November 9, 2023- Immunosuppressives: Dr. Wu

Becky Strong: Welcome, everyone! This webinar is now being recorded. I'm Becky Strong, IPPF Outreach Director, and I will be your host for today's webinar. Thank you for joining us. I would like to thank you for being on the call with us and for the support provided by Sanofi and Regeneron, for making today's call possible. "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." We are excited to have Dr. Benedict Wu with us today to discuss immunosuppressives. Let me introduce you to our speaker for today.

Dr. Benny Wu is the Director of Inpatient Dermatology and Assistant Professor at Montefiore Einstein. Dr. Wu's clinical interests extend to inpatient and complex medical dermatology areas, including connective tissue disorders, autoimmune bullous disorders, immunodermatology, cutaneous presentation of systemic conditions, and cutaneous lymphomas.

Dr. Wu has been at Montefiore for 2 years and has acquired many complex cutaneous lymphomas, autoimmune bullous dermatoses, and connective tissue disorder cases. Lastly, Dr. Wu's enthusiasm and love for complex medical dermatology has led to the successful launch of the adult rheumatology-dermatology joint clinic.

Before we begin, I would like to go over a few housekeeping items. You will remain in listen-only mode through this webinar. For those of you who are on their computer for this webinar, you will see on your screen that you can access the audio either by using your telephone to call in or from your speakers on your computer. Click on the little carrot or up arrow next to "audio settings" in the bottom left hand side of your screen. As you see on my screen right now you have the option to select your computer speakers or to dial in by telephone. Please be sure to select the method that you will be using.

If you would like to ask a question, please click the Q&A button on the bottom of the screen and then type your question into the text box. We will try our best to answer as many questions as we can within the hour. Please feel free to type your questions into the text box throughout the presentations. Dr. Wu will be answering your questions at the end of the presentations.

On the webinar today we will be specifically discussing Immunosuppressives. If you ask a question that does not pertain to the webinar subject I will have to ask you to email me after the webinar.

For those of you on the call that aren't on the web, you will not be able to ask a question. So if you would like to ask a question, please click on the link that was provided to you in your confirmation email. Now, it is my pleasure to hand it over to Dr. Wu.

Dr, Benny Wu: Thank you so much, Becky, for that wonderful introduction, and I'll start off by sharing my presentation. Good evening, everyone. Thank you so much for attending the IPPF webinar tonight on immunosuppressive. Thank you for inviting me, Becky. It's a great pleasure to be in this group, and to serve as an advocate for our patients suffering from pemphigus and pemphigoid. So for tonight's lecture and presentation, I definitely wanted to just go over some highlighted points that I've outlined here, and as Becky mentioned, every patient's pemphigus and pemphigoid is unique to themselves, so we always have to take each advice that's given at these webinars with a grain of salt. So a bit of a disclaimer in terms of what kind of patients or population I see here in the Bronx. I usually see patients with very severe pemphigus and pemphigoid, and realize that that's not everyone's case. Some people have very mild cases of mucous involvement. So the style that in the setting that I'm in I might use very aggressive, immunosuppressive therapies compared to some clinicians, that outpatient settings so kind of keep that in mind. So I definitely do see a lot of severe disease, because they've been neglected in the community, that they've been misdiagnosed and mistreated in the community settings. So then they end up in a tertiary care hospital where I'm at.

So we'll also go over some. The main backbone and guidelines, and most of these guidelines are based on expert opinions. Unfortunately, because pemphigus and pemphigoid is still somewhat of a less common medical condition. So a lot of these guidelines are based on expert opinions and we'll definitely highlight some of the FDA approved treatments for Pemphigus and pemphigoid. So with Pemphigus and pemphigoid. They are complex disorders, and we try to personalize these treatments to each patient and make it unique for them.

And then, after we talk about some of the treatment guidelines with immunosuppressives. We'll go to the question and answer section, and then we'll leave an open form at the remainder of the webinar.

So I wanted to begin by giving the audience a clinician's perspective. And these are all the things that we try to take into consideration as we approach the diagnosis and management of our Pemphigus and Pemphigoid patients. So with a big belief of mine. And what I teach my residents is that some, the best treatments are usually ones that are affordable, effective, safe is easier, or have less barriers to implementing them so, and it causes the least least lifestyle disruption. So I think these are all really important factors to consider when we kind of design our treatment plan

for each patient. So what I mean by this is that not everyone is gonna come in with the same severity of disease and so for someone with more mild disease, we might stick with more topical medications, someone with more severe disease, will definitely go into more systemics that can take and part of infusions in the form of infusions or oral medications. Another thing we take into consideration is the age of the patient, and whether or not that person can become pregnant because there are definitely medications that we can not give pregnant patients. Such as Methotrexate and Mycophenolate, and in our younger patients who are affected by Pemphigus or pemphigoid, we really wanna take into account their active lifestyle, and to possibly recommend treatment, that is every 2 weeks or every 3 months, instead of taking a pill daily. So these are all kinds of lifestyle factors that we take into consideration. And then, especially also in our elderly patients, we have to take into account their comorbidities, such as diabetes. They might have cardiac conditions. So sometimes we can't give very strong immunosuppressives right off the bat because we have to keep it safe.

And then a big thing that I want all my trainees to know, and also my patients to know is that we really want to pay attention to all the symptoms that they feel. And it's not just about what we see with our eyes, because our patients might be really bothered by the itch or this oral pain, but they're not super bothered by the appearance of the blisters on their skin but they're mainly bothered by the itchiness. So we need to really pay attention to not just what we see with our eyes, and what the clinician sees, but what our patients are feeling. We have to not neglect those complaints as well. And then also we need to give a plan to patients that they can follow. And, for example, as a patient has blisters all over the body. We can't just stick with a cream or topical ointment, because how is that person gonna be able to apply it? And they might live alone at home and not have home health care. So we have to give stuff that is very practical, and that can be executed without extra extraneous efforts on behalf of the patient. So sometimes topicals are not practical or possible, or even medically safe, because the disease is pretty severe, so we do have to sometimes stick with short term prednisone add-on steroids, varying agents, or immunosuppressants that we'll talk about shortly, and then always, you know, including our topical agents.

So these are kind of the therapeutic medications that I commonly use in the hospital system, which is actually quite aggressive. So again, under treating the patient leading to inadequate report control of the disease is sometimes just as deleterious as over treating the patient. So we definitely wanna take into account both the skin disease burden and then also the symptoms that the patients feel. So these are just some of the 4 main immunosuppressive agents that are safely or commonly used in the hospital setting. So IV prednisolone, intravenous immunoglobulins,

Rituximab and the one amino suppressant that I listed here that we would talk about today is the mycophenolate mofetil.

So I wanted to go over the guidelines. And I put these in boxes of the immunosuppressants that we would cover today. And this is based off our guidelines in the Journal of American Academy dermatology. And this is kind of what we follow when we evaluate patients. So I put the red boxes, because that's kind of the algorithm that we would see Dapsone or tetracyclines, or what you might know as doxycycline and where that goes in the therapeutic armamentarium or ladder. As we approach treating Pemphigus patients. So as you can see from this, Dapsone and tetracyclines, doxycycline niacinamide, and mycophenolate and azathioprine are all listed here. but it kind of goes gradually as we need to bump up the therapy. Then, we add the mycophenolate or the azathioprine . But a lot of times we start off with the tetracycline such as doxy.

Again, this is more for severe disease. Right? Then we have to go down to the Rituximab route, IVIG. and then only if it's severely refractory. Sometimes they add on azathioprine or cyclophosphamide in very severe disease cases.

So this diagram actually shows the outline of Pemphigus, and it kind of illustrates the disease. In terms of a very simplified diagram of this is the skin up here, and then what you can see is the desmoglein proteins in the skin.

So what happens in the path of physiology of Pemphigus, as we all know, is that the Pemphigus antibodies are denoted by these rockets. There the Pemphigus antibodies are made by B cells which come from the bone marrow. So these pathogenic B cells produce all this antibody that then attacks the desmogleins that's what leads the skin to break apart. And then this goes to show all the different agents, and what kind of targets that they hit.

So, for example, the intravenous immunoglobulins, the IVIG neutralizes these Pemphigus antibodies whereas rituximab depletes the pathogenic B cells. So it hits the B cells over here, and so does plasma feresis where it removes all the pathogenic antibodies and then B cells.

So what the main immunosuppressives that we'll talk about today is azathioprine, mycophenolate and methotrexate. So these are the 3 main immunosuppressants, and then they hit both B cells and T cells, which is B cells and T cells here, but mainly the one that really hits both B cells and T. Cells are mycophenolate whereas Methotrexate hits more T cells.

And then the Alkylating agent, Cyclophosphamide, actually hits more B-cells as well and azathioprine or Immurand also hits mainly more T-cells than B-cells.

So moving on to pemphigoid. So the pemphigoid recommendations are similar to Pemphigus, as you can see there's still the doxycycline niacinamide that comes up, and then the dapsone. And usually they recommend having dapsone for a moderate mild to moderate disease to be on with prednisone. So as long as you're on prednisone, the guidelines recommend to also be on dapsone and then the doxycinemite, as you can see is a common entity that's also in pemphigoid.

And then, if those don't control the disease well, then, we have to bump it up to azathioprine or Methotrexate or mycophenolate. So similar to the pemphigus treatment ladder.

So again, if this mucous membrane pemphigoid is really severe, then we have to actually consider. Obviously, we're rituximab and cyclophosphamide in these patients. But again, some of these immunosuppressants, like Dapsone and niacinamide and mycophenolate, appear over and over. So it just depends on each unique case in our patients to see how severe their disease is.

So again, this kind of shows the same diagram of Pemphigoid treatment. So we have our azathioprine, mycophenolate and the Methotrexate. And with mycophenolate and the Cyclophosphamide being the ones that really hit the B cells here to prevent the pemphigoid antibody from being produced. And then, whereas the Methotrexate and azathioprine hits more of the T cells which will eventually affect the B cell activation. So it kind of indirectly targets the B-cells with the pathogenic antibody production.

Thus lowering the production of the BP. 1, 82/30, which will then obviously target the Hemidesmosomes in the skin which will lead to the blister formation and pemphigoid.

So I know, Becky, I kind of blew through that really quick, because I really wanted to go get to these really excellent questions that were raised and brought up to me. Because I think we'll go over each of those immunosuppressants in a lot more detail, and especially as it pertains to everyone's concerns and questions. So is it okay? If we just start everyone who's looking at this and we can go down this list.

So the first question is about what medications are considered immunosuppressives, what are the differences between these medications and how does it determine what medication I will receive? So as you can see from that previous algorithm prednisone is usually like the first line, unless it's oral steroids prednisone, or is it topical? It depends on if it's oral involvement or do you have just a lot of skin involvement. So these are kind of patient dependent. But to sum it up in a nutshell, immunosuppressives affects your and I have a beautiful diagram here. Immunosuppressants versus immunomodulators. So true immunosuppressants will cause your white count to be lower. It will cause decreased antibody production. It will cause decrease delayed hypersensitivity reaction, which means that true immunosuppressants will prevent you from mounting an

appropriate vaccine response. So that's why patients who undergo rituximab therapy. We recommend that you get all your vaccines 2 to 4 weeks before your rituximab infusion, so that your body has enough time to react to the vaccine to produce enough antibodies to protect yourself and immunosuppressants will also increase your risk of developing opportunistic infections and basically the true immunosuppressants. They inhibit your B cells and your T cells. So that's what's defined as a true immunosuppressant.

The difference with immunomodulators is that immunomodulators actually inhibit one of the small molecules or proteins that's made by your B cells or T cells. So that's why it's a lot more specific of a targeted therapy than something like a general amino suppressant.

So again, like, I'll go back to this slide about. What's the difference between immunosuppressants and immunomodulators is that suppressants really will drop down your white count, decrease your antibody production, which is made by your B-cells, whereas immunomodulators will not have any of these effects.I hope that answers part of the question, or at least the question.

How does it determine what medication I will receive? I think this is a great question, and it's really a lot of the hallmark treatments for pemphigus and pemphigoid does include immunosuppressants. Because the reason why we use immunosuppressants is because it works really rapidly, and it's really quick onset. So imagine if you have widespread blisters on your skin. If we depended on something like an immunomodulator it might take months to go into real good effect, and someone cannot be living with widespread blisters throughout their body for months. So one of this example is what we'll talk about is having prednisone, which is the immunosuppressant and combining it with something else which is a little bit more globally immunosuppressive. And then they work kind of synergistically.

How do immunosuppressants work? And then what is the usual dose of these medications? So the usual dose is shown here. So the immunosuppressive dosing of anti metabolites. So a lot of times with. And this is to show, like, how these medications and where do they inhibit so like when when the medication is targeting mainly cytokines and cubicons. That's more anti-inflammatory. So that's kind of like what your doxycycline and niacinamide is doing. So it's really affecting the neutrophils and cytokine production. So that's over here. So if you want the doses that usually will cause immunosuppression is by inhibiting your T cells with my Methotrexate. It's usually between 20 to 30 milligrams weekly. So that's for the Methotrexate family. Cyclosporine, we usually do it only for 6 months or less, and that's usually at 3 to 5 milligrams per kilogram. But that's not really used for pemphigus or pemphigoid. Azathioprine or imuran is about a hundred to 200 milligrams daily. Then, for mycophenolate if we want it to mainly hit the T cells it's usually between one to 2 grams a day. But then, if we want to hit mainly B cells, which is where we really want to be for

pemphigus and pemphigoid, because that B cell is producing all the antibodies. Then we sometimes have to go up to 3 grams a day. Usually that's a high end of for mycophenolate and then for azathioprine between 200 to 300 milligrams

In terms of immunosuppressives it is usually just they inhibit the B cells. T cells lead to decreased antibody production, which is the hypogammaglobulin which I showed in the other slide. And then they will cause leukopenia to decrease your white count. So that's how they really work.

And then does Pemphigus or pemphigoid respond better to immunosuppressants? Are they considered to be slow acting or fast acting? So prednisone as a global immunosuppressant works super fast. So that is why it's still our main workhorse that we like to use to rapidly gain control of the disease. and whereas the immunosuppressants the mycophenolate, the Methotrexate, and azathioprine, they take a little bit longer to work. So this diagram here kind of illustrates why we like to implement prednisone. And then the sparing agent, you can imagine this is gonna be azathioprine, methotrexate or mycophenolate. So usually, we if it's a pretty moderate to severe disease, a disease burden, we'd like to start off with prednisone you know, usually one milligram per kilogram. But at the same time we want to start this steroid sparing agent, such as Methotrexate or mycophenolate, because this will take about at least 4 to 6 months to kick in. So you can imagine you start over here. You start the prednisone and you start the cellcept over here, by the time your prednisone is tapered off to almost 0. That's when your Methotrexate or your mycophenolate is going to be at peak activity. So that's why we can safely taper off the patient off the predispone without the disease going back up into activity. Because by the time you bring the prednisone down the steroids varying agent will had time to go into really maximal effect. So that's why you can safely be off of prednisone and not experience this yo-yo effect like an erratic effect, because this is what we would like to see. We start off prednisone here, and we take you off of the prednisone over 4 to 6 months, and then, if we would have started the steroid sparing agent over here at this time. Then, by the time the prednisone is off the mycophenolate for example, will be at its peak effect. If we just take you off the prednisone, and we don't add another agent. Your disease activity is going to go up and down. So that's kind of the rationale of why we usually institute dual therapy, at least in the beginning, is to prevent this yo-yo effect from happening.

How do I know if this is the right treatment for me and if it is working. I think that's the beauty of dermatology, is it’s the skin and we monitor it. Now we have so much more advanced understanding. And then we have all these antibody assays that we can use to measure in the blood. But the beauty of dermatology is that we visualize disease activity by examining the patient, so not only will the patient usually feel less itchy with pemphigoid especially, and less skin pain with pemphigus and notice decreased oral ulcers. That's how we will know that it's working. But

you know, over 90% of cases are going to respond to prednisone to some degree. So that's pretty much that.

In terms of how long does it take for the immunosuppressives to work? Usually about like mycophenolate, for example, to really go into full effect. You have to give it at least probably 6 to 12 weeks. Usually, I say, 12 weeks with patients and that's after you up, titrate it.

And then what are the benefits to immunosuppressant therapy? Particularly doxycycline. So doxycycline is interesting because imagine if we use doxycycline niacinamide the doxy is the same dose we use for patients with acne. So, I think that acne and bullous pemphigoid for example, are 2 very different diseases. So are we really giving our acne patients an immunosuppressant. We're not. So by definition, doxycycline is more of an anti-inflammatory effect instead of an immunosuppressant effect. So we usually give doxycycline 100 milligrams twice a day. Same thing we give for our teenagers with acne treatment. So we're using it. We're really using the doxycycline as more of an anti-inflammatory effect than truly an immunosuppressant effect. So there's not really a particular side effect that has an immunosuppressant effect on the body with doxycycline, which is another reason why it's a very much safer medication than prednisone for our elderly patients with pemphigoid.

So in terms of special blood work or monitoring, each immunosuppressant is going to be very different. And I think that one of the questions later on we talked about azathioprine. We definitely need to measure a special enzyme called Tpmt. And it is important to measure this enzyme level, because in patients who are deficient in it. If you're deficient in this enzyme, then, if we give you this medication it's going to be converted into the active medication in your body, and your body is not going to be able to degrade it safely. So that means that you're going to accumulate it at toxic levels, and one of the side effects of this antimetabolite azathioprine is that it can cause severe bone marrow suppression, and cause your all your white count to be lowered and to have you be in a very dangerous immunosuppressive state, much more than what we intended to with treating your pemphigus or pemphigoid. So I think we'll hit that question a little bit later. But there's definitely monitoring guidelines. But in terms of mycophenolate the other immunosuppressant. It's a very safe medication, because inherently, it's not toxic to your kidneys or your liver. Whereas Methotrexate does have hepatotoxicity where it can be toxic to your liver over time, and that's usually over many years of taking it, and also, Methotrexate can cause your bone marrow to be suppressed if you don't supplement with folic acid, etc. So there's definitely routine blood work that usually needs to be done every 3 to 6 months with your doctor.

How long are immunosuppressants usually taken? How do I know when it is time to stop taking, or if I am in remission? So I think this is a really good question, but it's also a complicated one,

because it's really dependent on the individual patient's disease activity. So we kind of now have the thought of you using the blood titers like the desmoglein or the Bp180 antibody levels to kind of monitor the serologic status of our patients. But, more importantly, it's dermatology, so we can use our clinical eyes or our eyes to examine the patient, and the patient tells us, are they developing new lesions? How are they feeling? Are they feeling itchy, or do they feel like there's new oral pain or erosions that's in their mouth. So that's kind of how we can really gauge what the disease activity is, and then kind of maybe correlate that with the blood antibody level. And then putting those 2 parameters together, we can kind of see. obviously, is a patient in clinical remission, because there's no disease activity on clinical exam and then based off the serology. If all their antibody levels are undetected, then they're in clinical or serologic remission. So those are kind of the things that we have to take into consideration. and like anything we're now thinking, okay, you're in clinical remission and serological remission for 6 to 12 months. Maybe we can start tapering you off of the mycophenolate. Maybe you've been on mycophenolate 6 pills a day for the last year. You've had a really stable disease. Maybe we can start slowly titrating you off of it and kind of monitoring to see if there's any return of the disease. So it's a really personal process with each case. But there is definitely at least after one year of clinical remission I try to. It's very reasonable to start tapering people off their medications to kind of see if the disease will come back and some people are lucky that it doesn't. And a patient can remain immunocompromised for a long time after stopping sometimes for 2 years or more.

What test can be done to determine the patient's degree in immunosuppression after stopping rituxan. So this is about rituximab where it depletes all your B cells. So with that said, there's the specific type of B cells that has that CD 20 marker on it, because we're taximatted targets at the CD 20 positive B cells. So there's actually tests that you can measure the amount of CD 20 B cells in your blood. So that is a way that we can measure if there is how immunosuppressed you are by how depleted the CD 20 positive B cells are. So that's one way we can kind of determine the degree of quote unquote immunosuppression after stopping rituxan because we should be after 3 to 6 months of stopping rituxan, we should be able to see those CDs. 20 antibodies come back to life and be able to be detectable in the blood. 2 years or more is kind of long, like you shouldn't be immunocompromised, or at least have undetectable CD 20 B cells for 2 years. Usually it starts recovering after 3 months, because typically we give rituxan every 6 months to our pemphigus or pemphigoid patients, because that's about the half-life and before their disease comes back, if it's gonna come back.

Then most of the immunosuppressants like azathioprine, mycophenolate they're usually taken orally. Not many of them are given intravenously. There's some rare cases of cyclosporin that can

be given intravenously in Tacrolimus, which is similar to mycophenolate. But the majority of these medications are taken orally.

Is there anybody who shouldn't take immunosuppressive drugs? The main real contraindications to any of these oral medications is obviously, if you have some severe allergy to any of the components or if you have an active cancer, or an active malignancy or an active infection of untreated tuberculosis. If you have a severe respiratory infection. You should definitely try to hold off your immunosuppressants for a few days, and let your doctor know before proceeding with the medication.

Then, I hear for imuran you need a certain enzyme at a certain level. Why is this? So I wanted to show the audience. These are my notes from residency. So I know it's a little bit chaotic. This is the section as a side print. So this is basically the enzyme that you we need to check that you have or I mean, I'm sorry the tpm t, this enzyme over here because this is a drug azathioprine. So it gets converted by your body into theanine. And this is actually the one that is gonna inhibit your B and T cells.

So we have to measure this enzyme level right here, because actually, it facilitates the inactivation of azathioprine. So imagine if you didn't have this enzyme, then all this stuff is going to go into here, and then you're going to have too much of the thy wanting. That's going to be inhibiting all your B cells in your T cells. So it's going to be too toxic. So you're gonna have to have some of this enzyme to inactivate the azathioprine. So that is why we need to check it, because if you are actually deficient in that enzyme, then we will inadvertently cause you to have severe immunosuppression because one of the side effects of azathioprine is bone marrow failure. So if we're not only affecting your B cells. And we're depleting your T cells in your neutrophils, which are really important innate in defense systems. So that's why we need to check on that enzyme.

Are immunosuppressants used in combination with other medications. And if so, which one? That's a great question. And immunosuppressives are definitely used with other medications as shown by this figure here. So we commonly talk about drug combinations as additive or synergistic. We definitely don't want medications to be antagonistic, because that would not be good, because not only we're basically neutralizing its effect. And basically we're exposing our patients to high-risk drugs, and it's not going to be helping them. And it's potentially going to be hurting them. So we want our medications combined together to be at least additive, and if not synergistic, because that's gonna have an extra benefit and realize that by combining all these immunosuppressants. Obviously, if you combine 3 of these medications together, they're going to be more toxic and have higher risk. But if you know how to adjust them based on the dosages

then it can be still relatively safe. If you take up the appropriate prophylaxis and other safety measures with these medications.

So, for example, in this figure we can definitely combine. Commonly we combine prednisone, mycophenolate, and azathioprine. We can do prednisone and rituximab. So this is the one where we have to be mindful of combining prednisone rituximab and mycophenolate. So whereas with Prednisone, and mycophenolate we might do, let's say Prednisone is always going to be 40 to 60 milligrams a day but mycophenolate and when it's just the 2 of those together, the mycophenolate can go up to like 3 to 4 grams a day. But when we add rituximab and prednisone and mycophenolate we have to be mindful of it, because if we keep the mycophenolate, it's still at that 3 to 4 grams a day dosage with gonna be too high. So we have to decrease the mycophenolate to probably one gram a day. So as long as we are mindful of the dosages of each of these individual medications, and know the kind of effects that they have when we combine them together, then we can still safely implement using them, and they will become more effective in patients with more refractory disease. So we just can't just keep the same dosages, but just keep adding them together. We have to study, note about the drugs, half life and safety. So to answer that question in a long, winded manner. But we definitely combine these frequently, and we can definitely make them still very safe to use.

Are immunosuppressants considered a first line treatment for Pemphigus and Pemphigoid? Yes, the short question. Short answer is yes, and mainly the first line treatment. Surprisingly, there is no FDA approved first line treatment for pemphigoid but for Pemphigus the first line FDA approved treatment is prednisone and still rituximab. So we are still really behind in terms of FDA approved first line treatment for our blistering diseases as compared to other dermatologic problems. So immunosuppressives are still our main workforce.

What are the most common side effects you see from these medications? What can be done to prevent these side effects? So I think the most common side effects and most concerning for our patients and for everyone in the audience, and then also for the clinician is obviously we want the medication to be safe But we also want it to be effective for sure, but also to be very safe or as safe as possible. So there are side effects in terms of what patients feel as with mycophenolate they can cause GI upset or stomach upset, including diarrhea or nausea, and cramping. So some ways to circumvent it is mycophenolate is usually dose twice a day, so taking the medication with food or split dosing them, it depending on when it is that you take it like, is it the morning when you take it that usually feel nauseated, or you have diarrhea? Or is it evening? Some patients are just more sensitive whether it's in the morning or evening but definitely split dosing can help or if you have to take something like 5 pills a day, which is equivalent to 2 and a half grams a day. Then you might want to split them up like into a higher dose in the evening, or a higher dose in the

morning, depending on your system works, and if that still causes GI distress, there's a mycophenolic acid derivative which is a enteric coated mycophenolate, which is a lot more gentle and easy on their stomach. And that's something that you can definitely speak to your dermatologists about because if the mycophenolate works really well for you, but you just can't tolerate it with the GI issues, then there's a mycophenolic mycophenolate that is definitely a possibility. But I do have to say, most patients their GI symptoms do improve with mycophenolate even the plain mycophenolate. They might have GI upset for the first couple of weeks, but they do get better over time, even if they don't really adjust their intake habits.

So the other stuff with all the immunosuppressants and these medications I think the side effects that we really care about is also getting infections, such as strep, pneumonia or the influenza, you know, seasonal flu, we definitely want to keep our patients safe, and one of the fear complications is infection, and you know that can lead to a lot of other complications. So we really try to emphasize that our patient or I tell my patients that they need to follow up with their primary care. They need to follow the guidelines of vaccination. You know the pneumococcal vaccine. Now, with the shingles vaccine obviously with covid vaccines to really try to get their vaccinations to protect themselves because they are on these immunosuppressive medications. And then, as I said earlier, usually about 2 to 4 weeks before they get any hard hitting immunosuppressives. They can try to get all their vaccine series done by then, so that their body has time to mount a good immune response to the vaccines.

And then the next question is, what are the long-term effects on the kidney's, liver and heart from these medications? Luckily in terms of heart toxicity, the main one that I could imagine would be for prednisone. and luckily, you know, like I showed in the diagram earlier here, I really try to take my patients off of prednisone after 4 to 6 months, like I try not to expose them to longer than try longer than 4 months, because I try to add the steroid sparing agents, such as mycophenolate immediately when I start the prednisone. so I can really take them off as quickly as possible. So the long term in terms of the heart, like the heart stress. It's mainly from prednisone and that's how we can kind of circumvent the issue. And then, in terms of the main benefit of mycophenolate is that it's not toxic to the kidneys or the liver. So that's why we really like to use mycophenolate over something like Methotrexate. Methotrexate can cause liver fibrosis, and in rare cases cause pulmonary fibrosis as well. But that's usually when they used to use it at very high dosages, not at the, you know, 15 to 30 milligrams weekly doses that we use for blistering diseases, but over time it can cause liver fibrosis in certain patients and methotrexate is excreted by the kidneys, but it's not directly toxic to the kidneys. So some things that we have to be aware of is your doctor has to know that you're on Methotrexate, because, since it is excreted by the kidneys. if we give you an antibiotic that can be toxic to your kidneys, such as Bactrum, it can lead to inappropriate under

excretion of Methotrexate in the urine, and then that as a result is more accumulated in your body or circulating in our body and you can inadvertently be causing too much of the buildup of methotrexate and causing more side effects, such as bone marrow failure, and stuff like that. So those are important things to keep in mind.

How long do I know if the medication is working for me, or if I'm in remission? So similar to what we talked about earlier. It's the skin. It's a great organ that we can visually appreciate easily. So that's really how we know if the medication is working and especially with prednisone, it works so quickly, and patients usually feel relief really quickly. So that's how we know if it's working, and then we really try to give the medication a good 2 to 3 months before we put our hands up and say, obviously, this isn't working because some of these mycophenolate, methotrexate and azathioprine they usually take about 2 to 3 months to go into full effect. So if there's no clinical improvement, we're actually worsening, then we know that it's not working.

Can this class of medication be rapidly stopped without issue? So, the short answer is, yes, with the exception. And what I mean by rapidly stopping is, there's 2 different scenarios. It's okay. You're taking mycophenolate for a year, and you're doing really well with the Pemphigus. But then you suddenly get this really bad cold or flu, and you're knocked out in bed. You should not, you should put your mycophenolate on hold. So by this you rapidly by definition, stop for 2 weeks because you're overcoming this cold. So that is okay. Because it's out of safety concerns, because you have an active infection going on. So they won't. The only one that's really, truly quote-unquote, not ideal to stop rapidly would be something like prednisone that you're tapering off on a schedule. Obviously, if you are very sick, you can definitely stop it. And that's on a case by case basis that you definitely wanna have your dermatologists and your other physician be looped in so that they are aware of your current medical status so that they can safely see if you can withhold that medication for that time being, but for most of the cases they can be rapidly stopped without major significant issues.

How does Covid affect taking immunosuppressants? Are there special precautions I should take? So definitely with Covid around. We definitely need to be careful. Patients who have especially that are going to be under rituximab or these other longer lasting immunosuppressives we definitely need to make sure that the vaccinations are done right before we give these medications and any at any sign of any upper respiratory infection, or any other infection. Even, you know, travelers, diarrhea, or any of that. Those symptoms you need to inform your doctor of what's going on, because we do need to be vigilant about patients who are on immunosuppressants who are not overall well, because we definitely don't want the immunosuppressant to overtake their immune system and not be able to fight off whatever is going on in their bod at that time, and realizing that if you don't take your immunosuppressant for

3 to 5 days, your Pemphigus and pemphigoid is not gonna suddenly produce all these antibodies within those few days and come back and wreak havoc on you. So that's something to really take into consideration just because you skipped a week or 2. It's not gonna come back with a super vengeance within that short period of time. So your immediate acute illness is a lot more important than I'll be taking these medications religiously. I'm not saying that you shouldn't take it based on your doctor's instructions, but knowing that if you just skip a week because you're fighting off a cold that it'll be okay.

Any other special precautions? I think you should just exercise basic basically what we've been doing for the last 2 and a half years. Besides getting the vaccinations. And then staying away from others who are sick, etc. those are things that we can do.

How do immunosuppressants affect the covid vaccine? And so the timing is usually 2 to 4 weeks before you get the immunosuppressive medications that you should try to get all your vaccines done, and then will it be effective? I've been taking my medicine for over a year. If you've been taking your medicine for a year. and you have to get the Covid vaccine. Sometimes you can see if you can stop taking your medication for about 2 weeks, because some of these immunosuppressants have rather short half-lives. Unlike rituximab they have rather short half-lives. You can try to take it off for like 2 weeks to see, and then take the vaccine and then restart the medications. But in general, with these vaccines and your medications, if you've been on the medications. We still recommend that patients still get the vaccines and continue taking the medications with understanding that is better than not taking the vaccine, but also understand that it might not be as effective as mounting a mean response as if you weren't on the medication. So it's still better to take the vaccine and still stay on your medication. If it's not safe for you to stop the medication is what I'm saying. So in an ideal world you would not be on the medication, and then you would be able to take the vaccine, give it 2 weeks, and then start the medication. But understanding that real life doesn't work that way, and sometimes you have to, you have to start the medications immediately, because the disease is so severe. Just understand that it's you might not manage a great immune response, but it's still better than not taking in at all.

And will it be effective? Our recommendation is mainly the only contraindication is the live vaccines which we should not all be. We should have been done with our measles, mumps, and rubella as babies. Those who are the only kind of live vaccine that exists today. Even the new shingles vaccine is not live anymore. So there's no contraindications to the vaccines that we have for adults now. So we can still keep taking our medications and take the vaccine

So how commonly is Methotrexate prescribed? As you can see from the at least from the jad and the expert opinion guidelines. Methotrexate is still given for some of these autoimmune blistering

diseases. I, personally, don't prescribe Methotrexate for my patients with pemphigus or pemphigoid, because there's so many other great medications now. And so it's not super common. But there's definitely still dermatologists out there that do it, and that's very reasonable to do it as well. But there are definitely other medications around, such as mycophenolate that's great that can be used for both pemphigus and pemphigoid. The other thing is the thing that is less ideal in terms of Methotrexate is patients who take Methotrexate have to take folic acid. They have to remember to take the folic acid, and in elderly patients who might forget their folic acid. and they take their Methotrexate. It can really cause a lot of issues with their bone marrow, and also skin toxicity. and that can lead to a lot of complications. So I try especially in patients who might have to avoid methotrexate especially in patients having a difficulty adhering to like supplemental medications that they have to take, because they already have 5 different pills to take and now you're adding an extra layer to their daily regimen it sometimes gets to be a lot.

Monica says she has Mmp or mucous membrane pemphigoid with acute bullous pemphigoid and has been treated with cellcept in the past. Is there a better medicine that can help improve the oral Mmp other than prednisone? Is there a huge difference between methotrexate and mycophenolate when treating oral Mmp? So there's definitely with the guidelines. It says here with the pemphigoid. If there's ocular laryngeal esophageal involvement, so with that said you have oral involvement, there's definitely a lot more medications than just prednisone and mycophenolate, intravenous rituximab which is over here. It's definitely something that needs to be considered. So usually in these patients. We definitely, I tried to add, Ivig if you've been on prednisone and mycophenolate, and it's still you're having like still disease activity. Then I think that definitely the Iv rituximab should be added.

Is there any difference between mycophenolate when it comes to oral mmp? Probably if you're taking the prednisone with methotrexate, whether it's prednisone with Methotrexate or prednisone with mycophenolate. If you switch from mycophenolate to methotrexate is it really gonna make that much of a difference. I actually think it might worsen it, because mycophenolate has at least a lot more B cell activitiy than Methotrexate does. So my go-to would be to recommend considering the Iv rituximab rather than jumping from mycophenolate to Methotrexate in this case.

So I heard, I cannot take methotrexate if I have liver disease. Is this true of all the immunosuppressants? So that is not true for all the immunosuppressants and in patients, that we for us who treat patients with psoriasis. Psoriasi and Methotrexate, Methotrexate was commonly used to treat psoriasis and one of the big things we use. We ask about our patients is, do they drink alcohol? Because if they do, then Methotrexate is not an option because alcohol is liver toxic or toxic to the liver, methotrexate, can cause a lot of liver toxicity as well. So long winded way of answering that question is that it depends on what kind of liver disease you have. And then it's

someone who has liver disease. We definitely would not reach for Methotrexate as our first line agent if at all possible. A short way to answer this would be we prefer to not use Methotrexate in patients who have liver disease.

Then, which ones can I take with a history of liver disease? Mycophenolate or cellcept is not toxic to your liver or your kidneys, so that would be a very acceptable option. Azathioprine can also be a little bit pada toxic or toxic to your liver, so that would also not be a great medication to choose.

Mycophenolate seems to upset my stomach. Do you have any tips for taking this? Definitely try to split dose, or even split into 3 times a day. Undosing, taking it with food. Alternating to see if you want to take the higher dose in the morning or the evening, depending on how your stomach is during the different times of the day, I think, really play around with it. And I know that this is something that I can't really understand with my patients, because I've never taken it before. But I imagine that they complain about the GI issues for a reason, because they really have nausea, vomiting, or diarrhea and I definitely believe them. But the literature also says that it's supposed to get better over time, and I have seen it get better over time with my patients so I hope that you know whatever it's worth. I hope that if you can try to adjust the timing, and then also taking it with food to see if that will buy you some time until your body, adjust to it to the point where you can tolerate it better.

Do I need to let my doctors know if I got a flu or cold symptoms while taking those medications. When should I get worried and call my doctor? So I think you should definitely. I mean taking into account all your symptoms. Definitely the big red flags is when you should call your doctor to let them know you're on immunosuppressant, and you have these symptoms. I think the big red flags is real temperature, like, if you have a fever, you definitely need to let them know. Body aches, sores. All these kind of constitutional symptoms, you should definitely know, like seasonal allergies, or something like that might not be so necessary, not super important, but any type of objective evidence of fever and chills, and all this other stuff you definitely want to let them know. And the logical next step would be and he or she will, I'm sure, be more than happy to work with you and say, Okay, we need to hold your medications until you get better, and then there will be no consequences by holding the medication.

I think that was all the questions, at least for the written part. I think I went over all these other random slides as well to try to answer the question.

Becky Strong: You did amazing. You covered so many questions and gave such detailed answers. I know this is going to be so helpful for our community.

Dr. Benny Wu: Oh, thanks! It was a lot I mean, I don't know. I just kept blobbing on.

Becky Strong: It's good, great. I mean sometimes a little too much information is good, because there are some people where it's overwhelming. But other people really like that background so hopefully kind of hitting the mix in tonight.

Dr. Benny Wu: What I wanted to add with this slide is the Ivig, as a red bull is what I mean by that is that Ivig can be added to any of these kind of combinations on this slide, because it's truly not an immuno, like a long term immunosuppressant, because it doesn't destroy your B cells or T cells. It just neutralizes those antibodies that the B cells produce. So it's not truly like a super immunosuppressant. And it can be kind of added into any like slipped into any of these things to gain more rapid disease control

Becky Strong: Great. Thank you. And since you're on this slide. Joan asks, do you ever use niacinamide and doxycycline with mycophenolate mofetil?

Dr. Benny Wu: Yeah. So as if anyone's ever taking doxycycline it is a pain in the butt to take right, because you have to take it somewhat with food, because it also upsets your stomach. and it will cause nausea. So if you take doxy on an empty stomach, even our acne patients, I always tell them you know the thing is like they shouldn't take it with milk because of the the charges that interact with doxycycline doesn't get absorbed as much. But for those who have teenage kids and who start doxy and have acne. They complain commonly of GI upset so my qualm with starting doxy, niacinamide, mycophenolate. It's just GI toxicity or GI side effects. It's just gonna kind of be synergistic and not be very user friendly, to put it in a not so great way. So I just find that is really tough. And someone who is starting mycophenolate, the people that we use doxy, niacinamide for is usually patients who really can't tolerate any of the other immunosuppressants, such as mycophenolate or even prednisone. So definitely it's reasonable to add it with mycophenolate, but just be aware of the GI issues that patients will face.

Becky Strong: Great. Thank you. You had mentioned. Immunologic hardening earlier. And Diane is asking what that means. If you could just clarify that quickly..

Dr. Benny Wu: Yeah. So the immunologic hardening on top of this. Is that basically it's kind of like, imagine like your threshold of immunosuppression. It's gonna be you're gonna have to add higher doses of immunosuppressants to be able to lower your immune system. So that means that indirectly, you're going to introduce more toxicity because you have to increase the dosage of immunosuppressants to achieve that same immunosuppressive result as a lower dose. So if like, over here is the prednisone, and then over, here's your stereo sparing agent. So if you implement them at the same time, you're at this level. But then, if you only give prednisone and you don't give this one, then you're gonna be up here, and then you're gonna have to add something even higher to try to bring this down to originally where that baseline is. So that's kind of like what we mean by immunologic hardening. It will, if you introduce both of them simultaneously. You're gonna prevent that from going into a higher state to try to bring it back down, because then you're gonna have to go up to a higher immunosuppressant dose just to achieve that same effect. That's what we kind of mean by avoiding that immunologic hardening. It's just the intensity of what your immunosuppressant dosages to bring to the immune system down.

Becky Strong: That makes sense. Thank you. Charles is asking, he's saying his wife has. BP and it's pretty clear treated with clobetasol for minor flares. Is there really a need for immunosuppressives in that kind of situation? If your disease seems to be controlled with topical.

Dr. Benny Wu: No, I mean, I definitely think that that's a very reasonable approach is some people can be treated with just doxy, niacinamide and not have to have oral steroids, and some people with very limited disease. They can get away with just clobetasol locally. I think that she's a very lucky person to be able to get away with, to be able to respond to that and to have disease control.

Becky Strong: Thank you. A couple of other questions that I'm gonna kind of group them together. If you've had rituximab but it didn't work well. Is it better to go with Methotrexate or something like Ivig?

Dr. Benny Wu: Yeah. So I guess the definition of what didn't go well with it. What does it mean if it's like after several cycles, and you still have significant disease activity, So I think that's one of my questions. But if the rituximab didn't go well, I would not expect Methotrexate to go very well, either. I could maybe buy and understand that Ivig could be an alternative, and that could be effective. But what I would recommend is to consider all this combination therapy right instead of just monotherapy with Rituximab. Maybe you need a little boost with prednisone and combining it with the rituximab and then after the rituximab the infusion goes into effect for like 2 months. Then at that time taper off the prednisone, and maybe that's what that is that additive boost that you needed to really gain disease control. So I think, instead of jumping from rituximab monotherapy to something, some other monotherapy. Maybe we need to consider combining things and then tapering off one of those things so that the other thing can kind of go into full effect. So I think that might be an alternative that could be considered instead of just jumping to one other monotherapy.

Becky Strong: Great! Thank you. We've got another couple of questions you were talking about just talking about the Azathioprine and mycophenolate mofetil is one better or stronger or are they equal and it just depends on what works for somebody.

Dr. Benny Wu: Yeah, I think it does depend a lot on not only what works for somebody, but actually the dermatologist's experience in prescribing it because azathioprine is a much older drug and mycophenolate is a little bit newer, although it's still rather old. It really comes down to where the dermatologist trained what they were used to and what they used in clinical practice but from a basic science and pharmacological standpoint. We think about these blistering disorders as B-cell mediated and, pharmacologically speaking Mycophenolate by itself has much more suppressive activity on B cells than azathioprine alone. So I think, from a conceptual sense the mycophenolate has a better effect against the B cell mediated diseases like bullous pemphigoid.

Becky Strong: Great. Thank you. Edna is asking, do you ever notice an increase or change in body odor of patients who are on immunosuppressants?

Dr. Benny Wu: I think I'm not sure if that's what the question was, because when there's less macerations, less erosions, less blisters, less leaky fluid from the blisters. When there's an improvement in that, I think there is less body odor. So that's one thing that I would notice. The other thing is, if you feel like there is actually an increase in body odor. Sometimes it's a secondary skin infection, such as by staff or by candida or other bacteria that might be in them that might be macerated and hiding in the armpit the groin area as the blisters pop, that they might need a topical and pearson, which is an antibiotic or gentamycin in that area, and also very effective antibacterial soaps that's not stinging such as hipaa clans to to wash those areas that can help decrease the odor. So I don't think there's a treatment that directly causes body odor, though it's more of the secondary effects.

Becky Strong: That's really helpful. Thank you. There have been some questions about the covid vaccine, and I know you addressed it during the questions. But if you are afraid there's a couple of people that think potentially that their blistering skin disease was triggered by immunosuppressive therapy, should they consider getting it again.

Dr. Benny Wu: There's definitely evidence that in as especially in the connective tissue disease world as well with lupus and dermatomyositis, is that these patients actually have flare in their disease when they got the Covid booster, or worsening of their disease. So there's definitely evidence, to say at least, you know you wake up your immune system from these vaccines. It can cause your B cells and T cells to go into overdrive, causing disease to either unmasks itself or worsen. But at the same token if you're on immunosuppressive medications, it should at least keep you might not mount as well of a immune response to the covid vaccine, but in terms of exacerbating your disease it might not do it as much as if you were on the immunosuppressive medications. So I think that's a very case by case situation, especially if you have predisposed respiratory disease, such as COPD and you have concomitant bullous Pemphigoid, I think the risk of getting the vaccine far outweighs kind of a little flare of the bullous pemphigoid. Because if you were to catch Covid, your pulmonary issues are gonna be a lot worse. So I would say that you know, you have to take the risk and benefit into consideration into each different patient and their predisposing factors. So if you're on immunosuppressants, then it should actually help prevent a flare of the disease. For example, with the Covid vaccine.

Becky Strong: Great. If a patient only has and we've gotten a couple of questions. So I'm gonna kind of mix them together. If a patient only has like one or 2 sores on their gum. Should they consider taking an immunosuppressive or just stick with a topical medicine?

Dr. Benny Wu: I think it depends. So if the topical medicine obviously is not working, and it's still like the sores are persistent, then the patient might benefit from adding one of the.oral antibiotics, like the anti inflammatory effects like doxy,niacinamide, dapsone could be an option. Does a person need to immediately jump into prednisone like oral prednisone or even rituximab? I mean, that's a little bit. I do believe that that's a little bit aggressive. Obviously, if there's pharyngeal involvement, like in the back of the throat, and stuff like that which is much more severe in it, and it prevents you from eating properly. Then we definitely need to escalate therapy. But we need to consider the topical steroid ointment that we're using in the mouth. Is it the highest strength, like clobetasol or a class one steroid? Or you know, how can we optimize

the oral management better? But if it's just one or 2, I think that the heavy hitter immunosuppressants might be a little bit aggressive from that standpoint.

Becky Strong: Great susan is asking if an older patient who's 77 is taking Methotrexate 20 milligrams. How long should a patient be on that dose?

Dr.Benny Wu: 70 year old patient, 77. Okay, for how long have they been on it for?

Becky Strong: How long should an older patient stay on that dose? Is it something they can continue forever, or should it?

Dr. Benny Wu: They can stay the I believe the dosage that they have it's 20 milligrams per week. I think it's about, I believe it's 5,000 milligrams that we think about liver fibrosis or toxicity. I think that's very like, you know, people take it for 10 plus years, and then they're fine. So I think the release chances of having significant liver issues is gonna be very low at 20 milligrams a week.

Becky Strong: Thank you so much. Dr. Wu, I have to tell you. We're getting a whole bunch of comments about how educational and informative this is. So I just want to say, Thank you. I know we overstayed by 15 min, which is a lot of time when you're as busy as you are but we sincerely appreciate all the information, and that was really quick, but you covered so much information, and I think in a pretty understandable way. So thank you so much for joining us.

Thank everybody for joining us today, and of course, a big thank you to the support provided by Sanofi and Regeneron for helping to make today's call possible.

Thank you to those that joined the 2023 IPPF Patient Education Conference last week. It was a very exciting event and there were great presentations from our leading expert doctors along with stories and insight shared by patients. The IPPF will be sending out a follow up survey for those that attended to get feedback within the next week. Please take a moment to fill out the survey and let them know what you liked and what you want to see for next year's conference.

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This call recording will be sent out with the survey following this call. Thank you all for joining us.