when cortisone was introduced, the treatment of pemphigus vulgaris was hopeless. And he said how thrilling it was to observe extensive eruptions clear within a few weeks with adequate doses”. So without doubt, steroids are a lifesaver. Before the induction of steroids, pemphigus had an up to 95% mortality risk. And so now we are doing so much better for our patients and steroids are a no small part of this.

Dr. Lipman: But I also call it our best, worst drug because it's not a medication that is intended to be taken for the long term. Our bodies make steroids about five milligrams per day is what our adrenal gland produces, and it can make slightly higher doses during stress. So what is considered high dose steroids? It's somewhere around 15 to 20 milligrams. If you're taking steroids for long time, our goal is to monitor for the symptoms that can occur. So steroids can

have wide ranging side effects, everything from sleep disturbance, mood changes, it can lead to weight gain, can lead to hypertension or high blood pressure, affect bone health leading to increased risks of osteoporosis and fracture, can lead to increased blood sugars and diabetes development and infection risks. Eye health is another big issue. So when we're talking about using steroids, it's often in the beginning, we talk about another immunosuppressive steroids-sparing agent. So we can spare you the long-term effects of steroids.

Dr. Lipman: So while you're taking steroids, what should be monitored? I would recommend that you talk to your dermatologist and primary care doctor about watching your blood sugars, your blood pressure, how your mood and sleep is doing, how your weight is doing and bone health and thinking about infection risks. So if you're taking high dose steroids, that's more than 20 milligrams for a prolonged period of time, more than six weeks, you should think about, is there anything else that we can add on including an antibiotic to prevent against certain infections?

Dr. Lipman: One of the things that is really helpful is thinking, what can we do to reduce the need for systemic steroids? Because while we know it's a lifesaver, we also know it comes with all these side effects. And so Pascal Joly's group out of France published this really impressive study where they stratified patients to receive either topical steroid or systemic steroid for bullous pemphigoid. And so these patients had severe or moderate disease and they found that with adequate use of topical steroids, they actually had improved one year survival and improved risks of complications compared to the systemic group. So this is a good thing to talk about with your doctor, am I using my topicals to the most of their ability? Because if you are, you can sometimes reduce your need for systemic steroids.

Dr. Lipman: Now moving on to pemphigus, we know that there are certain medications that are favored as first line therapies and second line therapies, which unfortunately we don't have the same strong evidence or same strong consensus just yet for pemphigoid. But for pemphigus, we know that first line are those corticosteroids like prednisone, which act quickly. And the next medication I want to talk to you about are anti-CD20 antibodies, which you may have heard of before, the most common of which is rituximab.

Dr. Lipman: So pemphigus and pemphigoid are autoimmune diseases and like you know there's an antibody attacking either the desmoglein or the members of the hemi-desmosome family. So what if we could somehow cause a reset and allow your body to stop making these antibodies? And to do so we'd have to address the B cell and subsequently their plasma cells that are producing these antibodies. This is the basis of rituximab therapy.

Dr. Lipman: So rituximab is an anti-CD20 monoclonal antibody and CD20 is found on the target on the surface of B cells. B cells are the cell that then go on to make the plasma cells that produce the antibodies that then attack your skin. Rituximab has been approved to treat certain kinds of lymphomas in autoimmune diseases and was approved by the FDA in 2018 to treat moderate to severe pemphigus vulgaris. The approved dosage is an infusion and so you receive one gram on day one and then two weeks go by and you receive your second gram of the infusion and that's considered one course of the medicine. Now there are other ways to

administer this medicine including weekly dosing, but this is the way that it's currently FDA approved so this is what I'll mention today. The biggest thing when you're taking rituximab therapy is thinking about monitoring for infusion reactions in the short term. You'll always be at an infusion center where there will be a nurse checking your blood pressure and to make sure you're not having any symptoms of an allergic reaction. Rituximab is not recommended in pregnancy or those who are breastfeeding. And there are significant side effects of rituximab, most clearly infectious risks because we're depleting all circulating B cells and doing a reset of the immune system. So we don't get to selectively choose just those that are creating this reaction, this auto antibody for pemphigus or pemphigoid. It's important that you're screened for certain infections like hepatitis and tuberculosis before undergoing rituximab therapy and that you caution that after rituximab therapy you're not going to be able to respond to other vaccines. So it's really important that you get up to date with all of your vaccinations before rituximab therapy because if you're given a vaccine, you're not going to be able to mount a sufficient immune response to create antibodies to protect yourself.

Dr. Lipman: And Dr. Joly's group from France also had this very important randomized control trial where patients with pemphigus vulgaris were randomized to receive either rituximab with prednisone or prednisone alone. And the goal with these patients was to get them into remission. What does remission mean? It means no blisters and no remission off medications, which means no blisters and not on any long-term medicines. So at two years out, the patient group that was receiving the rituximab received 90% remission rate, which is great. Only 28% in the prednisone alone group were able to achieve remission. And over this period they also had higher side effects in the prednisone alone group. So this was a really important study to show that rituximab was able to induce remission and induce remission off of steroids.

Dr. Lipman: A lot of patients will ask me, what's the best way to dose my rituximab? And this is a meta-analysis. So this looked at a lot of different data that's out there and looked at over 578 patients across 30 different studies. From this they showed that rituximab at high dose, which means two grams was more effective to treat pemphigus than those with low dose. However, they didn't show any significant improvement between weekly, the RA type dosing versus what's FDA approved,, the one gram split over two weeks. There's different information about that out there and something that should be discussed for different individual circumstances.

Dr. Lipman: The next study I wanted to highlight is another randomized control trial which showed that rituximab should be considered as first-line therapy. So rituximab was compared to patients who were taking mycophenolate, which is another steroid sparing agent that we'll talk about in just a minute. They found that patients who were taking rituximab had an improved rate of remission in comparison to mycophenolate though, with a slightly higher side effect profile. So this is another information saying that for those who have severe pemphigus, most pemphigus physicians will say, do not pass, go. Let's go straight to rituximab to address the problem with the most effective treatment.

Dr. Lipman: Mycophenolate mofetil, the other medication considered is an oral medication and it both suppresses T and B cells as part of the immune system. It is not safe for pregnancy, it's not safe for breastfeeding and it is not safe to be taken if your partner is trying to conceive. It's

not safe to donate blood while you're taking mycophenolate. And a lot of patients will ask, well what blood counts do I need to have monitored and how frequently? For this medication, which is generally dosed twice a day, you receive baseline blood counts, liver and kidney function, and depending on your doctor's protocol, they might at first look at that weekly and then space you to monthly or even after several months the longer you've been on the medicine. The most common side effect I see with patients is stomach upset and like all immunosuppressive medications, there's increased risk for infection and for mycophenolate specifically, we worry about long-term use with risks for things like skin cancer and lymphoma. However, it's important to know that dose really does matter as well for this medication.

Dr. Lipman: The other medication that's considered often in the same category is azathioprine. This is a purine analog that converts using a enzyme called TPMT. A lot of patients may have heard that before they start this medicine their doctor is going to screen them for this enzyme because if you are deficient in this enzyme, it is not a safe medication for you. And that's because if you don't have this enzyme, you can't adequately metabolize the medicine and you'll lead to increased rates of bone marrow suppression or very low blood counts. The other thing that needs to be monitored apart from blood counts are your liver enzymes. So who else shouldn't take azathioprine, which is another oral medicine, those who are trying to become pregnant or who are currently pregnant. Also those who are using a medicine called allopurinol, which is commonly used to treat gout, can also have some side effects with this medication and should not be taken together. If you have a deficiency of this enzyme, that's also not a safe medicine for you. And for most patients they'll say, well, which one's better, azathioprine or mycophenolate? This is often a time of personal preference. In different people's practices they tend to use one or the other more frequently. I tend to use more mycophenolate, but both can be highly effective in treating disease.

Dr. Lipman: The next medication we'll talk about just briefly is something called methotrexate, which is more often used for pemphigoid family disorders. It's an anti-metabolite which when used at high doses can be used to treat cancers and when used at low doses can be used to treat autoimmune diseases. This is given for autoimmune diseases like pemphigoid as a weekly dose. Generally as a pill though there is an injection form available. You shouldn't take methotrexate if you're pregnant trying to become pregnant or nursing because it is not safe for a growing fetus. If you have kidney disease, if you have liver disease or you're taking medications that interact with methotrexate like a proton pump inhibitor, things like Nexium or pantoprazole or NSAIDs, things like Aleve ibuprofen as these can change the levels of methotrexate in the blood. And the other thing is it's not safe to drink heavily with methotrexate. If you're unable to abstain from alcohol, that might not be the best choice for medication. Monitoring blood, again, you need blood counts, kidney and liver function to be checked again in the beginning. It might be as soon as weekly and then spaced to every few weeks or every few months depending on your physician's protocol. Most common side effects are hair loss, oral ulcers, which can be really tough for patients who are already dealing with different oral ulcers, nausea, vomiting, GI upset. A lot of these side effects can be really reduced if you take your daily folic acid, which is for every patient on methotrexate, they should be taking a daily folic acid supplement.

Dr. Lipman: Lastly, I want to touch on one more medication that is on the older side and not very commonly used anymore. So cyclophosphamide is a medication for very difficult to treat pemphigus. It is a nitrogen mustard drug and what it does is it alkylates the DNA, which means that it kind of gets in there and cross links the DNA and RNA. And this suppresses T cell activity. It is certainly not safe for pregnancy and it actually can cause infertility. And so if you're planning to become pregnant, this is not the first choice for you. It has an extensive side effect profile, so it can lead to low blood cell counts, nausea and vomiting, hair loss. There's some cardiac toxicities to be monitored for. And the big thing is that there's a side effect called hemorrhagic cystitis, which essentially means that you can see new blood in the urine. So monitoring cyclophosphamide should be really intensive and that includes both blood counts, liver, kidney function, but also looking at the urine to make sure that there's no new red blood cells in there. And the long-term effect of this hemorrhagic cystitis is associated with certain bladder cancers and in the long run cyclophosphamide does have increased risks of cancer. So this is really for our most refractory pemphigus.

Dr. Lipman: Now the good news is that not all medicines we use to treat pemphigus and pemphigoid are immune suppressing. So among them that you may have heard of are IVIG, dapsone doxycycline and we're getting much more data about targeted medications such as dupilumab, dupixent or omalizumab to target patients who have bullous pemphigoid.

Dr. Lipman: So ultimately what most patients want to know is what's the best medication for me? And what I want to do is induce a clinical remission, which means no blisters off medications and patients want to know how they can do that with the least number of side effects. You have to think about in your case, what are my other medical conditions and how do I put them in balance? Is there heart disease that we need to think about? Lung disease, diabetes, bone health issues, liver disease? And also thinking about your individual priorities. It's important to know your patient as an individual and saying, well, where are you going to get your treatments? Is going to an infusion center going to be difficult? How about transportation? Is there someone who can give you a ride home? What's the time commitment that you can give to your treatments and how does that differ based upon your work schedule?

Dr. Lipman: At the end of the day, everything is risk and benefit and what might be right for one person might not be right for you.

Dr. Lipman: Another big question I've been asked is, well, how can I protect myself when I'm immune suppressed? The big things to think about are things that I'm sure a lot of you are already doing. So wearing a mask, having excellent hand hygiene. We talked about getting vaccines before you're immune suppressed so that you can protect yourself as much as possible and having those in your community and surrounding circle be vaccinated to help protect you. The other thing which seems like common sense but is avoiding big crowded settings. So a lot of patients, it's all about risk and benefit and I have conversations of seeing grandchildren or going on vacations and there are ways to do these things safely. It's really

about monitoring and saying is the risk of a cold or cough worth the risk of going on this vacation and how can we mitigate this risk and make it as minimal as possible?

Dr. Lipman: So I want to thank you all for your attention. Here's some references that I went through during this webinar and I hope that I can answer some of your questions. Here's my contact information and at this time I'm going to stop sharing and turn things back over to Becky.

Becky Strong: Great, thank you. We learned so much in such a short amount of time, you covered so much information. With that said, we do have some questions that came in. Vladimir is asking, what is the lowest dose of CellCept that you should be on to maintain disease control? And then a couple of other people have asked, how long can you be on an immunosuppressive like mycophenolate?

Dr. Lipman: Those are really great questions. For all immunosuppressive medications, our goal is the minimal effective dose, which means that we want your disease to be under control, but we don't want to overdo it. We don't want to use more medicine that's needed to keep your disease under control. And so oftentimes it depends because I have patients with pemphigus who are doing quite well at 500 milligrams twice daily of their mycophenolate, but others who need a higher dose, like one gram twice daily. And the other question is what is the long-term plan? Is there a long-term strategy? For example, if we're going to be doing rituximab therapy, can we bring down the mycophenolate dose or avoid mycophenolate so we don't combine immunosuppressive medications. People can be on immunosuppressive medications for years and even decades. As you'll see, many patients who are taking mycophenolate for let's say kidney transplant are on these medicines for decades, but it does have increased risk the longer you're on these medicines in terms of other things like skin cancer risk or other cancer risks. It's really important to think about oftentimes, if we can cause a remission with rituximab, that's a really great option because it doesn't result in long-term immune suppression.

Becky Strong: Great, thank you for that. You had been talking about rituximab in the webinar as well, and Michael asked us the initial prednisone 15 milligrams have to be tapered before the IV rituximab can be administered.

Dr. Lipman: Great question. No, the initial prednisone does not. So different protocols will do the prednisone dosing in different ways. So for many folks who are receiving rituximab, part of the infusion protocol to avoid infusion reactions is actually that you'll be receiving a dose of IV solumedrol or the IV form of prednisone and that's to avoid allergy type reactions with your rituximab. And so this is just given as a one-time dose. Now let's say that you were on prednisone for many weeks leading up to your rituximab, that's a different situation. You might need to be tapered because it's not really safe for your adrenal glands to be exposed to high doses of prednisone for months and then go cold turkey. So for many patients what you might experience if you've been on prednisone for more than a few months, that your doctor may start tapering your prednisone down slowly to get your body's adrenal glands to kick back in and start making your own prednisone without being suppressed by the ones that we're giving from the outside.

Becky Strong: Great, thank you. Marcia is asking, and I think you covered it in your presentation, but how often should you get the infusion and what would trigger the need to have another infusion?

Dr. Lipman: That's a great question. So generally right now for pemphigus vulgaris, the FDA approval is for one gram given for one course, so that's split by two weeks. In that two week period you receive two infusions and that counts as one course. Now depending on the physician, and you may receive another infusion at six months and that might be half a gram, but it depends on your particular disease course. And so one thing that can be really helpful is monitoring something in the blood called the desmoglein antibody level, which we talked about is the auto antibody that is causing the blistering for pemphigus. And so if your desmoglein antibodies are rising, that may be a symptom that it may be necessary to do another rituximab infusion. For something like bullous pemphigoid, it might be a little bit more nuanced. We can monitor BP180 antibodies in the blood, but also we want to pay attention to other symptoms you're having. Are you having an increased itch? That can often be a sign that the disease is about to flare and so every patient, it's really checking in with your doctor frequently enough so that we know, is your disease under control on our physical exam, in your blood work and based upon your symptoms.

Becky Strong: Great, thank you. Jean mentioned that during the presentation you said that the mycophenolate mofetil is not recommended when pregnant. Is there an alternative that patients who are wanting to get pregnant or are pregnant can take?

Dr. Lipman: Mycophenolate mofetil is not safe during pregnancy and even for six weeks after, before you're trying to plan a pregnancy, but it doesn't mean that you can never become pregnant if you've been exposed to mycophenolate. The other thing to think about are some of our non-immune suppressive medications. So IVIG could be a really great option because it's been studied in pregnancy, it's non-immune suppressing. The antibodies that are given with IVIG cross the placenta, but really it's another great alternative option. That's a great option. There's some other options that are more off-label. It's really a risk benefit and we definitely want to talk with your obstetrician and your primary care provider and you to make sure that we weigh all of those risks and benefits.

Becky Strong: Great, thank you so much. Staying on the topic of mycophenolate, Jack is saying that he gets an upset stomach. Are you supposed to take it on an empty stomach or with food?

Dr. Lipman: I have most of my patients take it on a full stomach. I tend to see that that helps a little bit more. There's two formulations of mycophenolate and so there's the mycophenolate mofetil and there's also the Myfortic and some patients find that the Myfortic, the other formulation of it is a little bit gentler on the stomach. That might be another option to talk to your doctor about to see if there's another formulation that might be a little less distressing to the stomach, but it's a really common thing that a lot of patients deal with.

Becky Strong: Great, thank you. Janet asks are immunosuppressives recommended when you have mucus membrane pemphigoid only on the gums in your mouth or is a topical medicine preferred at that point?

Dr. Lipman: That's a really great question and one that I encounter all the time. I think at that point we really have to talk about what is the severity of the disease, the quality of life, and that really drives for that individual patient whether immune suppression is worthwhile. For example, if you've tried the topicals and things are under control and you have a strategy that's working for you, for a lot of my patients it's avoiding maybe citrus fruits or tomatoes that seems to be a big trigger. Working through that, and they say, you know what, I get one blister once a month if I eat some pizza but I use my topicals and it goes away. That's a different story than other patients who have such severe mucous membrane pemphigoid that they actually have difficulty swallowing or they're losing weight. That might change the conversation we have and say, you know what, I think it's time we get more aggressive on this and talk about these immune suppressing medications. And again, not all immune suppression might be the same. And so for those patients starting with a medication that's maybe a little less immune suppressing might be a good option rather than going straight to rituximab for example.

Becky Strong: Great, thank you. You had mentioned using steroids, mycophenolate and rituximab. What's the benefit of using mycophenolate and rituximab together if it takes a couple months for the mycophenolate to work and three months for the rituximab to start working?

Dr. Lipman: Great. Well, so oftentimes I would also say that you have to be cautious when using rituximab and mycophenolate together because they are both immune suppressing and so they have an additive quality. Definitely you'd want to start tapering some of your other immune suppression as the rituximab is taking over. Generally the situation I see is that folks are on steroids and we start the mycophenolate as a way to get them off the steroids. So their disease might be adequately controlled or on the road to control with their steroid and the mycophenolate, but we don't have a long-term plan for how to get this pemphigus under control. That might be where the rituximab comes in. We're not in an emergency anymore, but we don't have a long-term strategy. So for the situation, I don't think usually I throw all three on at once, but more we know that it takes a couple months for rituximab to take over and it takes a couple months, like you said, for mycophenolate to really kick in. I tend to use things in a stepwise fashion depending on where the patient is.

Becky Strong: Great, thank you. Lisa is asking if it's safe to have hemorrhoids surgically removed while you're on prednisone or if it should be delayed if you currently have active lesions? So I guess generally like any surgery when you're on prednisone or immunosuppressives?

Dr. Lipman: Steroids especially, but immune-suppressives in general can delay wound healing and so that may be a big consideration for the surgeon and I would highly recommend you talk to the surgeon to see their level of comfort. Now being on five milligrams of prednisone might be very different from being on 80 milligrams of prednisone for your wound healing. Those are good things to consider. Really it's a situation of if your disease is not under good control then

you might not be optimized nutritionally to have a good surgery or something else. Trying to stage this and say, what is the priority of the surgery? When does it need to happen and what's the priority of getting my pemphigus or pemphigoid under control and when does that need to happen? And again, the risk and benefit, it's every single day for every decision. It's always a risk and benefit.

Becky Strong: Great. David asks, if you could repeat the name of the blood test to be taken to assess if pemphigus is seemingly flaring up?

Dr. Lipman: For pemphigus, like we talked about, it's caused by the autoantibodies. Your B cells are producing these antibodies that are attacking the desmoglein. It's called desmoglein and some people abbreviate that as DSG, but desmoglein 1 and 3. For pemphigus foliaceus it might be more desmoglein 1 that's active. For pemphigus vulgaris in the mucus membranes it might be desmoglein 3. If you have pemphigus vulgaris that affects both your skin and your mouth, it might be both. And so those numbers can be helpful for tracking disease activity.

Becky Strong: Great, thank you. There is a question asking, does rituximab affect the effectiveness of antibiotics?

Dr. Lipman: Good question. So rituximab in itself does not, it affects the B cell activity. For antibiotics generally, they're either bacteriostatic, meaning they kind of stop the activity of bacteria or bactericidal, which means that they actually kill bacteria by attacking their cell walls or various aspects of the bacteria. Maybe the DNA of the bacteria, the RNA of the bacteria. And so in itself, no, the antibiotic should work just as well. However, are you at higher risk for needing an antibiotic or being immune suppressed and being at risk for infection? Yes.

Becky Strong: Okay. So if an antibiotic doesn't work, it just may be that the infection has taken a stronger hold because we are immunosuppressed?

Dr. Lipman: It could be that the antibiotic was not the right match for the right problem. Whenever we prescribe antibiotics, we look at what we think is most likely to be causing this problem. But for example, if it's a urinary tract infection, we try to get a urine culture so we can identify the bacteria and then even run sensitivities on the bacteria to know what antibiotic is going to work the best. Sometimes we can't get those cultures, but generally we try to do culture directed antibiotic therapy. And for things like viruses, antibiotics unfortunately are just not going to work. And so for not all infections will an antibiotic work, which is why it's so important to protect ourselves with vaccines for those that we can.

Becky Strong: Great, thank you. Ellen says that she's been on steroids, mycophenolate and Rituxan, but now the dermatologist is suggesting that she try Rinvoq paired with mycophenolate. Is Rinvoq effective in PV patients when used in combination like that?

Dr. Lipman: There's not really significant data at this point. There's definitely some case reportable data, but the most evidence right now is for rituximab, which is why it has FDA approval. So while there's interesting studies out there and there's certainly lots of interest in Rinvoq and in JAK inhibitors, there's not enough right now to make it a first line therapy.

Becky Strong: Connie asks, does taking amoxicillin cause or affect bullous pemphigoid?

Dr. Lipman: Great question. Bullous pemphigoid can be triggered by medications. Most commonly we see them to certain kinds of medications like diuretics such as Furosemide or Lasix. Or gliptin medications, those are some of the diabetic medications usually, but it can be triggered by an antibiotic like amoxicillin. It would be rare, but it could happen. If your bullous pemphigoid started very soon after taking this antibiotic, it's something to be considered. That being said, a lot of folks who have bullous pemphigoid are at high risk for getting a secondary wound infection, so antibiotics may often be needed. Likely if you do not have a drug induced bullous pemphigoid, then taking the antibiotics should be perfectly safe.

Becky Strong: Great, thank you. We've gotten a couple questions about taking rituximab and mycophenolate but still getting lesions. How do you know when that combination isn't effective and works for your disease and you should let your doctor know?

Dr. Lipman: So the goal with rituximab would ideally be zero lesions, and we talked about how rituximab works. It attacks the B-cell population, which goes on to make these plasma cells that send out the antibodies and those are the things that are attacking the skin and the mouth. But there are certain, the longer someone's had pemphigus, the harder it is to get full remission with rituximab. That's why we're using it now as a first line treatment because we know it's much more effective if we use it early. For those who are having recalcitrant disease or still some oral ulcers, you have to ask yourself, one, how are my symptoms doing? Can I tolerate one ulcer in the mouth that clears within a few days. Or is this unacceptable the amount of disease I'm having? Do we need to change the frequency at which I'm receiving my medications, the dosage which I'm receiving my medications, or do we need to consider adding on another medication for really recalcitrant disease?

Becky Strong: Great, thank you. Amber asks, what percentage of people with mucous membrane pemphigoid achieve a full remission with a single dose of rituximab? Or is it even possible?

Dr. Lipman: What a great question. The issue with MMP is that it is not one disease. It is a big family of diseases and we showed a picture of that hemidesmosome that has a protein, but there's so many different proteins that are being attacked in mucus membrane pemphigoid, oral or ocular disease. And we don't have great testing out available commercially that we're able to test for all these different subtypes. So I do have patients who are under control with rituximab. However, for every individual therapy, there's no promise that one dose of rituximab will send them into remission. It may be that rituximab helps get you to remission, but it's not a guarantee. That's where this is even the more rare, among the more rare diseases. It can be really challenging, so looking individually for each patient and making sure you have a great team. For me, I work very closely with a group of GI doctors, a very talented cornea ophthalmologist, and making sure that we're addressing all parts of the body that are being affected by mucous membrane pemphigoid.

Becky Strong: Great, thank you. Groff is asking if there is one medication immunosuppressive that is associated with a higher relapse rate?

Dr. Lipman: Well, I would say from some of the data we reviewed today, we can definitely say that prednisone versus rituximab is associated with higher relapse rate and failure to clear the skin. But in terms of other diseases, I'd really have to take a good look at the literature. When coming off of the medicine, that is really when the rate of relapse is highest. To flip your question around, I would say that rituximab is likely associated with the lowest risk of relapse rate, but comparing azathioprine to mycophenolate to others, it is very hard to say.

Becky Strong: Great, thank you. John said he read that you should limit your sun exposure while taking mycophenolate mofetil. Is that true and is it true of all immunosuppressives?

Dr. Lipman: That's a great question. As a dermatologist, I would say absolutely limit your sun exposure no matter what. But mycophenolate, as you know, can increase the risk of skin cancer when taken for prolonged periods of time and cause photosensitivity. So yes, especially with mycophenolate, it's important to be protected from the sun. So yes, especially for mycophenolate mofetil. For other immunosuppressives, less reported for rituximab or prednisone. However, prednisone is associated with skin thinning for prolonged use and that plus sun exposure in the long term can also increase risks for trauma to the arms and legs and difficulty with wound healing. So really for every patient I would recommend being very judicious with sun protection.

Becky Strong: Great, thank you. Someone asked in the questions, how far in advance do you need to get your vaccines before taking rituximab infusions or starting immunosuppressives?

Dr. Lipman: So that's a wonderful question because the vaccines take some time for your body to create this B-cell mediated response. Generally I recommend for my patients that we wait at least a month from their vaccination to start their rituximab therapy. And in general there's some insurance authorization and clearance time that goes into planning for rituximab therapy. So as long we're not in an emergency situation, generally we do have the time to get everything in order.

Becky Strong: Great, thank you. Andrea says that she received her first round of rituximab in 2021 and at that time tested positive for PV via a blood test. But two years later she had a resurgence of blisters in her mouth and it was visually PV but didn't test positive during the blood test. Could the rituximab change the blood makeup for that to happen?

Dr. Lipman: The rituximab, what it did is it targeted the B cell clone that was creating that anti-desmoglein antibody. However, it does not clear all of the resident areas. So you can still have positivity or sores without a positive desmoglein level, which is why I said the caveat of the desmoglein can be helpful to monitor your disease activity, but it's not the only thing that's helpful in monitoring your disease activity. So your symptoms are by far the most important thing. But rituximab does a great job of really reducing the burden of this antibody, but it does not address all of the plasma cells that were in circulation, only the B-cell population.

Becky Strong: Great, thank you. Jonah also asks that once you're in remission after receiving rituximab, does a patient continue to receive rituximab and for how long can you take rituximab and remain on it safely?

Dr. Lipman: What a wonderful question. This is one of the areas that there's a lot of research going into right now. I think that Pascal Joly's group just published some new interesting data about the Ritux 3 and rates of relapse. Our goal is to provide you with the least amount of immune suppressive and have the highest response rate. And so oftentimes it's a watch and wait response. Some patients do require more frequent rituximab dosing even every six months. However, for several patients, a single dose of rituximab course at day one and day 15 may be sufficient to get them into remission. Then following their desmoglein can be very helpful to say, what is our risk of relapse? Then re-dosing based upon that. Rather than keeping you immune-suppressed every six months where you could have years that go by without a relapse where you don't need to be immune-suppressed.

Becky Strong: Thank you. We've had a few questions asking to confirm patients with PV, there's no issues with getting the shingles vaccine or the pneumonia vaccine, any of those kind of vaccines before or after treatment?

Dr. Lipman: The big thing is when you are immune-suppressed, it's important to avoid live vaccines. So after treatment, when you're on treatment, whether it's rituximab, mycophenolate, you name it, you should avoid live vaccines. What's a live vaccine? Something like hepatitis A, the nasal version of the flu vaccine, which most people don't receive the nasal version of the flu vaccine. It's completely safe for you to get non-live vaccines. The regular vaccines like flu and covid, those are not live vaccines. Now, if you're on rituximab, they're not going to be very effective if you receive your vaccine right after your rituximab because you need that B-cell population to produce efficacy of your vaccine. Now before taking your immunosuppressives, it is safe for you to get your vaccines. Some people are concerned that it may cause a flare of their underlying disease process, which can happen, but it's always really a risk and benefit, saying if you have underlying lung disease, is the risk of being immunosuppressed and having covid pneumonia higher than the risk of having a small flare of your pemphigus knowing that we're going to get you on treatment. And so for my patients, it's really an individual discussion there, but I highly recommend protecting yourself as much as possible.

Becky Strong: Great, thank you. One last question. I know we're coming up on our hour. Erin asks, is there a big cost difference for patients between the different immunosuppressants used in our community?

Dr. Lipman: Great question. Some of them are older, so for example, methotrexate. And I would also just recommend everyone check out a website that's called GoodRx, if you haven't heard of it before. That's a website that, if you don't choose to use your insurance but choose to go outside of the insurance, you can see at different pharmacies what the different cost of medications are. Insurance will really be needed to cover things like rituximab or other infusion therapies, which are just exorbitant and it would be so difficult to pay for out of pocket. But things like methotrexate, which is an older medication might be more affordable, whereas

maybe something, a more novel medication might be a little bit more expensive. So you really have to check with your insurance and what formulary they have and what other resources or coupons are available to see what medication is going to be most available and most cost effective.

Becky Strong: Great. Thank you. You have answered a lot of questions for a lot of us and covered a lot of material in such a short time and we sincerely appreciate that. So thank you for being with us Dr. Lipman and thank you everybody for joining us. Before we go, I do have a few announcements. We are excited to announce that this year's Patient Education Conference registration is open!! The conference will be held IN PERSON in Newport Beach, CA. on October 26th and 27th. Attendees will have the unique opportunity to meet others living with pemphigus and pemphigoid, interact with IPPF Peer Coaches and medical advisors, and speak directly with disease experts. We hope to see you all there so we can finally meet you in person! As a reminder space is limited. See you in October!!

Becky Strong: If you want to stay updated about upcoming webinars, events and important news in our community you can opt into our mailing list. You can join our mailing list by visiting our website, www.pemphigus.org, scroll to the bottom of the page and enter your email into the "Join Our Email List" box.

Becky Strong: Have you explored the IPPF's Guide to Pemphigus and Pemphigoid? This guide offers medically reviewed answers to common questions for those newly diagnosed, along with valuable information on managing and treating these conditions. With this guide and other IPPF resources, we aim to empower our community with the essential knowledge needed to make living with pemphigus and pemphigoid more manageable.

Becky Strong: Don't forget to check out our Find a Doctor Directory! This handy tool lets you search for doctors in your area and worldwide who the IPPF believes are experienced with pemphigus and pemphigoid, using a variety of criteria. Simply scan the QR code or visit our website to access the directory.

Becky Strong: Want to help doctors and researchers better understand pemphigus and pemphigoid? Wish there were more and better FDA-approved treatments? Join the IPPF Natural History Study today! Sponsored by NORD and the FDA, this patient registry ensures your information is private and protected. Your participation will help advance research, improve treatments, and move us closer to a cure. Share your journey and make a difference for everyone affected by these diseases. Get involved and visit www.pemphigus.iamrare.org to join today.

Becky Strong: A heartfelt thank you to everyone in our community for your generous support of the IPPF. Your donations make it possible to connect patients with vital support, resources, and experts, and to raise awareness. Thanks to you, we share patient experiences with medical and dental professionals, advocate at the government level, and promote crucial research. To continue making a difference, scan the QR code on your screen or visit

www.pemphigus.org/donate to donate today. Your contribution ensures our programs remain available to all who need them now and in the future.

Becky Strong: Lastly, The IPPF hosts virtual support groups nationwide. If you'd like to join a meeting, please visit our Event Page to register. We're also looking to expand our support network. If you're interested in starting a support group in your area, please contact Becky Strong at becky@pemphigus.org. It's easier than you think and a great way to help others find the peer support they need.

A recording of today's presentation, along with a survey, will be sent out after the webinar. Thank you all for joining us!