

Becky: Welcome everyone. This webinar is now being recorded. I'm Becky Strong, IPPF Outreach Director, and I'll be your host for today's webinar. Thank you for joining us, and I'd like to thank everyone for being on the call and the support provided by Sanofi and Regeneron for making today's call possible. I'd like to start the webinar off today with a quick poll. Please let us know if you are currently taking or considering using IVIg therapy for the treatment of your pemphigus or pemphigoid. And while you're answering the poll, I'd like to introduce today's speaker. Dr. Kyle Amber is an international leader in the field of autoimmune blistering diseases as well as complex medical dermatology. He has published over a hundred peer-reviewed manuscripts, as well as numerous book chapters pertaining to the diagnosis and treatment of autoimmune blistering diseases. He created Chicago's first Dermatology infusion center at Rush, providing care for patients with blistering diseases and other conditions requiring intravenous therapies. His research lab focuses on the mechanisms of innate immune activation in pemphigoid with particular interest in single-cell transcriptomic approaches. His work aims to identify treatment targets that can reduce or eliminate the need for corticosteroids during the acute phase of disease. Dr. Amber serves on the editorial board of the American Journal of Clinical Dermatology, in addition to serving as a peer reviewer for over 40 journals. He has served as a grant reviewer for several international granting bodies, including the National Institute of Health. Now I would like to go over a few housekeeping items... (Reviews Housekeeping Slides). Now it is my pleasure to hand things over to Dr. Kyle Amber to discuss IVIg therapy.

Dr. Amber: Thank you, Becky. Are you seeing the slides?

Becky: Not yet.

Dr. Amber: Ok, sorry about that. Let me pull this back up.

Becky: We can see your presentation now.

Dr. Amber: Okay. Thank you. Well, there, my name is Kyle Amber. I'm an Assistant Professor of Dermatology at Rush. So today I'll be speaking about IVIg which is intravenous immunoglobulin. I know we've gotten a ton of questions already. I tried to integrate some of those just into the powerpoint material but it's really an overview of the treatment, when we use it, why we use it, the goods, the bad and then we will leave time to to be able to sort of tackle more of some of the nitty gritty of the questions. So

what is immunoglobulin? Immunoglobulins are antibodies that our bodies make to attack things, those things are ideally against bacteria, infectious agents, that's what gives us immunity. But in an autoimmune disease, we make immunoglobulin against ourselves. So when they attack the pathogen, whether it's bacteria or fungus, they're good but when they attack you they're called autoantibodies, and then they're bad and we don't want them.

Dr. Amber: This ties into some of the prior series in terms of integrating with what are the other treatments and when do we use those versus the others. And I put this here just to sort of reference where Rituximab sits and what does Rituximab do relative to where IVIg falls. So if you look here, it's basically a timeline of B cells from basically a baby B cell to a grown-up B cell that we call a plasma cell. Those cells are the ones that actually release antibodies, those are the ones that actually cause the disease if you will. Problem is Rituximab only works before that line there. So basically the infant or the toddler cell, not the grown up. So you have to wait for the grown up ones to basically die off and not get replaced. IVIg tries to answer the question of, what do we do during that waiting period of time, or while trying to decrease the amount of secretion of those antibodies.

Dr. Amber: A general I get often is, is my immune system working poorly? And I don't think there's good or there's bad. I think of the immune system as too far to one direction or too far to the other. In one direction you're immune deficient. You're not fighting off bacteria. On the other side of things, your immune system is working way too well to the point that it's attacking yourself. Where we really want things is to be right in the middle, where you can attack bacteria, fungus, etc. but you don't attack yourself. The goal of treating autoimmune is to try to bring things back to center. Stop making the bad antibodies while, continue to make the good antibodies to decrease the immune response to yourself, so that you're not attacking your own tissue or a skin, etc., but still be able to fight off bacteria and whatnot. It's the goal, it's not always the easiest goal but that's sort of where we aim to set things. So what strategies can we do that? One of them is inhibiting the inflammatory response to an antibody. An antibody binds to something and then something happens. And what we're trying to block in that step is, something happening. It doesn't really fix the problem per se but if I hide it or mask it and

there's no symptoms, there's no disease that's a big plus and we're sort of fixing the aftermath.

Dr. Amber: The next thing is to remove the circulating antibodies from the blood, and in this situation the cats out of the bag, the cells have already released the antibodies, but if we can take them out before they bind to the skin ideally then we don't get symptoms from it. The problem is that this approach only works temporarily. Antibodies that are already on the skin are causing disease, and as soon as you take out old antibodies, new ones will be made to replace them. Now, moving higher up into the immune system, we can try to decrease the antibodies that are being released by the cells. We have those cells that are producing these antibodies, can we decrease the amount that they release even if we're not able to necessarily kill that cell, we can decrease sort of the damage they're doing. Then the furthest step up the immune system is, can we just kill the cell then we don't have to worry about these antibodies. And it's unfortunately not as easy to do that as it sounds since the plasma cells are the ones that are really doing it. Our treatments are really guided towards killing the precursor, the baby plasma cell, if you will, in which case you have to wait a while for those cells to naturally die off and not be replaced and that can be upwards of 2-3 years. That's why we use all of these approaches in treating a patient, because each one has their pros and cons, and different safety profiles.

Dr. Amber: So what is IVIg? IVIg is really at the most basic level just normal human immunoglobulin, normal antibodies against everything. If you take thousands of donors, you purify their antibodies, then you mix them all together. They are screened for viral infections like hepatitis and HIV, since they are a product from human blood. Then you give them to people for the anti-inflammatory effect, and then we'll sort of talk about why they actually work and what they're doing. There are a ton of different formulations, and I don't want to say they don't make a difference, but they don't really make a difference. It's basically how the antibody is purified and how do they preserve it. Do they put a little sugar in there? A little salt in there? Very subtle things, but the principal product is unchanged, regardless of the formulation.

Dr. Amber: So one of the main ways we think IVIg works is something called FcRn. And what this does is basically, there's a receptor in most cells that internalizes these antibodies and spits them right back out. By sort of hiding the antibody then releasing it,

it keeps the antibody alive for a lot longer. If that system isn't working, these go away in about 5 days or so. If the system is working, the half-life is about 3 weeks. That's one way they work, and then is sort of with the newer treatments that are being looked at, FcRn inhibitors that's just one aspect.

Dr. Amber: But IVIg also does presumably work by several other aspects and some of these are sort of probably too detailed. Basically, they can block the effect of bad antibodies, they can also affect the immune system as an anti-inflammatory to try to decrease the amount of antibodies being secreted or kill the precursor cells that make antibodies. So it has an imprint pretty much on all of those aspects. We talked about anti-inflammatory reducing levels in the blood, reducing the amount secreted from cells and reducing those cells. So it really targets all 4 of those mechanisms to various strengths that we don't necessarily know exactly how much it does for each of them.

Dr. Amber: So going back to those 4 ways of killing autoimmunity. One of them is to inhibit the inflammatory response. The antibody is already on the skin. Here, it's been shown it can help in protecting cells in pemphigus. It can block a little bit of inflammation, not its primary effect, but it works. Removing circulating antibodies from the blood, so it dilutes bad antibodies. If you have a hundred bad antibodies and now I give you a billion good antibodies, your body starts to try to get rid of all this excess, and by definition, if I just keep giving you normal you're going to get rid of the abnormal antibodies.

Dr. Amber: The next step is in immunity. In terms of decreasing antibody release it does have some anti-inflammatory effects as we talked about. Killing plasma cells, no, we still can't do that very well, it just affects the precursors to a small degree.

Dr. Amber: How is IVIg given? It's an IV treatment. The standard dose is really throughout the literature, pretty much the same for everything. It's going to be 2 grams per kilogram. It's a per month or per cycle, which is usually monthly to start with, at least. How many days you give it over can be anywhere from one day, which I generally would not recommend to typically 3 to 5 days. Sometimes in a hospital setting we'll do it over 2 days. It's just divided, it's the same dose and whether you give it all in one day or all in 5 days, you just divide accordingly. It's typically given by an IV. For some people, if they're on treatment for a long time, they have a lot of vein problems so a port is always

one option. One question that comes up because there is something called subcutaneous IVIg, which is used in patients who don't make enough antibodies. It's not really possible to give it for treating pemphigus and pemphigoid. The reason is, the dose you're using is much higher to treat autoimmune diseases rather than not having enough antibodies. You would essentially have to inject yourself, I did the math once for a patient who really didn't believe me, I think it was 36 locations on your body and have a little tube in there for 2 hours each. It's one of those things that it is not possible to get the dose done. Like I mentioned, it is typically given monthly because of the way IgG, the antibody in your blood, is destroyed after a month you're sort of back close to where you started from.

Dr. Amber: So there's something called the rebound phenomenon that I want to touch on. Basically when you give IVIg, you start to get rid of the bad antibodies but there's a phenomenon where you get them back. Your body sometimes even actually makes more than you started with. Our immune system is unfortunately much smarter than any of our treatments. Basically, your body tries to compensate for that decrease in bad antibodies by making twice as much. For this reason, we typically use a second medication to prevent that from happening otherwise, every cycle we're shooting ourselves in the foot. We decreased 50 antibodies, now we made 100. We decrease a 100, and you just keep going and going. So it is rarely given on its own except for certain situations which we'll discuss a little bit.

Dr. Amber: The big question is, does it work? Yes, overall and we'll talk about the individual situations but the data is not unfortunately as strong. Because it's not a drug where basically a company makes drug and that's the only drug available, IVIg is made by several different people or companies, etc. They're not a lot of clinical trials looking at IVIg, because there's not really a large interest unfortunately. They don't have to show that it works better than another drug to get FDA approval. It's an old medication, because it's really not a medication, it's a blood product. We do have 2 studies, which have their limitations. Basically, there's a study in pemphigus and a study in pemphigoid that both show clinical improvement, but the limitation on these is it was only given for a month. IVIg in general is more of a, I don't want to necessarily say long-term treatment, but a longer term treatment. A single treatment is usually not that impressive, but they were able to show it was effective enough with just one dose or one cycle to be able to

get approval in Japan. And for that reason, thankfully, we can get insurance usually to cover this because we know it works from individual treatments, from patients, from treating small groups of patients, but not in that robust setting that we often see for a drug to be approved.

Dr. Amber: The best data we have in terms of effectiveness are going to be retrospective studies. Instead you give patient A this drug, you have patient B and you treat them for 36 weeks and see how they do compare it, very rigorous. Retrospectively, we treated 100 patients, let's tell you about our experience of treating 100 patients. and So in a few studies, in this one it was about a 12% overall relapse rate, with a prolonged course of IVIg with other medications. The numbers look pretty nice there. Then another study of these long-term remissions, again lasting quite a long period of time, patients were still in remission 5 plus years out. With those less rigorous types we have nice data that does show really quite a nice decrease in relapse rate.

Dr. Amber: Relapse rate is also important because Rituxan for example, is incredibly effective, especially in pemphigus but the relapse rate can be problematic. If in 70% of people, the disease keeps coming back, we keep going back and forth with treatment. So for me personally as a goal, it's always what can I do to decrease that risk so that we're putting the disease in long term remission.

Dr. Amber: I added just a few recent studies. This was just a review of all the data and this showed an 86% remission when combining Rituximab and IVIg. Again for IVIG, getting a loan is not too common. They also did show 88% and 100% in 2 different studies in bolus, pemphigoid, and some in mucus membrane pemphigoid as well. It works across pemphigus and pemphigoid

Dr. Amber: We recently had a large international conference in Japan, for investigative dermatology, and then also for a symposium on autoimmune blistering disease. One of the things I've missed most about conferences is just talking to people and seeing how things are done elsewhere. An interesting thing I learned was that in Japan, Rituximab was only actually approved just a few months ago, and was basically never used to treat either pemphigus or pemphigoid. Instead, IVIg has been approved for several years there. So it was interesting to hear the differences in sort of how in the U.S. we use Rituximab 80% of the time and IVIg, maybe 20%, versus the other way where it's

90% and 10%. A couple of studies recently out of Japan looking at real world applications is If you give IVIg to patients with bullous pemphigoid, the survival improves. This basically looked at survival before IVIg was approved versus after and they did find a 1% decrease in mortality in bullous pemphigoid. Looking at the nitty gritty, it doesn't decrease the number of blisters and itching and all of that. It doesn't look so much at that but the fundamental thing is, does it overall decrease mortality, which I don't want to say is the most important but probably the biggest indicator that it's working, and it did. Then another study just treated a very large number of patients and this was more sort of the nitty-gritty and looked at disease scores and we do see a significant decrease in the amount of steroids needed, antibodies in the blood as well as disease severity. Helpful data that shows it works because we don't have as good data with IVIg because of those limitations.

Dr. Amber: So those are the benefits, now, what are the risks? I think of it as a fairly low risk treatment, but not risk-free. There's no no such thing unfortunately. Headaches are going to be by far the most common, and those are particularly going to be in patients with a history of migraine. Most of the time it's manageable, every once in a while it's not. Then we'll switch to a different IVIg formulation, give more fluid or sometimes we have to scrap IVIg if all of those things don't work. Blood clots there's an increased risk of that with IVIg but seemingly quite low. My personal experience will say it's higher in pemphigoid than pemphigus. There's some data that shows pemphigoid itself increases the risk of blood clots, regardless of IVIg. So we don't necessarily, I would say, do anything preventatively, because it's not like blood thinners have no risks but if somebody has multiple blood clots, that's probably not a great treatment for them or we need to put them on a blood thinner if that's the only treatment. Another thing is excessive fluids, so swelling or changes in blood pressure. We see it sometimes with infusion, sometimes you just give it a little bit slower and that fixes it. Usually not an issue that requires stopping treatment or a lot of adjustment. Then fatigue or as some patients say getting their butt kicked, there's no rhyme or reason to who gets it or who doesn't get it. Sometimes it can be a difference if you give it over more days, you tolerate it better, or you switch to a different brand. Again, no rhyme or reason to why switching from one versus the other really works but we do see changes in that and that can make a big difference too. And the last thing is, it's time intensive. So if you're giving 2 grams per kilogram divided over 4 days for example, it's typically going to be about 4

hours per day, 4 days in a row. With some exceptions, we can sometimes give it separated a little bit but it's still about 4 hours a day for 4 days per month. So 16 hours which is not a negligible amount of time.

Dr. Amber: What are the plus sides with those risks? There's no one size fits all for treatment for every patient. There's sometimes when it makes sense, sometimes when it doesn't make sense. The benefits with IVIg is it's not immunosuppressive, so it does not increase the risk of infection. In patients with very severe disease, or even technically not severe disease, it allows you to come off the steroids a little bit faster. Basically, if somebody needs a really high amount of steroids to get their disease under control and you do IVIg, you can start getting off of the steroids faster than normal. And then the other thing is, wow you're off of steroids, the disease is in a good state, IVIg can help prevent a lot of the relapses that we would see without needing a long term steroid to control that. So I really like it in severe disease that I know is going to be difficult or in relapse disease that is not a mild relapse and to really get long term remission. And overall, it's generally pretty safe.

Dr. Amber: So who is the right patient versus the wrong patients? Like I said, my feelings are patients with very severe disease to the point that I'm hospitalizing them or their steroid dose is something like 1.5 milligrams per kilogram, so usually over 100 milligrams, that tells me this is going to be tough I need all the help I can get, otherwise we're just stuck on steroids. Pregnancy is also another one, IVIg is safe in pregnancy whereas most of our other treatments have some issues. Not that we can't use them, but there's more of a consideration. Long standing disease, more and more literature is showing for example in Rituximab if you give somebody who has the disease for 20 years Rituximab, they do not do anywhere near as well as somebody who's had the disease for only 2 years. IVIg can help bridge that gap, IVIg doesn't really care how long people have had the disease as far as the way it works, and where in the role of autoimmunity it works. The other one is a discussion about the time investment in the beginning. I think of it as more pain, more gain. Sometimes in a severe case of pemphigus for example, Rituximab will probably still work, it may take a little longer and the dose of steroids may be higher. There's going to be a higher relapse rate, just doing that without doing anything else. but it is a lot of time to invest, so for some people they are like no, it's not worth it. Others are like, give me whatever you need, so I can ideally

never have this again and give me the best shot. I think those are the ideal patients who realize that. Again, I want to reduce relapse rate. Depending on what study you read with Rituxian alone, that can be greater than 60% in 2 years. I use it generally for over about 2 years to get the disease in remission, keep it in remission, and then ideally be able to stop treatments. We can sometimes just use a few doses here and there in acute disease.

Dr. Amber: So who's the wrong patient? When time limitations preclude 3 to 5 days of infusion per month. A lot of things like work schedule, family commitments, etc. make that a bit of a challenge. We have ways, like I try to get home infusions for patients to make that a little bit easier, so they don't have to come during working hours to an infusion center. But still that can be difficult for patients working nights, patients working weekends, etc. Another one is poor prognosis or health status. I think just being realistic, if someone has severe dementia and other issues, is it worthwhile giving them a prolonged IVIg course to increase remission? Probably not, because the relapse rate in 2-5 years becomes less of an issue at that point. Whereas a younger patient with a better prognosis, I really want to get that person in remission and not have the disease pop back up because they've got a long time for that to happen and I really want to minimize that. The last thing is really just patient goals. I think there's some people who, getting Rituxan every couple of years, once a year or here and there, is completely the right decision. Verses for others, especially if they've had issues with steroids in the past and problems from them like bone fractures and things like that, you want to be more aggressive because you really can't get steroids again, or else you're in a lot of trouble.

Dr. Amber: Managing side effects, like I mentioned headaches are usually pretty manageable with the change in formulation, pre-hydration and fluids are usually quite helpful. Aggressive Tylenol, especially Tylenol a few days after, all the way through the infusion to a few days later. Sometimes migraine management, medication specifically for migraines. Dividing the dose, so maybe I'll give Friday, Saturday, one week, Friday, Saturday, the next week. Usually not farther than that, but that can also help or give the dose over 5 days instead of 3 days, we tend to see that decrease. Blood clots, we have no guidelines for what we should do. Generally, if there is no history of blood clots there is nothing to do. But if a history, then we do recommend blood thinners or choosing a different option based on those risks. With high blood pressure issues or changes in

blood pressure, sometimes just changing around the settings on the infusion, or again splitting the dose. Like I mentioned, for fatigue change in formulation, dividing the dose and giving it over more days.

Dr. Amber: A little of why I like to use it for more long-term management, and my feeling is the immune system, if you think of autoimmunity in the same way you think of vaccines for example, every time you have a flare of disease, your body sees the thing you're attacking, and says let me turn on, let me bring the soldiers out and start fighting this thing. So a flare of pemphigus really gets the immune system going. So the goal is a long period of time of no activity whatsoever. And there are different ways you can do that. You can hide it, you can mask it. If you were to give somebody 10 milligrams of steroids so they never relapsed, you're overtreating presumably, but that would prevent any of those flare ups. With IVIg, if I can prevent those flare-ups for a couple of years, it just gives a better chance that the immune system will kind of shut itself down and stop trying to fight this skin protein off. We don't really want to restart that process, or else it just keeps coming back and coming back. I generally taper every 6 months. If somebody's off of prednisone, they're totally clear on other therapies whether they've gotten Rituximab, Doxycycline or any of those things, if for 6 months of monthly IVIg everything looks good, then I go to every other month for 6 months, then every 3 months for 6 months, then that's where I stop. That is part of how I do it and a few others. But unfortunately, there's not a good guideline or rationale. We can only just follow data from prior studies and do our best. Technically, if you gave the drug for 10 years, probably close to 100% of patients will do great. But now they've gotten 10 years of treatment when that's probably overkill. So we are constantly, always trying to figure out a better way to do what we're doing.

Dr. Amber: Common questions, will insurance cover it? Yes, actually. It's on the Medicare formulary for treatments because again from older data and those clinical trials. I'd say about 90-95% of the time I can get patients home infusions if they want to. And usually because it's pretty well tolerated, I try not to bring people into the infusion center for it. Most of the time that's covered, with some exceptions it's not then they have to go into an infusion center. The other thing is it's a super expensive medication. Unfortunately, I feel like most medications these days are now \$40,000 plus. Insurance covers it but obviously everybody's insurance is different. Sometimes that means, it's

free, other times it's like congratulations, it's covered, it's only \$10,000 a month which is not really covered in my opinion. There are different manufacturers and infusion companies which will offer financial assistance or manufacturer discounts. Most of the time they unfortunately will not tell you this unless you ask. But it's really always worthwhile asking. It's quite surprising that some of the income requirements are actually really lax to the point that I feel like Jeff Bezos would be able to get some discount to that level. So it's always worth asking to see if there's a high copay or anything like that. Then the other thing is, not all infusion companies are the same. Some are good with authorization, others are really crummy. Nursing can be inconsistent between them. So you may have a great nurse with one and one not so great so that can be a little bit of a challenge in finding sort of what works best for you and what unfortunately, does your insurance sometimes require? Because some insurance will say, you can only use this company, and that's it and those tend to be frustrating.

Dr. Amber: A couple notes, not everybody may be told about IVIg, not everybody may recommend it. Some people will say no, you shouldn't do it. Why is there more, I don't want to say controversy but why is there more variability? A couple of things, not all dermatologists are trained in IVIg in blistering disease, whereas Rituximab is much more trained so that's one reason. Protocols for long term IVIg, as well as the evidence, is just more limited because of the nature of the treatment. With Rituxan we have a nice trial that says it works within a 6 month period or so. With IVIg, we know that one month kind of works but not amazingly. But how do we do it better, there's a lot more discrepancy there. Cost is another consideration, it is an expensive therapy. Then the other thing is goals of care. There's different reasons to use different medications. I think for some people it's a good choice and for other people it's a bad choice, and it really all depends on patient goals. But there tends to be just more of this heterogeneity and who recommends it, who doesn't recommend it and basically just based on personal experience unfortunately.

Dr. Amber: So how do I do it? There's a billion ways to do the same thing. For me, this has worked the best over time. The same dose is going to be divided over 3 to 5 days. Generally, my way is over 4 days unless somebody has a lot of medical problems like heart failure or kidney problems, then I'll do it over 5, that it's a little bit more delicate. I'm

pretty much always giving that alongside either Rituximab or Cellcept, more and more these days Rituxan than Cellcept. I've personally just found it to be more effective especially in pemphigus. With doxycycline, I like to prevent mini flares. In bullous pemphigoid we have good data that it works like low doses of prednisone. So my feeling is if someone were to have a little tiny flare, and I'm giving them the equivalent of 5 milligrams of prednisone, maybe that will stop the flare and stop the immune system from getting going again. That's the rationale there. Then usually steroids in the early phase of disease, unfortunately our biggest treatment gap, which I hope one day we will be better at is, there is nothing great when someone comes in with 40% of their skin missing, there's nothing that works anywhere close in the first couple of months as steroids. Everything else is about making it easier to come off of steroids and preventing needing steroids again. That's why, even though IVIg has some short-term effect, steroids are unavoidable, especially in the early stage when things are bad and the early phases. Like I mentioned, I'll do monthly infusions until off of steroids, and then the taper sort of every 6 months as follows. Really at that point in time, I stop everything. I don't always check blood work for antibodies which is another question that comes up. There's very mixed data, there is more data coming out about numbers that are helpful for predicting relapse. So I've been checking a little more, right before stopping everything but it's a type of blood test where, when the data looks good, you pat yourself on the back and say okay, great. When the data looks bad you say, oh no, but still do it anyway, because ultimately someone can have high levels of antibodies and have a nice remission, and vice versa. Someone can have great looking blood, and their skin can look terrible. So I try to treat the person sitting in front of me, not the blood test.

Dr. Amber: I know there were a ton of questions. I tried to touch on some of them and I'll be happy to take all of them.

Becky: Great Dr. Amber, you answered a lot of the questions that I've been coming in through the chat and I really appreciate all the time and effort you put into really preparing and answering our community's questions. One of the questions that came in is, what kind of testing or vaccines do I need to have prior to starting IVIg therapy?

Dr. Amber: Because it doesn't increase risk of infection you don't have to look for anything like hepatitis, HIV, or tuberculosis the same way you would with any immunosuppressant with an exception I'll touch on here briefly. The important test that

you need is this one called IgA. The reason we look for that is rarely people are born not having IgA, which is a different type of antibody. We know those people who have low levels are more likely to get an immune response to IVIg and basically get anaphylactic or have a severe allergic reaction. I screen that in every single patient and technically that's all that you have to do. Basic labs, if I'm giving a big gun medication, I kind of just want to know what someone's body is doing. If their kidneys aren't as good as they told me they were or things like that, then that can change how many days I give it over. If they have really low hemoglobin that also sometimes is an issue since you're giving them a bunch of fluid and you're diluting whatever red blood cells they have. Another consideration, that's a little less important. Those are the 2 tests sort of across the board. Even though IVIg does not increase the risk of infections, why is it still worthwhile to check hepatitis and whatnot beforehand? One of the things is, when treating with an immunosuppressant we check those things yearly, especially with Rituximab you have to check hepatitis every year. It's on the label, it's bad if you treat it. One of the quirky things is IVIg can give you a false positive and I've personally had this a ton over the last 2 years, and it's been reported elsewhere. If you check hepatitis B, it's negative. You get IVIg and now it's positive. It's not that you presumably got infected, it's that it's messing up your blood test. So it's better to know before starting IVIg what you're working with in case you add Rituxan in the future. Otherwise patients are getting worked up for hepatitis and they're seeing the red flag on their medical records saying, oh no, they have hepatitis C, and it's like, no they probably don't have hepatitis C. It's just helpful to have that baseline to know just so it doesn't complicate things. Once you're off of IVIg for a couple of months those all go back to normal. But just in case, say, your doctor starts IVIg and then says, let's do the labs for a Rituximab, now all of a sudden it's positive now you're stuck. You're seeing hepatology. They're going back and forth only to find out it's a false positive. Sorry, complicated there, but that's been coming up more and more, and I think it is important.

Becky: Great, thank you so much. Another question that you kind of touched on is, can somebody with heart or kidney issues be treated with IVIg? And are there any extra precautions that would be necessary to take place if that's the case?

Dr. Amber: So the short answer is yes in both of those situations. Depending on how the kidneys are working, how the blood pressure is in respect to the kidney, and then

how much heart function is still left. So overwhelmingly yes, you just want to be more delicate about it. So those are the patients that I'm doing it over 5 days, that I'll probably want at the infusion center just for a little closer monitoring. But overall yes you can. Now, if somebody is on dialysis, or if they have awful heart failure to the point that they're on the list for a heart transplant, not the best treatment because you are putting a strain on both of those things. It's really the fluid in both of those conditions, you just don't want to give somebody a couple of liters of fluid, and that's what you have to do with the IVIg. It's not impossible and if we need it, we need it. But that's a factor in deciding, is this the right treatment or should I maybe use something else where I don't have to worry about that. But short answer, yes, it's okay.

Becky: Great, is there a waiting time from the time that you prescribe IVIg to the time that a person receives this medicine and how long is that waiting period?

Dr. Amber: This question pains me so much because I would say it's anywhere from one week to 9 plus months in my experience. So it's entirely up to insurance. My real belief is that the person who stamps the paperwork on insurance, if they're having a good day, it can be as early as one to 2 weeks. If they're having a bad day, it becomes this protracted months-long process which is really unfortunate, because you can send them the data and show it's effective and it overwhelmingly will be approved. It's just, do I need to call them 3 times, do I need to write them a pretty letter? And then another letter, and then another letter, and then finally get it through. So unfortunately, as an expensive treatment option, insurance is particularly inclined to make it difficult to actually get in patients hands. While I'll say overwhelmingly it is covered because the data is good enough to justify it, that doesn't mean it's not without a fight and a significant fight which just delays care and does nobody any good except the insurance company.

Becky: And what I'm hearing is don't give up.

Dr. Amber: Don't give up. One thing I'll mention, my small physician soapbox on insurance is, insurance companies do not care about your physician whatsoever. I can call them, I can tell them I've treated X number of people and this is this paper, and they do not care. They hang up on me. They say they don't get my faxes. The patient is the customer, and they may not have the best customer service or care that much about the

customer, but they're still a customer. So the thing is, if you keep attacking the insurance company and go after them relentlessly, things move way way faster. It's a team effort unfortunately. Should it be that way? Absolutely not. That's a whole other conversation which the IPPF has thankfully been proactive about. But definitely patients being proactive with insurance speeds things up, put simple.

Becky: Great. Then we had a couple of questions, you had mentioned that it is covered by Medicare and the question is, what part of Medicare does IVIg fall under?

Dr. Amber: It's actually under part B. With straight Medicare it's usually covered in full and that's not an issue, at the infusion center it's fine and typically at home is actually also covered. Where we sometimes run into issues is when people have different D coverage that can affect home coverage, but not infusion center coverage. Then if there's the supplementals, sometimes they actually add barriers in the way to straight Medicare. Straight Medicare is usually through part B, and it's a really simple process. There's not really an approval process. They just say, if it's indicated, we'll cover it. It's on their book so therefore it's indicated and we get a patient scheduled in a week or 2.

Becky: Great, thank you. Rob is asking, if his doctor needs to prescribe IVIg does it need to be at the same time as Rituximab or can IVIg therapy be added after using Rituximab for a while?

Dr. Amber: So it's at any time. It's sort of independent of them. In a perfect world where insurance didn't exist, I won't go with that controversial, but basically it would be Rituximab on the first week. Whether you do a few additional Rituximab is controversial, and then IVIg at least a week apart. Just because Rituxan takes so long to work, that basically once you've given it, now 7 months of waiting for it to do its job. So the IVIg buys you that time. My preference is Rituxan first. Realistically, a lot of times one will get covered before the other, in which case I don't care. Basically, if I can get IVIg the first month, and then Rituxan a couple of weeks later, great! At least, I was doing something to try to bring that steroid dose down and basically get the patient better while waiting for Rituxan to do its lovely but very, very slow job.

Becky: Great. Thank you. At the beginning of the presentation you mentioned that there are different brands of IVIg but essentially, IVIg is IVIg. We have gotten quite a few questions in the chat and then submitted ahead of time. Are there specific brands that are better for pemphigus foliaceus or PV or MMP or OCP?

Dr. Amber: It's going to make no difference between them as far as we know. All of them have the same amount of antibodies. Now, there's a question of does it matter if I

get a thousand people from the Northeast versus Southwest or something, is that antibody pool different? Since each one is an individual human, they're probably batch to batch differences, but that can even depend if the same company and same batch all of a sudden gets blood donors from another place now you have variability. So there's no data that shows really any difference. It's just one brand may study theirs. So generally speaking, I don't think I've ever been like oh, I should use this brand, or anything like that. It's the same thing. It's just how it's processed slightly differs.

Becky: Great, thank you. How has COVID affected the IVIg donation process and the process for patients to receive IVIg?

Dr. Amber: Good question. Things are better now. There was a period of time when people were doing plasma. Basically, you would take plasma from healthy people, vaccinated people who have antibodies and give them to patients with COVID, which was being done in late 2020 early 2021. That resulted in some significant shortages on IVIg. Unfortunately, as a human based product, there are always shortages of one brand versus another brand, and things like that. The supply chain and all of that. So there's some shortages that pop up. But things are basically, essentially back to normal from that respect. One of the other things that we don't really know the answer to is, since IVIg has antibodies from average healthy people, are you getting antibodies against COVID? Which would be good, especially if you're getting things like Rituxan which may affect your ability. Probably, nobody's really looked at it to my knowledge. But since it's fairly recent IgG, that's taken from patients blood, it's not like 10 year old blood sitting there. Every year we get more and more of the population that's been vaccinated or previously infected, in which case, you're presumably getting antibodies from vaccinated people, especially nowadays now that we're farther out.

Becky: Great. This is a great question, and Edena is asking what is the best way for me to prepare for my infusion?

Dr. Amber: Bring a good book, or a laptop or something. The biggest thing is it's very and it's very boring. I mean the ideal thing with an infusion is it should be incredibly uneventful, and that's generally the expectation. Pre-medication is usually with Benadryl and Tylenol. The Benadryl can make people kind of sleepy. It's needed to prevent some infusion reactions. I like to keep it there, even though people would probably prefer I removed it from that. But I do think it serves an important role. So it's basically 4 hours

of sitting there with an IV and really not much to expect. So I really mean, plan for what to do for 4 hours because, unfortunately, it just takes a lot of time.

Becky: Are there any foods or beverages that they should avoid before or after an infusion?

Dr. Amber: Good question. I would say have water in general. A standard is we always give fluids before IVIg. We know if you don't give fluids, side effects are going to be worse in all respects of fatigue, headache, etc. Assuming good kidneys, good heart, drinking a little extra water that day usually is helpful as well. I can't say there's anything I can think of off the top of my head. Maybe highly salty meals. If you were to have not great blood pressure that may affect things a little bit, just because we're giving you fluids and now you're swelling up because you had a bunch of salty foods. That would be the only one I would not intentionally try to have like a bunch of soy sauce right before, or something like that, but otherwise there really shouldn't be not much of a consideration.

Becky: Great. There's a few questions that we've received, once my blisters go away how long do I need to have IVIg? And then how do doctors determine if I'm taking IVIg, if I'm in remission or the medicine is just working?

Dr. Amber: Good question. There's different ways of using IVIg. So sometimes, even if the plan isn't to do it for a long period of time. Let's say somebody's on a very high dose of steroids and not doing well and our goal is, let's get that dose down as fast as possible. Okay, so now the blisters are gone. Then there's a discussion to be had is, do we just stop it at that point? For some people that is the right answer. The other question is to keep it more long term for prevention of relapse and flares. Both are potentially the right answer depending on the situation and long term goal. The question about remission is interesting and a bit challenging. So there's remission on-drug versus remission off-drug. With IVIg, the problem is while you're on it and in remission, you're still in remission. But is that just because the medication is working or not? There's not really a good way to prove it other than stopping the medication, which isn't a great test, because if it comes back, that's not ideal. That's why I mentioned that arbitrary tapering. There's studies where they treated people for up to 9 years on it and those patients did amazingly well. That's probably longer than they have to but if you stop it right when blisters stopped, that's almost definitely too short from the perspective of remission. So somewhere between one month and 9 years is where the right answer fits. How do we use blood testing? How do we use clinical course? All of those are things we're trying to figure out, how to not over treat and not under treat. But there's not a good answer. There's not a good test to tell you, okay, now is a great time, you can stop. The IVIg isn't

actually working. It's actually that you're in remission and can be off meds. We don't have a good way.

Becky: Great, thank you. Sandy is asking, is Rituximab better with IVIg or is Cellcept better? Is there a preference?

Dr. Amber: That's a good question. So there's a retrospective study of 129 patients, and that showed no difference between Cellcept with IVIg and Rituximab with IVIg. I've been doing this now, close to 6 years, originally starting with the Cellcept and IVIg. From my personal experience, I do think Rituxan works better than Cellcept with IVIg in pemphigus. In pemphigus, there was a nice clinical trial of just Rituxan alone versus Cellcept alone and Rituxan is just more effective. I pretty much stopped doing that, even though the prior study didn't show a difference, my experience has been quite different. In pemphigoid, it depends. Pemphigoid does not have as predictable of a response to Rituximab so sometimes Rituxan is more effective, sometimes Cellcept is more effective. I'm trying to figure out who and why that is and sometimes you just kind of have a sense that I think this is the right choice. But we don't have any data to really suggest it. Again, risk factors such as is Rituxan safer or better option for this person than Cellcept? That's how we choose it generally, or I choose, at least in pemphigoid. The data doesn't really point one way or another.

Becky: Great. Thank you for that. Rebecca is asking, is IVIg available in the UK?

Dr. Amber: That is a good question that I don't know the answer to. I'm fairly certain the answer is yes, but I would imagine, just with the health system, it's probably not a first line available. In which case usually you'd have to fail X number of things to justify incorporating it. So it would probably not be as easy to get for example, if somebody walks in the door and I say, yikes, Rituxan and IVIg, let's get it started. Not that it's super easy here, but I would imagine you'd have to do Rituxan for X amount of time and then justify it before they'd sort of let you do it.

Becky: Great, thank you. Stacy said that she had her first infusion 2 and a half weeks ago. When will she get relief?

Dr. Amber: With IVIg I don't want to say you don't notice the improvement. You need it with other stuff for example. If you're having significant symptoms, the steroids are what's getting rid of those symptoms, not the IVIg. What the IVIg is doing is, if someone

has horrible disease and they're on 100 milligrams of prednisone and everything looks great, congratulations now, how do I get them off of 100 milligrams of prednisone? The IVIg will allow you to come off of it faster. Now, if you say I'm going to do it without prednisone, I'm just going to do it with IVIg, it is a very long process, like 3-4 months and a lot of times it's just not quite enough. So in the short term it's helpful to improve things a bit, but if things are bad enough, you almost always need to use it with a steroid. Think of it as basically, how do you get off the steroid once the steroids works? That's where it really shines. And for most of our treatments unfortunately in pemphigus and pemphigoid they are the same. If the steroid works, how do I get off the steroid faster?

Becky: That leads really well into my next question. Sandy is asking, how long will it take me to get off the steroids if I'm taking the IVIg?

Dr. Amber: That is a good, very patient-specific question. There's so many variables in that. It's impossible to say. So like how severe is the disease, whether the mouth or just the skin is affected? How long has the disease been there, what other medications are being used? There's not a one-size-fits-all answer, and it's pretty disease-dependent. The biggest thing that I'll say is, when you taper steroids without using anything else, you hit a wall somewhere. Almost everyone who is well controlled on 100 milligrams of prednisone will be able to come down. The question is, if you don't do anything, say at 40 milligrams, oh, shoot, they relapsed again. Now we have to go back up. And that's why all these other treatments exist because we are like, how do we do that better? Everybody will be able to taper to some degree. Where all of these medications come in is, to keep tapering and keep it going smoothly. So some people, for example, and I find this a bit more in bullous pemphigoid, you taper down and you're at 40 milligrams, great the medicine is working. We're going down to 30. We're getting a 20 and a 7.5 now you've hit your wall even with the medications. It lowered the wall because it would have been 40 milligrams if you did nothing else but that's where the other medications come in. So how long, there's way too many factors on that one to be able answer that, sorry.

Becky: No, we appreciate it. Kate is asking a great question, too, about what kind of screening is done to ensure the donor who is donating for the IVIg is healthy.

Dr. Amber: So, generally speaking, the plasma donation companies have a whole vetting process. They go through a screening process to select donors that are

considered lower risk donors. Then the next factor they have for the donations is they screen the batches for the major infectious diseases. The common cold shouldn't be in the blood but let's just say it is for all purposes. If that wouldn't be screened then there would technically be a risk of infection because there are viruses that aren't screened, but with their sort of multiple screening processes of trying to find a low risk donor pool and screening for the major bad things that are preventable. Then the assumption is, those will capture the major things. So it's not like there's zero risk of getting a viral infection that we may not know about, or or a blood-borne one but there is screening for all of those main ones that we do know of to minimize that risk.

Becky: Great, thank you. Angela is also asking, what is your experience in using IVIg versus Rituximab in an adolescent?

Dr. Amber: I do not treat a lot of children, I will say so. I typically treat adults. I don't have enough experience on that to comment, especially for those under 12, and whatnot. Higher age, I would say it also depends on the disease, because some of the diseases that we see in the younger population, like linear IgA will use those treatments, and that sort of has a bit of a different prognosis from everything. Being disease agnostic it's a little difficult to answer that question also without having a ton of pediatric experience. I'll say, for young adults, teens and whatnot with pemphigus or pemphigoid really, it's going to follow the same course. The pediatric version of bullous pemphigoid has sort of a different prognosis, same thing with linear IgA. So those kind of differ.

Becky: Okay, thank you. Paul is asking if you are familiar with the efficacy between IVIg as opposed to Xolair for treatment?

Dr. Amber: Good question. With my experience, I'll say IVIg works more consistently and effectively. The actual head to head data is non-existent unfortunately. The mechanism of IVIg is very broad. Xolair is much more limited. Really, the only studies we have on Xolair are single case reports here and there, and my experience hasn't been fantastic with it. For some people, yes, but we don't really know who's the ideal candidate for Xolair. We use it when we need to, but it's not like this patient will respond. IVIg tackles a wider pool of things so it's more likely to do stuff, but there's no head to head data.

Becky: Great, thank you so much. Sandy is asking, does IVIg deplete any vitamins or minerals? And should you take a supplement of anything while you're on it? A sub question to that is, what if you're on steroids and IVIg?

Dr. Amber: There are no issues. Basically with the IVIg you're just essentially getting water and antibodies so now your blood has large amounts of antibodies. You eat up those antibodies faster, then you're sort of back to how you were. Nothing really necessary even with steroids there is no difference.

Becky: Okay, great. We've gotten a few questions about this. You had mentioned, if patients have a severe case, you consider this as a treatment for them. But is IVIg ever used in less severe cases, maybe a mild to a moderate disease?

Dr. Amber: It can. When I have the risk-benefit discussion, a factor in my mind is, okay what exactly is the relapse rate with Rituximab. You can see it anywhere from 20 to 80% depending on if you find a paper that feels strongly one way or another. I'm gonna say it's about closer to 60% in my experience. Some papers show that too. Put simply, with a new diagnosis pemphigus vulgaris, 2 doses of Rituximab plus a booster here or there. You say, okay, there is a 60% chance the disease doesn't come back, 40% chance the disease does. Now I say, the data on IVIg says, there is probably about an 80% chance it doesn't come back. So we went from 60/40 to 80/20. Is that 20% worth it? I would argue and a lot of people, probably not. If it does come back we can also use another Rituximab or we can switch the protocol. It's always a delicate balance of trying not to overtreat where you don't need to. Now with more severe disease, my experience is a much higher relapse rate, harder to get under control and that's why I'm very proactive about saying I don't want to wait 7 months to find out the Rituxian on its own didn't kick in quite enough, because the steroids are going to be atrocious, and it's just going to gonna be too long. In mild to moderate disease, it's not necessarily wrong, but it's most likely overtreating when you don't need to. Now, for some people, especially if they had a horrible reaction to steroids, they might say anything I can do to up my odds. I think it does up your odds a small amount. But does it make sense? That's where the gray areas is.

Becky: Great and then my last question for you is one that we've gotten a couple of times today, and that's are you accepting new patients into your practice?

Dr. Amber: I am. I will tell you there's a trick. I'll probably give you an email address Becky. This is generally going to be true, I will say of those calling any place with a large multi-specialty group, is hospitals like to centralize everything. So if you call a call center, and somebody who's never heard of these conditions books an appointment,

they say the next availability is like 2024 or something like that. If we don't know, we can't do anything about it. So there are direct ways of contacting our clinic and this is going to be true of not just my clinic. Especially those of us who specialize in this, do not want you waiting for months on steroids to get a definitive diagnosis or treatment. I know several have contacted the IPPF and it is great. I do have an email address, or like our clinic service to bypass that. I don't think it is unique to me, I think it's most of us try to do our best, and unfortunately, the call centers universally seem to like to just click a button and be done with it.

Becky: Well, great. This has been an extraordinarily educational hour, and it's also been very quick. I really appreciate you being on the call with us today, Dr. Amber and I also want to say thank you to everybody who joined us. This has been really amazing, and I know our community is going to be very appreciative of the information that you share. I'd also like to give a huge shout out and thank you for the support provided by Sanofi and Regeneron for helping to make today's call possible. I have a few announcements before we go. Our next Patient Education Webinar will be on July 17th with Dr. Heather Holahan, Health Sciences Clinical Instructor at UCLA Dermatology to discuss Skin Care for pemphigus and pemphigoid. Registration is now open and you can register online today using the QR code on the screen.

Becky: Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! Visit www.pemphigus.iamrare.org and join today.

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