

Becky: Welcome everyone, this call is now being recorded. I would like to thank you for being on the call this evening. Our speaker this evening is doctor Abdul Razzaque Ahmed, thank you for joining us today. The call will focus on intravenous immunoglobulin or IVIG for pemphigus and pemphigoid.

First let me introduce you to our speaker for this evening. Dr. Ahmed is the director of the Center for Blistering Diseases in Boston, this is the only center of its kind in North America. He graduated from the from the All-India Institute of Medical Sciences, New Delhi, India.

He immediately migrated to the U.S. where he was trained in internal medicine, dermatology and clinical allergy immunology. He received a Doctorate of Science degree in molecular immunology from the Faculty of Medicine of Harvard University. He has a Master's Degree in Public Administration from the prestigious Kennedy School of Government at Harvard University.

He identified beta4 and alpha6 integrins as pathogenic autoantigens in mucous membrane pemphigoid and was the first clinician-scientist to describe pathogenic IgG4 and nonpathogenic IgG1 autoantibodies in pemphigus vulgaris patients. Amongst his many clinical contributions, the most important, relevant and universally beneficial are the use of intravenous immunoglobulin (IVIg) and the combination of IVIg and Rituximab in treating patients with recalcitrant autoimmune blistering diseases. For these contributions, he received the Walter Lever Memorial Lecture Award. It is given once in 25 years because the contributions need to be confirmed and its benefit verified.

In 1988 he established the Boston Blistering Diseases Support Group that meets on an annual basis for the last 29 years. Dr. Ahmed's commitment to patients with pemphigus and pemphigoid is evidenced by his 400 publications but more importantly his unique, personalized way of treating each patient based on their individual needs and concerns.

Dr. Ahmed: Thank you very much. I am in Boston so it's evening and good evening to everybody in the United States, I presume that in some places that it still may be the afternoon, so good afternoon there.

Becky: Great, thank you. Do you want to jump right in to questions?

Dr. Ahmed: Yes of course.

Becky: So, can you explain to us what exactly is IVIG and how do they work?

Dr. Ahmed: IVIG is the abbreviation for intravenous immunoglobulin. Intravenous meaning that the drug or agent is given intravenously or through the vein and immunoglobulin means antibodies or IgG. This is simply a preparation which is normal in other words, IVIG is not prepared in a test tube, it's not prepared in some factory

somewhere and it is not made by some biochemical molecular mechanisms of synthetic processes. It is something that is present in the blood of all of us in the world and what IVIG is just a concentrated portion of IgG or antibodies from normal human beings. So, the companies that manufacture them collect a large amount of blood from a large number of people and then from this blood they separate the liquid part of the blood, or the plasma and then from the plasma they separate only the antibodies or IgG. Then they pool them into a bottle and that is how IgG is prepared and because it is given intravenously it's called IVIG. Now to answer the question of how it works, the mechanisms by which IVIG work are not one hundred percent understood. It is very clear that it has many, many actions and basically it is all of those actions by which the body is defending itself. You have to remember that between our lungs, spleen, kidney, heart, liver, brain everything that is within us and everything that is outside of us, that's radiation, that's the sun, air, the rain, the snow, everything that surrounds us we are protected by all of these biological and non-biological agents by the defense mechanisms of our body or the immune system. And one of the principle agents, one of the principle mechanisms that provide us this immunity and the ability to defend ourselves are immunoglobulins or antibodies and that is what IgG is. The simplest ways, one of the things that IVIG does is protects us. Protects us from everything that surrounds us and everything that could be harmful or detrimental to us. And that I think is the simplest explanation of what IgG is.

Becky: Great, thank you. What are some side effects of IVIG and what are the more serious side effects that patients can experience?

Dr. Ahmed: The most common side effect is headache and I would say that it is in a very large number of people. Typically, only the majority of patients deal with that, the minor side effects are sometimes people feel "yucky" or run down for a day or two. Occasionally a little nauseated, sometimes people's blood pressures go up a little bit and heart rates go up a little bit. Other than that, there really are no true major kinds of side effects to IVIG. There is a very small number that experience some of the more serious side effects. At one time there used to be a great concern for renal failure but almost all of those renal failure patients developed renal failure because of the powder form of the drug and that really is not used that much anymore. So that renal failure issue is really gone and is not much of an issue of concern unless somebody deliberately chooses to use the powder form of the drug. The second side effect is acute meningitis or something that is called aseptic meningitis. Varying people will get exquisite headaches, nausea, or vomiting. Again, if you look at those patients very carefully most of them have had a history of personal or family history of migraines. Migraine headaches can be triggered by IVIG, that said rather few people who don't have a history of migraine headaches can still develop a very serious headache, vomiting and then they go to an emergency room and the emergency room doctor does a lumbar puncture and tells them they are aseptic meningitis and that often becomes a complication. When I treat patients I always ask every single patient "do you have migraine headaches?" or "is there someone in the family that does?" And if they do I treat them prophylactically and then they never go on to develop a migraine headache.

There are some patients who develop clots in their legs or in their blood vessels. Sometimes these clots can dislodge and go to the lung and cause a pulmonary embolism. Most of these patients who develop these clots are either people who are sedentary, they are sitting in one place, such as working in an office and sitting in one place all day long or lying in bed because they are ill. A lot of big clots found in such patients. And then there are patients with something called factor V deficiency and because of their deficiency of that factor they can also develop clots. Finally the one system that needs to be of concern and needs to be of some degree of caution to all patients, is that a small degree of patients that develop strokes, transient ischemic attacks or even arrhythmias which is changes in the rhythm of the heart, or heart disease. Now these patients who develop either strokes, transient ischemic attacks of the brain or heart attacks are often people with preceding heart disease or preceding brain disease. My recommendation to patients is that if they have a preceding heart disease or a preceding brain disease before they get IVIG insure that the doctor who is giving you the IVIG has consulted with the person who has treated you for your neurological disorder or the cardiac disorder and make sure that this doctor thinks it's safe and it's comfortable to give you IVIG. If he or she says that it isn't then one should not get the drug. So I think that those are the kinds of side effects that I think are really the most important ones and if one is cautious and thinks about them ahead of time it is fairly easy not to develop them.

Becky: Wow, great. That was a lot of information but it was great information Dr. Ahmed, thank you. Deb is asking, "Will IVIG treatment work for pemphigus foliaceus? If it will, will a patient with PF need several treatments in order to see remission and how is that determine how many treatments?"

Dr. Ahmed: I think that there is no doubt in my mind whatsoever and there are many publications to show that IVIG works for pemphigus foliaceus. I think the response is very individualistic. Why, because how much pemphigus foliaceus any patient has will differ from patient to patient. Number two how much pemphigus activity you have will also differ but how severe it is will also differ so the amount you need will depend upon the extent and the severity of the disease and how well your body responds to it. In my hand, one of the key things I do the most is use topical therapy. I tell patients to use all kinds of soaps and baths and stuff like that so it decreases the burden of the disease on the skin and it decreases the burden treatment on the body. Number of treatments will depend on two things, number one how quickly does it take to clear up the skin. So if the skin has disease activity how quickly does it become disease-free. And once it is disease-free it is not a good idea to stop IVIG immediately. IVIG gradually needs to be decreased from say once a month to once every six weeks, then eight weeks, ten weeks, twelve weeks, fourteen weeks and the last is at sixteen weeks. Slow tapering or withdrawing of the IVIG teaches the immune system not to make the antibody again. Patients that are treated in this way remain disease free for a very major portion of their lives if not all of it. I think that the amount you need will be variable based on disease severity and extent. There is no doubt in my mind whatsoever that patients with pemphigus foliaceus will unequivocally improve on IVIG.

Becky: Great, thank you. Giada says, “I have ICS-IgA antibodies, scars in both eyes and dry eyes. A skin biopsy proves relation to IgA-pemphigus but no direct relation to mucous membrane pemphigoid and the conjunctiva scarring in the eye. I do not have blistering on my skin. I currently take Cyclosporine Eye drops. Is IVIG the next step in treatment? I don’t want to delay any crucial treatment especially for my eye and at the same time not start any systemic treatment if it is not necessary.

Dr. Ahmed: I think that there are two things that she needs to think about. IgA pemphigus can affect the eye but very rarely does it do so. One of my concerns is what is the diagnosis being made and while my nature and personality is that I never criticize another doctor neither do I condemn what other people do and I think that each physician does what they think what is best for them and also they have to deal with the circumstances in which they are dealing with. Here is my take on this, scarring of the eye, scarring of the conjunctiva in pemphigus is exceedingly rare as part of the disease process itself. In other words if you were to take a patient with pemphigus, whether it was pemphigus vulgaris or IgA pemphigus the statistically chances of scarring of the conjunctiva are extremely, extremely rare. When scarring does occur in the conjunctiva in patients with pemphigus it is generally because the conjunctiva is secondarily affected with herpes virus. Now the conjunctiva when it is affected with pemphigus is oozing because it has blisters everywhere and it is easy for the virus to grow. And one of the bad parts of herpes virus is it can cause scarring. So I think the main concern I would have for her is to get to a good ophthalmologist, somebody who is an expert on external eye disease or diseases that are more on the outside than the inside. Have this person have a careful assessment of her eye, whether the scarring in her eye is consequential to actual herpes or not. The second issue would be I am not sure that IVIG would do anything for the scarring at all. Once the scarring is established, IVIG does absolutely nothing, nothing whatsoever. It’s an expensive drug and I would not recommend it but what is possible for her is if she gets into the hands of a very good cornea surgeon a corneal surgeon who is very sharp and experienced. He or she might be able to do a cornea transplant and see some of the very superficial scars in her conjunctiva can be removed and replaced with a cornea transplant. The corneal transplant will then give her very good vision and she will be able to see virtually as she did twenty years ago. So my recommendation would be rather than getting IVIG get to a good ophthalmologist. I think the IgA pemphigus is now a long gone story if she does have no active disease at this point in time in her skin then she has no active disease at all. And I think that the key thing to do is to find what best she can do for her conjunctiva not so to give her IVIG. The IVIG will not be of any benefit to her and will cost a ton of money. And more than likely the insurance company will not pay for it.

Becky: Well great, thank you for the advice. I’m sure she appreciates it.

Dr. Ahmed: And hopefully not too far from her should be an expert who knows how to deal with external eye disease.

Becky: Great, thank you. Naheed says, “She has had blistered in my throat and nose since 2012. They have cleared and then will reappear sometimes but not as bad as when she was first diagnosed. She says she is clear right now. Is she getting better or will they come back? If the blisters are not deep, is it because she doesn’t touch or scratch them, if they don’t come back is she a candidate for IVIG?”

Dr. Ahmed: I think in the case of Naheed, the first and most important question is the diagnosis. I realize she is getting blisters in her upper airway but there are many reasons why people can get blisters in the upper airway. And many of these blisters are such that they come and they go at a particular interval or they come and go at erratic periodic interval, in other word they could come every month or they could come every six months or they could come every six weeks. So before I jump to a diagnosis and recommend a treatment, my first question to her would be, does she have an established histological diagnosis. In other words, has someone gone into her throat, actually taken a piece of tissue for histology, one for immunofluorescence and come back and given her a definitive diagnosis? And so that is the most important question. If she doesn’t have a diagnosis then I am afraid she is shooting in the dark because we really don’t know what she has so I really think we need to know what she has. If she has another disease then obviously the answer is very different. Majority of the blistering diseases do not really tend to simply come and go, they are there and they tend to stay. So my recommendation would be that she really get a strong handle on exactly what she has and then proceed from there. If she really still does have a blistering disease that seems to come and go yes, she needs some form of treatment that will put this in a long-term clinically remission. I think that IVIG is one such drug but before she takes that drug I would like to make sure that all the T’s are cut and all the I’s have been dotted and there is no doubt whatsoever of the diagnosis of what she has and it is an autoimmune disorder.

Becky: Great, thank you. Leslie says that she treated with Rituxan under an RA protocol five years ago for a severe case of Pemphigus Vulgaris on the skin and most mucous areas. She went into total remission until four months ago when the sores in her mouth began again. Three months ago she received two Rituxan infusions of 1000 mg. She says she is not any worse but she still has mouth sores. Would IVIG be a good next step?

Dr. Ahmed: Yes, there are two things she needs to know. Number one, the statistical chance, I want to use the word statistical chance of getting a relapse or the disease coming back on Rituximab is as high as eighty percent when you get to five years. If you take patients who had Rituximab and you follow them for two years the relapse rate is about thirty to forty percent. As you increase the amount of time the rates go higher and higher. When you get to about five and six years the relapse rates are about eighty to eighty five percent. So the statistical chance of getting a second attack of pemphigus after first infusion after Rituximab is very high. In these patients it is often very beneficial to use IVIG because what IVIG does is what Rituxan does not do and that is Rituxan does not prevent a second relapse but IVIG should so long as it is used in the correct

protocol. There is a very specific defined protocol that was published in 2013 in the Archives of Dermatology and what I would suggest to her is to approach her doctor and show them this and discuss the paper with them, tell them she wants to be treated according to this protocol so the disease goes into remission for many years to come, twenty years to twenty five years.

Becky: Great thank you. Ting says, “I have had bullous pemphigoid for 5 years. I am taking prednisone every day. Can IVIG therapy replace the Prednisone?”

Dr. Ahmed: The answer is yes. Anybody who is on prednisone for five years and I want to emphasize to you very clearly that it is not just how much prednisone you are getting but also the duration of the prednisone you are getting. Why, because every day that you are taking prednisone it is accumulating. Do not think that because you swallow a pill by the mouth it goes into the toilet by the end of the day. It does not, it accumulates in your bones and thins the bones out. It accumulates in the stomach and causes a hole in the stomach. It causes high blood pressure and diabetes, all kinds of very bad side effects. So prednisone for five years is not a solution to treating bullous pemphigoid. I think that if you are having difficulty getting off the prednisone then certainly IVIG is a good alternative and IVIG may help you not only get off the prednisone but once you have been treated with IVIG again according to the correct protocol, chances are very good that you will remain without bullous pemphigoid for the major portion of your life. So IVIG does something very remarkable and that is, it puts patients into a prolonged, sustained clinical remission so that you are without disease and without any drugs for many moons to come. We have had patients now as far as twenty five years who have no disease and have no drug and live very normal lives because they got IVIG. I think that it is really worth it and certainly for someone who has been on prednisone for five years I would strongly recommend getting off of it, there is no two ways about that.

Becky: Great thank you. Helena says, “ So many people around me are coming down with colds this time of the year. Are there any instructions about being sick before getting an infusion. I suppose you can't get the infusion if you are really ill, but what about for example a sore throat with no other symptoms? Where do they draw the line?”

Dr. Ahmed: I think that if you are getting IVIG in the first place you shouldn't be getting sick at all. Why, because IVIG contains antibodies and these antibodies are against common viruses. All of the blood from which IVIG is made comes from North American so most of us who live here are exposed to the viruses that are commonly present here. People who get IVIG should be pretty resistant to common viruses and infections. But if not and you do feel sick because sometimes what happens is you have a grandchild or a baby or a small child, these children go to daycare centers or they go to nurseries excetera and they come home with rare viruses that adults don't have. So it is possible to catch a virus from an infant or small child or sometimes even for elderly people. If that happens, I would not worry. A cold itself or a sore throat is absolutely no complication to not go ahead and get the infusion and the infusion will not be one bit affected and on

the contrary you will recover from the cold quickly by getting an infusion so I would not let that discourage you at all. I would so go ahead and get it.

Becky: Thank you. The next question says that we are hearing about different protocols for steroid-sparing routes like starting with traditional IVIG therapy and only moving to Rituximab if a patient has significant progress. Some doctors are going straight to Rituximab after starting high dose prednisone. How is it determined what is the best protocol for a patient and how do they determine to do Rituxan versus IVIG?

Dr. Ahmed: I think that all of this is dependent on your doctor. There is no hard and fast rule, there is no discernable described very well characterized protocol that has been formed by the American Academy of Dermatology or by any organizations who treat blistering diseases in general. There is a very big push towards Rituximab because the manufacture is pushing it in a very big way and there are certain physicians who are pushing it in a very big way. There is a push to give prednisone and Rituximab why? The reason is that Rituximab acts like a bullet, it acts very rapidly. You could take the worse case of pemphigus and within six to eight weeks the patients completely clear up. So for the patients it is like a magic that they were so bad and then all of a sudden and so quickly they are so good. So the reason that Rituximab is used abundantly is because of its very rapid clinical response. That said the statistical chance as I said earlier of it coming back are very high. IVIG on the other hand acts a little slower but it has a durable action, it has an action that is going to sustain and a likelihood of preventing the disease from coming back again. A lot of physicians who tend to be conservative, physicians who tend to be more cautious and concerned about the long-term may begin with IVIG. If the patient very well on IVIG they may never go to Rituximab. And then there's a small number who actually give IVIG and if the patient doesn't do extremely well or doesn't do as well as they would like the patient to do, then they give the patient Rituximab, the patient will do very well they'll continue the IVIG, complete the IVIG and then the patient remains completely well for many years to come. So these are the kind of approaches you can take. The approach that a physician takes or a dermatologist takes is very much based on his or her choice. There is no hard and fast rule that says you should do this or the other. What is better or what is not better is also very often dependent on the experience of the doctor himself. What has he or she used, what has his or her experience been or if they have trained at a certain center such as Dallas, Cincinnati or Saint Louis or Chicago or New York or Washington. Wherever they have been trained, whoever was teaching them used it in a certain way and they will follow the pattern their teacher had used so that is how they become accustomed to doing it in a certain way. But as such, it is always worth trying IVIG. If it works, it is a great winner, and why? IVIG per say has far fewer side effects and works very well. It's basically less dangerous than anything else. With Rituximab there are lots and lots of side effects, number one. Number two Rituximab is a newer drug, it has been around for only six to seven years. We just don't know what the long-term side effects of Rituximab may be, ten or twenty years down the road. IVIG has been around for fifty-five years. So we know in fifty-five years all of the things that can happen over the next twenty or thirty years and nothing does happen. While as in Rituximab we don't

have that answer. Now I don't want you to get the impression that I am saying that something bad will happen because I don't know that, I'm just telling you that the question is, can Rituximab have long-term side effects and at this point we don't have the answer. Rituximab was originally a drug that was used in cancers and in cancer the issue is different because a lot of the patients die so we really don't know what will happen in twenty to thirty years because the patients don't survive for twenty or thirty years. But patients with pemphigus and patients with autoimmune diseases hopefully will survive for twenty to thirty years so we don't want them to come up with a new set of medical problems twenty or thirty years down the road. It is my reluctance and my lack of initiative to try and give everyone Rituximab just because it works very quickly so that is basic difference between the two approaches. I hope I clarified myself.

Becky: Oh absolutely, and you provided again some phenomenal information. Betty asks, "Should I tell my doctor if I have afib or if I'm on a blood thinner before I receive IVIG?"

Dr. Ahmed: Definitely, positively. You should let the doctor know both that you have afib. Chances are very good that he may not do a whole lot or she may not do a whole lot because of the afib. Because the afib is relatively easily controlled by medication and also should be really controlled. IVIG does not affect blood-thinning processes so unless you have this very specific deficiency of factor five which causes clotting of the blood then if those conditions don't exist then neither of them would really affect the therapy but that being said, it is very vital that every doctor to know all the problems a patient has. I mean I have a sheet of paper which I write on every single medical problem my patient has and I write down every single drug the patient is getting whether it affects me or doesn't affect me and whether it influences pemphigus and pemphigoid or not. But it is very important to have that information with you all the time. I keep it with me every single time I see a patient and if there are any changes I make sure that I have made those changes on that list. So I think it is good for the doctor to have a list of all their medical problems and all the medical conditions as well as all the medications the patient is getting. Personally I don't think that they will make a huge change because if the atrial fibrillation is controlled and the blood thinning is not a huge problem then IVIG is not contraindicated.

Becky: Great, thank you. Debbie says that she is a sixty-four year old woman and I was diagnosed with bullous pemphigoid around February of 2017 with blisters over ninety-four percent of my body. I still have blisters and itching however it seems to be localized to my hairline and scalp as well as my lower legs. Would IVIG help at this point?

Dr. Ahmed: Yes it would. It just depends on how extensive the disease is and what the previous therapies have been. So if you've had it for more than a year clearly somebody has been treating with something and I don't know what those things are. My brain tells me two things, one that whatever was given was either not given in adequate dosages so it did not clear up the disease completely from the hairline or from the feet or the

lower extremities so maybe more should have been given or the right amounts were given but they weren't sufficient to control the disease. The second probability is that a second drug could have been given and the second drug could have taken away the disease from the hairline and the feet. If both of those were done and the disease did not go away and the disease still persists around the hairline then I think IVIG will help because IVIG will surely clear it up. I think that it would be well worth discussing this with the doctor as to one, was the first drug used in adequate dosages and if it was used in adequate dosages would a second drug my mouth have been used and would that have cleared up everything? If that was done too, then perhaps is it worth trying IVIG because IVIG might produce a complete remission. So I have given all the possible scenarios that could have happened.

Becky: Debbie just messaged me and says she has been treated treated with Cellcept and prednisone.

Dr. Ahmed: Yeah, if she has had Cellcept and prednisone and the two have not cleared it up then Debbie that is a classical indication for using IVIG. I mean that is exactly what the literature says, I know that you are sixty-four years so you are not eligible for Medicare but if you look at the Medicare guidelines they clearly say if a patient has received prednisone and any immunosuppressive agent, such as Cellcept, for more than eight weeks and the disease has not cleared up, then IVIG is indicated. And all insurance companies, whether it's Blue Shield/ Blue Cross, Aetna and of course in different parts of the country we have different local insurance companies like we have Harvard Pilgrim and Tufts in Boston similarly there are other insurance companies with other names but to the best of my knowledge almost all of the insurance companies in the country now allow IVIG to be used for bullous pemphigoid. Especially in patients in whom they have not responded to prednisone and Cellcept. And Cellcept is a pretty strong drug, it is one of the stronger immunosuppressive agents. So if that has not cleared it up then it's categoric indication for using IVIG.

Becky: Great thank you. Erica asks, " If I have a CSF tear of my spinal cord can I still get IVIG?"

Dr. Ahmed: The answer is, is you will have to have either a neurologist or somebody equivalent be able to decide exactly how significant that tear is. In and of itself IVIG should not be contraindicated, no. You would still be able to get IVIG because the IVIG will not affect the spinal cord at all. It actually will just run through the spinal cord and come back into the circulation. As long as the tear, the key issue is is the tear causing you any clinical problems, is the tear causing you any medical issues that in any way sort of immobilize you or any any way incapacitate you? But if you are able to go on with your life and if you are able to go on with everyday activities and certainly life is going on then IVIG should be fairly safe to use, it shouldn't be a problem at all.

Becky: Great, thank you. Elliot asks, "Is IVIG cost covered under Medicare?"

Dr. Ahmed: One hundred percent, yes! Medicare covers IVIG nationwide. It is one of the biggest fights I had my career suffered heavily because of that. The local Medicare Director felt that she should and she was very upset that I was using IVIG, it was costing a lot of money. She once called me and said why don't you just let the patients die. And I said you have to be out of your mind, how can I let the patients die? My job is to save them. So I went straight to Washington D.C. and I spoke to the main Director of Medicare for the nation and he put together a committee of twenty-three people who listened to my for three hours and then they made a national decision. So for any of you listening out there there is something called National Medical Coverage Decision, it was made in 2005 or 2006 and its an October 12th decision and Clinton was president at that time and it was made by Medicare in Washington D.C. and I had the choice of asking for coverage only for Massachusetts because obviously I live in Massachusetts. But I told the Director of Medicare that no I wanted this coverage for the whole country. So the whole country now, all patients who have Medicare coverage which is A and B will be covered with IVIG for blistering diseases and ALL blistering diseases not one but all of them for IVIG. And zero payment, so in other words Medicare patient has to pay absolutely nothing, it is completely covered one hundred percent.

Becky: Wow, that is amazing!

Dr. Ahmed: And in private insurances they may ask for a co-pay and things like that because those are obviously beyond my control and each private insurance company is different. But for Medicare I put my foot down and I said one hundred percent coverage for all Medicare patients all over the country and Medicare did pass the law and no subsequent president has changed it. So as of this moment, as I talk to you Medicare allows use of IVIG for all Medicare patients in all the fifty states of the United States for all blistering diseases. It was a tough battle and I paid a heavy price for it but I did it because I think that patients in the long-term will benefit.

Becky: Absolutely, thank you Dr. Ahmed. Sylvia says that she went into afib thirty hours after her second infusion with Rituxan. Is there a history of either Rituxan or IVIG causing afib when there is no prior history in a patient?

Dr. Ahmed: Yes, you should be very careful Sylvia in talking to your doctor. So I don't know who gave you the Rituximab but there are well known cardiac side effects from Rituximab and unfortunately the people who come from this manufacture and talk to dermatologists don't always explain to dermatologists that there are cardiac side effects from Rituximab. Rituximab is not free of side effects and certainly its cardiac side effects are very well known so the person who gave you the Rituximab should go back and have a cardiologist check you out and see how your heart is doing. But you can get afib secondary to Rituximab, absolutely.

Becky: Great, thank you. Harriett says in 2017.

Dr. Ahmed: Oh by the way, before I forget Becky. This is documented, it's not I said, he said, she said, you said, okay. There are many papers published in which the cardiac side effects of Rituximab have been very well documented. And they don't necessarily have to be in patients who had pemphigus. Rituximab can be used in sixty nine other diseases but if patients develop cardiac side effects then they develop cardiac side effects even if they have pemphigus because the drug is the same. Did I make myself clear?

Becky: Yes, absolutely. Harriett says in September of 2017 I was diagnosed with PF and given Rituximab. A month later I was given another dose of Rituximab along with IVIG and she is currently being treated with IVIG every six weeks. Can she expect remission with just continuing IVIG or does she need another dose of Rituxan or another medication?

Dr. Ahmed: No, I think that she should be able to stay on IVIG and in the foreseeable future she should be in a remission. I mean I am presuming that the two infusions of the Rituximab cleared up the pemphigus pretty well the pemphigus foliaceus pretty well. And what the IVIG is doing is maintaining it and I would think down the road the IVIG can be slowly decreased. Instead of going every month, to going every six weeks, then eight weeks, ten weeks, twelve weeks, fourteen weeks, then sixteen weeks and she is gradually and slowly tapering off of it she should stay fine the rest of her life.

Becky: Great, thank you! Jasmine asks when a patient is started on IVIG therapy, how long does it take for blisters to go away? Does the patient need to be tapered on Cellcept and prednisone? Her blisters are in the mouth.

Dr. Ahmed: Okay, what I generally do is, I think it takes anywhere from four to six weeks before IVIG really kicks in but once IVIG has really kicked in and is working very well then absolutely discontinue the prednisone and discontinue the Cellcept and keep only the IVIG going. In other words, IVIG will then become monotherapy it will become the only therapy the patient gets. The prednisone and the Cellcept should be discontinued. There is no scientific or sensible reason to give somebody prednisone and Cellcept if the IVIG is working. I mean, it is a drug that will work by itself, it doesn't need the support. Why do you need to give IVIG and Cellcept and prednisone at the same time? Because it takes IVIG time to build up in your body so you need to have enough blood level of IVIG before it is fully effective and that can take four to six months. So between that period you might need it but once you get to that point then definitely stop or wean off, gradually get off the prednisone and get off the Cellcept as well. It's best not to be on these poisonous drugs.

Becky: Great, thank you. Lisa says, "I've been receiving IVIG for about two years and I'm still on low-dose prednisone, 5 milligrams per day. I'm male and have been exhibiting gynecomastia. Is there any known link between these medications and my condition?"

Dr. Ahmed: Yes, I mean low term use of prednisone will definitely give gynecomastia, there's no two ways about that. And 5 milligrams of prednisone is homeopathic so I am not really sure why somebody is giving 5 milligrams of prednisone a day, it's not doing much. So I think that I would have a very head-on conversation with my doctor and ask two very simple questions. Why am I getting 5 milligrams of prednisone and what do you think it is doing to my gynecomastia? I don't want this gynecomastia and I think that as the prednisone is discontinued and slowly wears off the body, hopefully then the gynecomastia will also decrease. But I don't think there is any sense in giving 5 milligrams a day of prednisone. Your normal human body makes 7.5, everyone of us makes 7.5 milligrams of prednisone a day, so giving 5 milligrams is meaningless, they are giving less than the body makes. So let the body make what it makes and carry on doing what it's doing. And what people don't realize is that even if you give a small amount of prednisone for months and years it accumulates, it doesn't disappear from the body. And it tends to bind into the fat tissues and as you very well know the breast is full of fat tissue so the prednisone is sitting in the fat tissue within the breast and you want to get rid of it. Did I clarify myself Becky?

Becky: Yes, absolutely. Perfect. Maxine says that I'm an eighty four year old woman with MMP. She is using Dapsone, Cellcept, and Dexamethasone rinse. It's not helping and she is going to lose her teeth, she can't chew anything. Is the use of IVIG indicated?

Dr. Ahmed: Yes, absolutely. Again, Maxine should know that she needs to go in to her doctor because this is exactly what IVIG was prescribed for. Patients who do not respond to Dapsone, prednisone, Cellcept, Methotrexate any of these drugs, Azathioprine, etcetera, for then IVIG is indicated. She is losing her teeth because the gums are inflamed and when the gums are inflamed the roots of the teeth in the jaw don't remain as firm and they are going to fall out and it is going to be a huge problem for her. She may be able to get implants down the road but I think that in this point in time it's very important for her to get on IVIG so her mouth can improve, she can eat better and at least she can have a better quality of life and better quality of health. So I think yes, IVIG is positively indicated.

Becky: Oh great, thank you. So we just have a few minutes left in our call so I'm going to combine some of these questions to see if we can get most of the questions answered. Is there one brand or one generic of IVIG and if there are multiple different kinds how does my doctor know or determine which is the right one for me?

Dr. Ahmed: Ok, I think that the doctor to some extent can determine which one you should get because they have degree of legitimate choice in giving it. When you get it by home infusion companies the home infusion companies make the choice for you but the choice from the doctor can be made if the doctor is ordering it and not the home insurance company ordering it. You want to tell your doctor to order the IVIG that has the highest concentration of the IgG itself. The difference between one IgG preparation and the second is purely the amount of IgG present within the vial itself. So if the IgG is

ninety percent or ninety five percent you are going to get more benefit from the drug versus sixty or seventy percent. So you want the doctor to say, I tend not to use commercial names because I can be accused of conflict of interest and I can be accused of favoring one drug company versus another and I just don't want to be targeted by some opponent of mine or professional colleague. So I tend not to use drug company names but if your doctor just calls the pharmacist and says, hey tell me which pharmaceutical preparation of IgG has the highest concentration of IgG, he or she will tell them immediately and that is the one you want to use, you don't want to use. Now, that being said when home infusion companies use, they tend to use the one that's the cheapest because they make the largest profit because the ones with the highest concentration are going to be more expensive but then they are more effective. I'm afraid that's the only way I can really answer Becky because if I use commercial names I'm just concerned that people might get upset.

Becky: No worries. Are there any instances or contraindications for IVIG?

Dr. Ahmed: There's one relative contraindication which I believe is incorrect. People say that if you have low levels of IgA you should not use IVIG. Now, people can have low levels of IgA if they have antibodies to IgA. So I think that if you have low levels of IgA you can still use IVIG the only thing you want the doctor to do is before they begin the infusion is to give some Solumedrol. Solumedrol is like a cortisone if you give it intravenously then you are fine and then you can go ahead and get the IVIG. That is the only real contraindication to IVIG, otherwise there are none whatsoever, IVIG can be used very safely without any problems. I mean people can hepatitis, people can have any infectious disease, they can have any other disease it doesn't matter. IVIG is something that we all have in our human bodies so just adding more of it will in no shape form or matter cause any problems at all. If people have very severe renal failure, very severe hepatic failure then yes, you want to be concerned because the liver will not be able to deal with it and the kidney will not be able to deal with it. In situations where there is no major problems the kidney or no major problems with the liver, no problems with the viscosity of the blood, some people have a disease called (indistinguishable) hyperglobulinemia a very high amount of antibodies in the liver because a blood cancer there might be some concerns but otherwise by and large it is very safe to give IVIG.

Becky: Great, thank you. Stacy says that I have MMP, high BP180 titers and did not respond to Rituxan. I'm currently on Cellcept which isn't doing much and I am considering IVIG. Is there a protocol for using Cellcept and IVIG?

Dr. Ahmed: I don't think there is a protocol for Cellcept and IVIG but there is a very good protocol for using Rituxan and IVIG. The combination of Rituxan and IVIG will probably work better than Cellcept and IVIG because Cellcept will not jive with IVIG. In other words the two will not work in symbiosis or in synchrony, while Rituxan and IVIG work very well in synchrony and you can very easily look up my name and I've described a protocol and it works dramatically particularly for MMP. It's an extremely effective drug, a very effective combination. So that if it were me, I would go with that

route rather than, you can always use IVIG with anything else, with Cellcept as well but I think that that combination will be better. But IVIG will work with Cellcept also.

Becky: Great, the last question from Briance asks, is there any pre testing that I need to have done for IVIG treatment? And another question that is similar to that, typically how long is it from the time I'm in my doctor's office and we determine that IVIG is right of me to the time of my first infusion?

Dr. Ahmed: The first answer is that the most important thing is to check before you get IVIG is you want to make sure that your blood count is okay, that you are not anemic, your liver is functioning, your kidneys are functioning and that all systems in the body are go, in other words nothing is wrong with any of the systems. The second thing you want to check is hepatitis profile, you want to make sure that the patient who is getting IVIG doesn't have hepatitis or hepatitis antibodies or hepatitis antigen already because if they get an infusion then you won't know what changes have occurred. So it's important to know those difference before you begin. From the time you enter the doctor's office to the time you get your first IVIG infusion should be approximately two to three days at the very most. Because all the doctor needs to do is check the CBC, check the blood count, check your liver, check your kidney just to make sure all the systems are ready to go. The electrolytes are okay, you are not a diabetic those kinds of things which are very easily checked within forty eight hours. So I would say that if you go into a doctor's office on Monday, your infusion should be given on Wednesday, maximum on Thursday. Shouldn't be any later than that. Now the only thing I am saying is I don't know how long it will take for the doctor to get the drug because if he is getting it from the manufacturer or from the local wholesale supplier that might take a day or two, but for us it's twenty four hours but you know my office gives IVIG everyday. So we take only twenty four hours, so if we call them today it's here tomorrow by eight o'clock so for us it doesn't take us more than a day. But I think that most doctors can do the same if they want to do it and if they know how to do it and have the set-up to do it. It's not at all time consuming the only time it takes to get the blood tests drawn is about forty eight hours. Forty eight hours is plenty of time to screen it shouldn't be more than that.

Becky: Great thank you. Well Dr. Ahmed it was very great to talk to you today this was a very quick hour and I just want to say thank you for being on the call with us today.

Dr. Ahmed: Well I hope I was able to answer some practical questions and give people some insight with my twenty five plus years of using IVIG. I was the one who began the use of IVIG in these diseases and continue to use it extensively and literally all over the world. I think I've spoken in forty five countries about IVIG because it is being used so extensively all over the world. I mean your patients must know that this is a drug that is being used everywhere. And personally I have spoken in forty five countries which is to say that I'm sure that it's being used in more than forty five countries, these are just the countries that invited me to speak. So it's a drug that works very effectively, is being used everywhere and has a good profile and is very effective as well.

Becky: Well awesome! Thank you again for being on our call and a big thank you to everyone who is joining us today.

Dr. Ahmed: Thank you so much for inviting me.

Becky: Thank you and you're welcome. Our next Patient Education Webinar will be on March 26th with Professor Jennifer Harmon from the University of North Carolina school of Dentistry to discuss oral health and care in pemphigus and pemphigoid.

I would also like to remind you that the IPPF's Research and Advocacy fundraising campaign has kicked off with a goal of raising \$15,000. Your tax-deductible donation enables the IPPF to advocate for patients and collaborate with stakeholders for the development of research of pemphigus and pemphigoid (P/P). We provide the most current information to clinicians treating these diseases, researchers investigating potential cures, and to patients. With your support, we maintain relationships with congressional representatives and other rare disease support organizations who provide the IPPF with the opportunity to advocate for favorable state and federal legislation, research funding, and policies that benefit those affected by pemphigus and pemphigoid. Your tax-deductible donation will help the IPPF continue to provide the promise of new therapies, improved access to treatments, and a better understanding of these diseases through our advocacy efforts, research grant program, clinical trial support, natural history study, and biobank.

And speaking of the IPPF Natural History Study, a new patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Register today at www.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!**

The IPPF is pleased to announce the date and place of the 2019 IPPF Annual Patient Education Conference. The 2019 conference will take place in Philadelphia from October 11-13th. This is our 25th year as an organization and we hope that you will join us this year for an educational and fun weekend in the city of brotherly love! More registration details to come in the next few months. We hope to see you there!

Lastly, If you have a question that didn't get answered on the call, or have additional questions please e-mail our Outreach Manager, Becky, at becky@pemphigus.org, or call me at (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. Goodnight everyone.