

## March 3, 2021 Patient Education Webinar- Back to Basics: Treatment #2 IVIg

**Becky:** Welcome, everyone to the Back to Basics Treatments Series, webinar #2 to discuss IVIg. This call is now being recorded. I'd like to thank everybody for being on the call with us this evening and a big thank you to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, agrenx and Cabaletta Bio for making today's call possible. Information is the key factor in treating and living with any condition however every patient's situation is unique. The IPPF reminds you that the information you find on the internet or during presentations should be discussed with your own doctor or healthcare team to determine if it applies to your specific condition. Before we begin, I would like to take a quick poll to see how many people are currently taking IVIg as part of your treatment regime. And while you are answering the poll let me introduce you to our speaker for this evening. Dr. Amber is an Assistant Professor in the Division of Dermatology and the Department of Dermatology at Rush University Medical Center in Chicago. Dr. Amber was born and raised in Miami, Florida where he attended medical school at the University of Miami Miller School of Medicine. After completing medical school, he completed a transitional year internship in Chicago, followed by his residency at the University of California Irvine Department of Dermatology. Dr. Amber runs a research lab focused on the role of local skin inflammation in pemphigoid. He leads a specialty clinic in autoimmune blistering disease and developed Chicago's first dermatology infusion center to directly provide care for patients with pemphigus, pemphigoid, and other dermatologic conditions. It looks like we have quite a few responses here. It looks like 34% of people on the call, Dr. Amber, say that they do take IVIg and 66% said no. Great. Thank you. (Then reviews Housekeeping Rules and slides). It is my pleasure to introduce Dr. Kyle Amber to answer your questions about IVIg for the treatment of pemphigus and pemphigoid.

**Dr. Amber:** Hello, everybody. Are you able to see my screen now? So this talk is, basically, I received a lot of the written questions. So, I sort of tried to save the order of things to preemptively answer a lot of those. But basically, this is not a heavy duty immunology course. But there's a little bit of why does it work and what does it do? And why do I use it, etcetera? So hopefully I'll be able to preemptively hit those. But certainly, I'm happy to take questions after. So what is immunoglobulin? The most basic thing is, what is it? It's an antibody is the other name for it. Immunoglobulin basically are in our immune system with the goal of attacking pathogens. Basically you make antibodies against bacteria, viruses, etcetera. Using perhaps the example we are unfortunately, most familiar with is you get a vaccine against Coronavirus to make antibodies against Coronavirus. And that's how our immune system protects us. The problem is when your immune system attacks you. When you look on the right, this shows you deposition of immunoglobulin on the top right for pemphigus and on the bottom right, for pemphigoid on the different areas of the skin. This is when antibodies go bad. So immunoglobulin, they're actually several types of them. But the main one we'll talk about is IgG and that's what intravenous immunoglobulin is. IgA is an issue in linear IgA disease and some bullous pemphigoid. IgE also has a role in bullous pemphigoid but the number or the amount of

them the blood compared to IgG is pretty minuscule. So generally speaking, we think most of these diseases other than pure IgA based, are really IgG diseases, so we'll go from there.

**Dr. Amber:** So what makes immunoglobulins? I think I proceed the Rituximab lecture so I'll try not to go too much on this. But basically our B cells, or lymphocytes are the cells that make plasma cells which then make antibodies. So it makes all different types of antibodies. Good antibodies, and in the case of autoimmune disease bad antibodies. I like this figure because it shows basically where does Rituximab fall into this process of immunoglobulin and where doesn't it? If you look on the bottom here, you see CD 20 expression and that's basically a marker of B cells. If the cells show those, you can kill them with the Rituximab. If the cells don't express that you can't. As you see, the cells that are actually secreting or where the antibodies are coming from, actually don't respond to Rituximab due to timing, unfortunately. The way I kind of conceptualized treating autoimmunity is, how do you stop making bad antibodies, while continuing to make good antibodies? And then taking the antibody part out of the situation, is how do you inhibit the immune response against yourself without affecting the immune response against other things? Pneumoniae versus an autoimmune disease, obviously you need to find somewhere in between and as you see there's the seesaw where unfortunately one is outweighed on the image.

**Dr. Amber:** So the strategies I think of in treating auto immunities, is to inhibit the inflammatory response to the antibodies. Basically, you have the antibody that binds to your skin or whatever the target is. It brings in a lot of inflammation. Let's mask the inflammation. I kind of think of that as putting a band-aid on things. You didn't stop the antibody, but you stopped the response to it so you may not even know that it's there. This works generally better in pemphigoid versus pemphigus but it still is a band-aid in my view. Remove circulating antibodies from the blood. So this would be, if you get your blood taken out, you take a bunch of antibodies and they put your blood back in, which we sometimes do in hospitalized patients. It works temporarily but the antibodies that are already on the skin are going to cause disease and last for a while because they're there. Then the problem is, you remove the antibodies all of a sudden you get a new batch because your cells are constantly producing them. The other thing is to try to decrease antibodies being released by the plasma cell. So if you make the cells secrete less, then you ultimately get blood. The problem is, that's not specific. If you tried to do that, you stop making antibodies against bad things and stop making antibodies against autoimmune conditions. Everything you see here is a double edged sword of things. Then the last step is obviously to kill the plasma cells. If you get rid of the source, then that should fix the issue. We only kill the plasma cells indirectly. We kill their precursors and wait for them to die, but these can take 2 to 3 years. So as you see, there's a lot of challenges in autoimmunity and treating it accordingly.

**Dr. Amber:** So what is IVIg? Thousands and thousands of donors pool together, IgG. I mean just thousands if not hundreds of thousands depending on the manufacturer of IgG. Now these are blood products, it's not really a drug and because it's based on the donor, that can change very much. I mean if you happen to have 50,000 donors who have a really good immune response against strep throat, you will happen to get that pool but that can vary over time. The idea is really to overwhelm the body with immunoglobulin to anything essentially, as a distractor and we'll go into how that works. So as a blood product, concerns are of course infection, so all the blood products are screened for hepatitis B, hepatitis C, and HIV. There are theoretical risks of less common viruses that may or may not have a known role. Each formulation has a different pipeline of how they go through and screen for all of those things. Unlike medications, where you say, okay, there's three different medications that do similar things, in IVIg it's basically different formulations. A company will pool 10,000 patients together, and then they screening for hepatitis, HIV, et cetera. They process it a certain way or heat it a certain way. They add a little bit of something to keep it stable and that's really how they differ. The actual medication is about the same and then there's just some subtleties to it.

**Dr. Amber:** So the first thing is how does it actually work? So you give someone a massive amount of antibodies against everything. So why does it do anything? Our body has a system that essentially recycles antibodies and this is why they last so long. So generally speaking, in certain animals for example, their antibodies replenish every few days. In us, it's about the half-life of three weeks for IgG. And the reason is this system called FcRn. You'll hear a lot of the FcRn inhibitors are medications on the pipeline. The way these work is by essentially recycling the IgG. So you see in the image below, what happens is basically you have IgG in your blood, your cell internalizes it and protects it and spits it right back out. So this is what keeps our IgG lasting for a very long time. Now if you block this receptor, either through giving a high dose of random immunoglobulins in the case of IVIg, all of a sudden your blood just starts eating up these circulating proteins. They don't last as long. So you can basically fairly quickly decrease the amount of antibodies in the blood.

**Dr. Amber:** That's one of the ways that works. There's a lot of other ones, basically, sort of going, I guess, counterclockwise as it has some anti-inflammatory effects. It can block the bad antibodies or autoimmune antibodies from binding to the skin, for example. It also can affect B cells on its own to a small degree. And the bottom one shows that sometimes can help the way skin cells respond in pemphigus but again, but that is a smaller mechanism there.

**Dr. Amber:** So, where does it come in? We discuss what are the steps and autoimmunity as I conceptualize them if you will. So inhibit the inflammatory response to an antibody. Does it do that? To a small degree because it blocks antibodies a little bit, you can sometimes decrease the immune response but that's not really where it works so much. That's why it doesn't work so quickly. Removes circulating antibodies from the blood. Here's where it's helpful. The whole

thing about antibody circulation, what it actually does is you eat up your antibodies. If I give you 100,000 good antibodies and you have 10 pemphigus antibodies, I've just diluted it so much that statistically the odds are that, that's going to get eaten up before all the good antibodies do. And that's really where it has its biggest effect. Also it has some effect on decreasing the release of antibodies, but that's again, a smaller thing, and it doesn't kill plasma cells, which we're still not very good at doing unfortunately.

**Dr. Amber:** So how's it given? It's intravenous and standard dose is generally two grams per kilogram per month, and we'll talk about is it really per month or how often should it be? That's divided over 3 to 5 days, depending on risk factors. For example, how's somebody's heart or how well do they handle fluids, headaches, et cetera? I tend to prefer over four days, on average. There is just lower risk of blood clots compared to three. To some degree, it's a balancing act of what's medically right and patient convenience. It can be infused by IV or port. Now, I know one of the questions I had received preemptively was the Subcutaneous IG. Unfortunately, it doesn't work, because the amount of IVIg you have to give to treat autoimmune disease is different than the amount you have to give in inherited immunodeficiency. So, because of that you would need to essentially have 20 different ports put on you and multiple days to even get the dose. It's not feasible to get the dose. So, unfortunately, it's IV essentially.

**Dr. Amber:** On one thing I did want to discuss, it doesn't really get a lot of attention. This does tie into a little bit of why we often use a second medication when using IVIg, is the concept of rebound phenomenon. So, the IVIG makes you essentially decrease the amount of bad antibodies and not really affect the good antibodies, but our body is as smarter than we are unfortunately. So what it does is, you start to decrease the, let's say pemphigus for example, you decrease the amount of pemphigus antibodies, but our cells say, hey, this isn't in circulation, I need to make twice as much to make up for it. And that's why you see this spike usually about a month in, when not only do you rebound back to what you would normally make, but sometimes you can even make more of the bad antibodies than you would have otherwise. So, this is really prevented by using a second medication like Rituximab, Azathioprine, Mycophenolate, Cyclophosphamide, et cetera. And choice of that is specific, obviously, what you have.

**Dr. Amber:** So the next question is, does it work? Well, hopefully I wouldn't be giving a lecture on it if I thought it didn't work, or the IPPF wouldn't give a lecture. I'll say there's two large randomized clinical trials on it that I don't really like personally, but I'm thrilled that they happen because that means I can't get insurance to approve it. These trials basically used IVIg for one month, to show some improvement in patients in a month. Why don't I like it? Well, it doesn't work magic in one month. It's actually a very prolonged period of time, six months to multiple years for IVIg to really do what it's supposed to do and we'll go through that. So the studies showed, yes, in the short term period, it can improve symptoms. It can decrease a little bit of steroid dose. But those studies, randomized controlled trials, the best thing we have in

medicine. Nobody's really done the trials the way it's done in actual practice. So, this was a study and I'm biased, it was my mentor back at Irvine, who basically did a lot of the work on IVIg and looked at a multi drug regimen for this. This is retrospective, so it's never as strong as these big clinical trials. But the interesting thing is it's sort of real-world use. And we know from clinical trials that those don't always actually translate to real people, if you will. Real people tend to do odd things instead of clinical trials where everybody is the same person. In this case, the time of patients off of drugs or should I say receiving the IVIg was actually a pretty prolonged period of time. And in this situation, there was basically the average follow up but after five years using this regimen, only 12% of patients relapse. So, essentially 88% of patients were in remission, off of medications, five years out. That's good. Those numbers are good. And if you compare those numbers to Rituximab they are a lot better. But the rituximab relapse can go from 60 to 80% if you do it the way the FDA says to do it. Now, most of us don't use it the way the FDA says because we know that there's some studies to show if you get more, it tends to work more effectively. But it's just helpful to have that number in your mind of 40 to 80% relapse rate with Rituximab versus 12% relapse rate with IVIg. Now, this is a single study, obviously always limitations. There was another study in New England Journal that showed 10 years out patients who had received Rituximab and IVIg, off of all medications in long term remission. So, for me personally I think in certain patients there's a goal of basically can I treat the disease, get it to go away, not come back and not need medication. I don't think that's practical for everybody as in terms of the regimen, realistic in certain situations, but that's my goal. And I think that's where the IVIg helps me, is when I look numerically at relapse rates I'm not as impressed by some medications that work really well but then after two years, everybody relapses. That's kind of crummy that you have to do something every single year and worry about what if this is the year I relapse, et cetera? So, that's sort of my thoughts.

**Dr. Amber:** Now, the risks of IVIG, by far the most common, are going to be headaches. This is particularly true in patients with migraines. Sometimes you can premedicate them with some Tylenol or even treat the migraines. But generally, of all of these it's the limiting factor, I think, in the ability to use it. Then the other thing is blood clots, low risk but seemingly a little higher in pemphigoid. I'd say just because we know patients with pemphigoid have a slightly higher risk of blood clots than the average person so that may actually be what we're seeing. And then the other thing is excessive fluid. If we're giving you an IV infusion with a lot of protein, you can get swelling or increases in the blood pressure and that can require a little bit of finesse to manage. Fatigue. And then the most severe, if you will, is it's time intensive. Three to five infusions every month just stinks. I had no better way of saying it's time intensive, and that that tends to be the biggest issue patients have with it, more so than true side effects.

**Dr. Amber:** So why use it? I don't think there's a one size fits all for everyone. I think there are patients who it's the right choice, and then patients who it's the wrong choice. I think plus sides, it's not immunosuppressive, so it doesn't increase your risk of infection. Basically, everything else we have other than maybe Doxycycline which are antibiotics that we use for anti inflammatory purposes, pretty much all of the other drugs are dropping your system. The other

thing is because it's safe in longer term use over a course of years, without dropping your immune system, you can get off of steroids and stay off of steroids for ideally the long term future. And the thing for me that I find most important is the long term remission rate when it's used correctly. I couldn't underline correctly enough times because I often see a lot of people who get it, maybe one month, two months, and then they relapse three months later and then they are like, "I don't understand why?" Or even get six months of therapy and they relapse. It doesn't work a little bit, but that's not really where it's a strong suit.

**Dr. Amber:** So, who is the right person for IVIG? I think people who've had the disease for about two years or more, I think that is a bit more of a stubborn disease. Some data supports some data conflicts, but I think if you've had the disease for 20 plus years, and had just Rituxan and those things, it just doesn't work as well. So I become a little more pessimistic about how well I can treat the disease using sort of the shorter term stuff. The treatment generally is about a two year course and my goal is ultimately for the disease to go away. And there are realities of when is that feasible and when does that make sense? So, for example, like I was saying with the relapse rates in Rituximab, if somebody doesn't mind getting their Rituximab infusion once a year and then that's fine. That's probably a less time intensive option, though it is immunosuppressive. But for somebody who says I can't go through this again. That's where I find IVIg is a better option. Usually people have relapsed after Rituximab. The other thing is greater time investment in the beginning versus greater reward in the long term. I have no way to sugarcoat that it takes a lot of time but the goal is to not have to go through it again. So, yes, it's more of a time commitment. The greater reward in the end is a good remission rate. Longstanding disease is sort of one of those special cases that I just find it's helpful. And it's safe to use in pregnancy. So really, that's one of the few good things we have in pregnancy. The other thing for a patient who has severe disease and may have required hospitalization, requiring multiple therapies, that's an ideal candidate.

**Becky:** I have one question, is IVIg for patients who have gestational pemphigoid, are those patients a candidate for IVIg or is it strictly pemphigoid or pemphigoid?

**Dr. Amber:** Sure, they are candidates. You don't always need it though because traditional pemphigoid because it is self limited you know there is an end game insight. Let's say you have bullous pemphigoid during pregnancy, you not only want to treat it, but you know after the pregnancy the pemphigoid is still going to be there so then you tend to be a bit more aggressive. So you don't always need it in gestational pemphigoid. In severe cases, yes, you absolutely can use it.

**Becky:** Thank you.

**Dr. Amber:** So who is the wrong patient for IVIg? I'd say for those who have time limitations that precludes 3 to 5 days of infusions per month. In a busy working person, there's some ways we can work around it by doing non consecutive days, but it's a realistic challenge. Poor prognosis in health status. So, I was kind of badly saying this, but if somebody's severely ill with multiple comorbidities or poor life expectancy, why go through a more rigorous treatment to have long term remission when I can do something, maybe a relapse in two years, but maybe if they have another diagnosis that only gives them two years, it's not worth it. So, I think that that's always a tricky conversation. Does this make sense? So I find my younger bullous pemphigoid patients who are in the sixties, I think it's a good option because, presumably, they have a nice long life to live with it. But a 99 or 100 year old bullous pemphigoid patient with multiple comorbidities, probably not the ideal candidate for it. And that all ties into basically patient goals. What are the expectations of treating the disease? My hope would be off steroids at a minimum, off of steroids and offers everything else, and then how long off of everything else? It's basically just having that conversation about what the goal is. and what's realistic.

**Dr. Amber:** A little bit on managing side effects. Headaches, like I said, are the most common thing. There's a lot of different things you can do. You can change the formulation, how much fluid, Tylenol, migraine management, dosing adjustments. Very, very rarely is someone not able to get through it after you've switched everything, you've done everything right, and they still get such horrendous headaches that they can't do it. Most of the time you can switch something up. Now the question is whether people will want to go through 10 steps before it goes away, that's another story. Blood clots, we don't have good guidelines for prevention. If somebody has a history of clots or develops a clot you can still use it, you just need to be on anticoagulation. And then swelling or high blood pressure, again, similar. I guess, the opposite spectrum of whatever you do in headaches you kind of do the opposite in swelling. Fatigue is a vague one that's always particularly hard to manage but again, you can change the formulation or divide the doses and give it over more days. Even though it sounds counter-intuitive, because you're giving lower doses per day, it's a little less stress on the body.

**Dr. Amber:** So just sort of an issue about flares and why this prolonged course? Let's say six months the disease is clear, you're off of steroids and you're off with everything, why continue for another year? The whole idea is, basically think of a flare and autoimmunity in the same context of a vaccination. So if you get the, let's say a tetanus vaccine, and then you get a booster. After the booster your immune system is that much stronger. So when you see on this graph, your primary vaccination is basically the first time you're exposed to something. And then the booster, you get a much stronger response. So the thing is, the same way that it works with vaccines, it also works with our own bodies. If you're immune to yourself and you have a flare, basically that flares makes an even stronger immune response. So I think of a disease flare as essentially a vaccine booster against yourself, which makes me particularly aggressive about little flares because the way I view a little flare is it's a ticking time bomb to a really severe flare because you've continually telling the immune system, this is okay, this is something I should be fighting. I really want none so that the immune system can, essentially,

forget that it's immune to yourself. So that's really the rationale for long-term treatment. As far as the timing of how long we actually use it? That's probably the greyest area in all of blistering disease literature. I tend to do, based on the protocol from my mentor, I've modified a little bit, but essentially it's another continued six months of monthly infusions from the time basically off steroids and completely disease free. At that six months, after monthly infusions and everything is good, then we start doing every other month for six months. Then after that, if things are still good, every three months or six months. So that's a year and a half after being off of steroids which you know steroids itself will take several months to get things under control. The reason I do that, even though some people will continue to give it longer is, basically I need to, in my mind, have an end point that makes sense. I think you could give IVIg for four years and increase the chance that it'll never come back but when do you say stop? My view is by doing at least something standardized that has data to show 12% relapse rate, that's a number I can cling to and if I do it this way, I know I'm dealing with about a 12% relapse rate. It's not that that's the right way or the wrong way. Can I get away with three months less, maybe, but I don't have any data to support it. Should I do six more months? Well, I'm already a 12%, how much more is it worth it? I can't prove that. So that's sort of, just for me how I conceptualize it.

**Dr. Amber:** The big thing, if you're in the American healthcare system, will insurance cover it? The answer is Yes, surprisingly and often with the ability to do home infusion so you don't have to go into the office 3 to 5 days a month. So I run a dermatology infusion center and I prefer to manage my patients at home because I don't want to drag anybody in 3 to 5 days a month. I wouldn't do it if it was myself and I feel like they deserve the same as I would do. That's doable with most insurance. There's a little state to state variability, but that depends. Different manufacturers and the infusion companies can offer patients assistance programs and manufacturer discounts too. For example, being in the Medicare donut hole, there are ways around it. It's an unfortunate symptom of our healthcare system. Generally speaking, for 95 plus percent it's not an issue. And the last thing I'll say is not all infusion companies are the same. So, a lot of insurance will require you to use their company and those companies drag their feet on everything. Other ones can be a little bit better.

**Dr. Amber:** So, just a few notes, not all Dermatologists are trained on using IVIg in blistering disease. I think there's a bit of a regional thing and it's kind of who did you train with? Who did this person train with? And so I'd say it's not always offered as an option, mostly because of that. Like I said, I don't think it's right for everybody, I don't think it's wrong for everybody. I think there's the right and wrong person for it. I would also say that the protocols for long term are not as well described, which also makes people a little less comfortable doing a prolonged course because we only have a few retrospective studies. The problem is, that's all we'll ever have because it's not one drug, that they can put all their money into a big study, and then get the study approved, to say, our drug works X amount of times. There are 12 to 15 competing companies, so there's not really an incentive in them to do the proper study. That's why they're only those one month studies that say, oh, it works in this not realistic situation. Realistically, I think the best will ever get of these studies. Then the last thing, which I can't say enough about, is the goals of care. I think that really everybody has sort of a different idea of what they expect.



I think for certain people, it's a good option and makes sense and for others, it's not the right option. But I think that conversation is really, probably the most key thing to anything and treatment and in any of these webinars, I think will depend on having that conversation.

**Dr. Amber:** So just briefly, how do I use it? Well I already told you, I do the two grams divided over 3 to 5 days. I basically, almost always, unless someone's pregnant, will use either Rituximab or Cellcept along with it because I think it makes it work a lot better. And I like Doxycycline as well, assuming people can tolerate it just to prevent mini flares. Essentially the way of saying like, if you just have one blister, you say, oh, that's not bad, it could be worse. Well, I really don't want that one. I want to mask it so that I can get the immune system to forget it. Then steroids, there's no way of getting around it. If the disease is bad in the beginning, you need steroids and that's the only thing that will calm it down quickly. But the goal is, use it with the IVIg to get off the steroids faster. Like I said, I do the every six months drop everything, and then the goal is a year and a half after being in remission off steroids, you stop everything and you cross your fingers and hope you're in the 88% based on that study. It's always stressful but the odds are in your favor. So, I'm totally open for any questions that anybody might have.

**Becky:** We did get a few questions, and one of the big questions is, are you taking new patients and if so, how did they get in touch with you?

**Dr. Amber:** Yes, I am. I wish I remembered the phone number for the office off the top of my head, but I relocated not too long ago. Easiest way email me at [kyle\\_amber@rush.edu](mailto:kyle_amber@rush.edu), with your contact info and then I can forward it to the office. Let me, if you are in remission and steady, let me know, or if things are going horribly also let me know.

**Becky:** Great, thank you. If you didn't get Dr. Amber's email we do have his contact information here at the IPPF so please feel free to contact us as well. One of the questions that Robert is asking is, do you see IVIg as a front line treatment for PV, or only for refractory disease?

**Dr. Amber:** I'm a bit of a contrary, so I don't separate mild, moderate, and severe, particularly, and I don't really separate recalcitrant because the way I view it is, there's a good chance it'll come back statistically speaking. So there's some people who will say, well, let me do Rituximab and see if it works. If 2, 3, or 5 years in remission things are good, great you never had to do it again and that's fine but the odds are slightly against you in that situation. So I think I prefer it because I just play the odds all the way. If there's a 60% odds against you versus 10% odds against you, what is the risk benefit of that? I think both are reasonable to use as a frontline, I certainly prefer that. And I'm biased because I see a lot of patients who relapse on Rituximab. When it was approved, there was an article that was published that called

Rituximab a magic bullet for pemphigus. That for me, I think there's a lot of people who are frustrated. There's a little bit of my bias of seeing the relapses but either is right.

**Becky:** Great, thank you. You had mentioned during your lecture that there were many different kinds, like 12 or 15 different kinds of IVIg. How is it determined who gets what kind or what brand?

**Dr. Amber:** Generally speaking it's insurance that picks one. I don't particularly feel too strongly about the formulation. I essentially write for a few, the ones that I'm used to using the most. But to be honest, insurance changes it so often that if I had a strong feeling about it, I would be an internally sad individual from getting rejected all the time. It doesn't make much of a difference for me. The only exception is, if you have a problem with one, then I'll switch you to another, et cetera. And it's easier to switch from one to another in that situation. It's not like there's one formulation out there that I think, oh no, you got that one, that's the one that causes all the headaches. No, it's really very individual, and then I just switch to another one. And usually, if I switch to a different one the insurance doesn't give me trouble about it.

**Becky:** That's great information, thank you. You had mentioned that IVIg can be administered at home and that you also run the infusion Center. What determines if somebody can get the infusion at home versus and they need to come into the center?

**Dr. Amber:** I think safety of the infusion. So IVIg, generally speaking, is a pretty safe infusion to give. Rituximab, sometimes will do it at home, but have to get the first couple an infusion center as a safety measure to make sure there's no heart issues, et cetera. I've always felt sort of mixed feelings about it and I think as a dermatologist, not having an infusion center before, sometimes you're biased one way or another. I breathe a little bit easier when I do most Rituximab there. That said with the IVIg, as long as you have a reasonable protocol in place, the safety of it is good that I just feel like it's more of an inconvenience that brings people in for that without an adverse risk to safety. I will say 5% or less of the time, insurance may say, no, we won't do it. Or one of the issues I'll sometimes get is, the insurance will say, we're only going to cover the infusion and you have to give it over two days. I don't like to do that sort of a course because I think it's a safety issue, and then I'll have to say, I wouldn't do it at home in that situation. But it's sort of medication based, there's some medications that are safer than others. And then choosing where's the right place to get it. And of course, it's American insurance so it is what they regulate.

**Becky:** Great, thank you. If you prescribe IVIg for a patient, say that I'm in your office right now and you're like, hey Becky you need IVIg. What happens between you saying that to me and

me getting my infusion and how long does it normally take? I mean, I understand insurance is in there but is there blood work and testing and that kind of stuff or how does that work?

**Dr. Amber:** Sure, so I would say I have had a range of about two weeks to six months before getting it, depending on insurance. And one other thing is, depending on the infusion company. Like I said, there's some insurance that requires you to use their one person or company and the problem is, because they're put together with the insurance company, they're not incentivized to help. They don't care whether the patient gets the medication or not, it's not in their interests. The problem with that is, you can imagine, they said, we've faxed you papers and I never got papers. And unfortunately, a lot of them drag their feet with that. Good companies, it's fast and it's simple. So, it's basically submitting a form with a lot of insurance back and forth. The blood work, there's a test and I always check something called an IgA level just to make sure that people have it because there's a small risk if you don't have IgA or have a severe reaction. It's kind of one of those things that the book says to do it, not everybody agrees on it. I don't want to say in retrospect, I wish I had followed what the book says, even though a lot of people don't do it. It's a simple add on to a regular blood test. I don't care so much about the rest of the blood work because it just doesn't really change a whole lot.

**Becky:** Okay. Cliff says that he was diagnosed with bullous pemphigoid last July and to date has had six IVIg infusions and gets 240 grams over the course of four days, once a month. He says he's been waiting off prednisone, but every time he gets down to around 10 milligrams he gets a breakout. He's currently back up at 50 milligrams because of another flare. His question is: How many more infusions should I go through before it's time to say that maybe this treatment isn't working?

**Dr. Amber:** I would say that, generally speaking, another treatment is necessary like Rituximab or Cellcept or one of those. It's sometimes hard, if you just do IVIg and prednisone alone, I'm not super impressed with it. I mean, you can get someone off prednisone with that but I think 6 to 9 months is a pretty reasonable range. It takes a while. Even if you look at Rituxan for example, it takes on average 7 months to kick in. So you see some improvement by 3 or 4 months, but it's not like the drug didn't work, the drug takes 7 months to work so you have to wait for it. So I'd say to look at the specifics about what else but I think six months is not an unreasonable time to still be stuck on steroids if you only do IVIg on it's own without any other medication like Rituximab or something like that.

**Becky:** Great thank you. Anandi says that she was on IVIg for 1.4 years until the pandemic hit and then stopped. She thinks she's okay to not start again because she thinks she's in remission but wants to hear what your opinion might be and if there are tests to determine if she's in remission or is this something that's just subjective?

**Dr. Amber:** Both. So you can check blood work and antibodies but I don't like it because the thing is, not uncommonly I see people with severe disease whose blood work looks fantastic. According to the bloodwork, they barely have any pemphigus and then vice versa. Someone who looks amazing, has the worst blood work you've ever seen. So I treat them, not the blood work. I think at a year and four months out, it's close enough to having finished the whole thing that personally, I wouldn't stress myself out and check the blood work. We know that it correlates with the disease coming back but it doesn't actually mean it will. So I think that's enough time that odds are in your favor. You may not be at 90% but maybe you're at 80%. It's not worth it to necessarily be starting again.

**Becky:** Great. We've received a few questions about COVID. Nancy wants to know, does IVIg have an impact on the effectiveness of the COVID vaccine and the timing of IVIg versus the vaccine have an impact?

**Dr. Amber:** We don't know. So, one of the things is if you're on a second medication, other than IVIg, then that's the dominant part. That's the one that's really going to be having more of the effect like Rituxan. Now IVIg, on its own, is in theory, safe to get the vaccine, absolutely. Does it affect the effectiveness of the vaccine? Probably to a degree, but probably to a lesser degree than any of the other medications because IVIg, for over a long term is trying to dilute the antibodies. Also at some point in time, immunized people are going to be donating and then you're gonna be getting immunized people's Ig. So, there's going to be sort of an odd overlap period. It's hard to give you a confident yes or no. My feeling with IVIg is basically if I was going to get the vaccine and if it's like three week apart, I'd say, scientifically speaking, waiting like two weeks into the infusion. And then, doing the other booster the 3 or 4 week one sort of again in the middle of the cycle so that you're not washing out the effects of the antibody, but it's entirely theoretical honestly. I just don't think it has as big of an effect on short term immunization. Basically the goal of IVIg is to use it for years to make the body forget it's immune to something. In the case of the vaccine, you're blasting it right then and there to get an immune response.

**Becky:** Great, thank you. We've also received a couple of questions that mentioned how IVIg is being used to treat COVID. How is that affecting the availability for patients to get IVIg treatments for pemphigus and pemphigoid?

**Dr. Amber:** So shortages are always a problem. And I'd say shortages are a lot about navigating the system and one of the things that's frustrated me as a dermatologist and made me want to set up an infusion center is, I feel like dermatology patients get put to the bottom of the list. If you go to an Oncology infusion center, they're like, this patient gets IVIg and I am like, what about the pemphigus patient and they are like, well we ran out today. Shortage is not necessarily unique to the COVID situation, there's been a shortage before that. Generally speaking, it hasn't had an effect, you have to just navigate the system a little bit to make sure

you can get it which is one of the challenges. As far as treating for COVID, they're using plasma in general, and also there's less plasma donors going around. So presumably there will be another prolonged shortage, but I think with these companies, they know what they're doing enough to step up production so that there's not a bigger shortage than there was even prior to that.

**Becky:** Great. Thank you. Somebody else asked if they can get their family members to donate their IgG to them and if so, how is this done?

**Dr. Amber:** Unfortunately not. So the issue is, if you donated just one person's IgG, first of all you wouldn't get enough of it for it to work and you would likely have some immune responses. The way IVIg works is if I give you two people's IgG you'll probably have a bad reaction. But if I gave you 100,000 people's IgG, then you get no reaction whatsoever. I think of it as kind of immune chaos to make your body sort of distracted from autoimmunity. So it's not the type of thing you can crowdsource people to do, unfortunately. And there's also a whole protocol of cleaning the blood and all of that stuff.

**Becky:** Sure, thank you. Another question is about what medications do I need to take before, during, and after my infusion for IVIg? You were talking about reactions.

**Dr. Amber:** Generally speaking, Tylenol and Benadryl are pretty standard, mostly for headache and any like swelling or just immediate reaction. Some people get nauseous and can use Zofran, but that's not too frequent. It's really going to be those. I rarely ever have to use steroids for premedication for IVIg. Sometimes if somebody's having a lot of issues with it, I'll use it then but that's not one of my standards.

**Becky:** Great, thank you. How long after giving an infusion can a reaction occur?

**Dr. Amber:** So it's a good question. Usually most of them are fairly immediate. I have seen some delayed headaches like 2 or 3 days out. Fatigue, usually by the last few days, tends to peak. So people may feel fine during their two infusions and by the fourth it starts, then it starts to persist on. But it's pretty uncommon other than sometimes maybe a 48 hour lull with headaches, to get like a delayed reaction. Hives or something like that, that's that's generally pretty immediate.

**Becky:** Great, thank you so much for answering that. Karen is also asking that you had mentioned something about having an increased risk for blood clots and if you could expand on that a little bit further.

**Dr. Amber:** Yeah, so we know, basically because we're giving so much protein, basically the blood gets sticky if you will. So things like deep vein thrombosis, blood clots or clots in the lungs can happen. We know it increases the risk, especially if you infuse it over a short period of time, which is why I'm kind of a stickler about not doing it in over two days because I just think it's an unnecessary risk. So that that helps, but we still know if you increase the viscosity of the blood, you're at a higher risk of having a clot. Most of the data shows it's so low that it's not worthwhile that you should start taking something every day so you don't get one. No, not necessarily but if you've had one before, then that's a concern and if you have the symptoms of one, obviously that's a big concern.

**Becky:** Great. thank you. Another question comes from Nancy and she says I've been an IVIg for 3 years and have weaned off steroids and Methotrexate 6 months ago. I'm on an every 6 week IVIg schedule, can I start weaning off IVIg soon and how is that done?

**Dr. Amber:** That's always a tough one. Yes, would be the short answer. I think that obviously, the timing of the disease course and all of that stuff would limit me telling you, why are you one it so long? But I think for that long a period of time, assuming you're off of steroids, I think it's reasonable to be able to start weaning off. Again, this is a thing we don't have good data to go off of. In my mind, I need an endpoint. What's the difference between 3 years and 10 years. There is none. We know the longer you're on it, presumably the better your odds are, and at what point does it make sense to say, well, today is as good as any day to try it. The immune system, we know, the plasma cells die out after about 2 to 3 years, so I try to time it on what Immunologically makes sense. I wait for all those cells to die out, that's a perfect time to be able to wean off and hope that everything's going to go okay.

**Becky:** Great, fantastic. Another question is: How much do IVIg infusions cost, and are there any assistance programs to help with out of pocket expenses? How do patients find them?

**Dr. Amber:** A lot. It really depends. Some programs will offer assistance for uninsured patients, but it's really one of those things that it's very expensive if you were to try to not do it through insurance. As far as, with insurance there's usually two different sides. The companies can have Patient Assistance programs. A lot of them won't tell you about it unless you ask and then people don't ask. The other one is sometimes the manufacturer of the IVIg can sometimes have a discount. Those are generally the ways of going about it.

**Becky:** So essentially, anybody that we talk to you about IVIg, ask them if there is any out of pocket assistance from our insurance company, to the physician's office, to the infusion company, to the manufacturer?

**Dr. Amber:** I'd say on the physician office side, it makes no difference. It's all outside of our hands. I'd say the infusion company and the manufacturer. Then they go through a financial assistance thing but it doesn't always work out. They may say, oh you make 100,000 dollars and 75,000 was the cutoff. You don't qualify, but that would be a starting point.

**Becky:** Great. Thank you. Another question that has just come in, Janet is asking how effective is IVIg for pemphigus foliaceus?

**Dr. Amber:** I don't view it as any different between the different diseases, unlike pretty much all the other treatments. So, I think it's as useful in pemphigus foliaceus as pemphigus vulgaris, if not slightly more helpful because pemphigus foliaceus is a more stubborn disease. Pemphigus vulgaris can be more severe and requires a higher dose of steroids. But once you get it under control, it just tends to be a little easier. Pemphigus foliaceus, you get under control and then a few months later you're like, oh no, it's back again. So I like IVIg, probably in some ways a little more in that case because of the disease cycle that pemphigus foliaceus goes under. I want to do something that keeps it away long term and not have it just keep coming back and coming back.

**Becky:** Great. One more question and this is asking about what to expect either at home or for an infusion. Once the infusion starts, you had mentioned before about monitoring and premedication and things like that, but after that can I walk around? Can I do things or once the infusion starts, I'm grounded and I'm sitting there?

**Dr. Amber:** You can walk around your home. It's one of those things that it's just kind of boring. It's not like you're going to go out with an IV pole and go food shopping or something. But, if you walk from one side to the house to another, that's fine. You may be a little sleepy just because of Benadryl, but it's not the type of thing that you can't move or anything like that. It's more like, what can you do with an IV pole or the equivalent of it feasibly in the house? I wouldn't do heavy chores, but if you want to go from room to room, that's totally fine.

**Becky:** Great, thank you. It has been a super quick hour, but before we go, I would like to give you the chance to give out your email again so patients can get in contact with you because we've got a few more questions about that as well. And also, there's some questions about do you only manage the infusion center at Rush or are there other centers around the country that you're involved with?

**Dr. Amber:** Sure. So my email is [kyle\\_amber@rush.edu](mailto:kyle_amber@rush.edu). As far as with my own infusion center versus others there, it is very tricky because there are few free standing institution centers that any physician can write an order for. A lot of the infusion centers are kind of territorial. And they

won't let anybody write an order for it, unless you see one of their doctors. That was one of the real reasons I don't like having too many cooks in the kitchen. It drove me insane, and I don't think it contributes to the patient's care. I don't run multiple across the country or anything like that. There's some flexibility outside of my individual one, and same thing with any physician practicing outside of their healthcare system, but there's a lot of barriers which just make it difficult.

**Becky:** Great. Thank you so much for everything today. This has been a really great hour, very informational, and your slide presentation was amazing and answered a lot of the questions that came in, so thank you. I would also like to give a huge thank you to everyone on the call for joining us today and thank you to Genentech, Principia Biopharma, a Sanofi company, argenx, and Cabaletta Bio for helping to make today's call possible.

Before we go, I have a few announcements:

Our next webinar in the treatment mini series will be Tuesday, March 9th to discuss Immunosuppressants with Dr. Animesh Sinha, Professor of Dermatology at the University at Buffalo in New York. Registration will open tomorrow.

Friday is FDA's Rare Disease Day Virtual Public Meeting. The meeting will focus on several related topics regarding rare disease product development. Specifically, the meeting will focus on rare disease partnerships and collaborations, scientific advancements, patient involvement, and strategies to support rare disease product development during COVID-19. This public meeting will consist of presentations and interactive panel discussions. If you are interested in attending there is still time to sign up. You can register for this meeting online at [www.surveymonkey.com/r/FDARDD2021](http://www.surveymonkey.com/r/FDARDD2021).

March is Autoimmune Awareness Month. We have paired up The American Autoimmune Related Disease Association (AARDA) to spread awareness about autoimmune diseases such as pemphigus and pemphigoid. Keep an eye out for emails about ways you can help us spread awareness this month. Also, the IPPF has several upcoming regional support groups that will be meeting virtually this month. You can visit our website at [www.pemphigus.org/events/](http://www.pemphigus.org/events/) to find out more about upcoming events.

The IPPF has been looking towards the future and how we can continue to help you and our community. We need your help to grow our community of Healing Heroes. Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small, even a \$5 or \$10 monthly donation goes a long way and continues to allow us to provide for the greater good of our community.



If you have not registered for the IPPF's natural history study we encourage you to do so. The IPPF Natural History study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). You can register today at [pemphigus.iamrare.org](http://pemphigus.iamrare.org). This online data system collects, stores, and retrieves patient data for analysis in research studies. The more data we can collect, the better the information we can give to researchers, the sooner they can find better treatments, earlier diagnosis, and one day – A CURE!

Lastly, If you have a question that didn't get answered on the call, or have additional questions please contact me at [becky@pemphigus.org](mailto:becky@pemphigus.org) or you can (916)922-1298 x 105 and I would be more than happy to help. This call recording will be sent out with the survey following this call. Thank you for joining us. Everyone! Good night.