

## **Back To Basics: Treatments #3 Immunosuppressants Webinar Transcription**

**Amethyst:** Welcome everyone, to the Back to Basics Treatments Webinar, to discuss immunosuppressant. This call is now being recorded, and I would like to thank you all for being on the call with us today and to our sponsors, Genentech, Principia Biopharma, a Sanofi Company, argenx and Cabaletta Bio for making today's call possible. "Information is a key factor in treating and living with any condition. However, every patient situation is unique. IPPF reminds you that any information found on the internet, or during our presentation should be discussed with your own doctor or health care team to determine if it applies to your specific situation." Before we begin, I would like to take a quick poll to see which immunosuppressant medications that you guys have been on for the treatment of your pemphigus and pemphigoid. So, if you can take a quick second to answer that, and while you're doing that, I'd like to introduce our speaker for today. Dr. Animesh Sinha, is a Professor in the Department of Dermatology, University at Buffalo, Buffalo, NY. Following the completion of his M.D. degree in 1982 from the University of Alberta, Dr. Sinha received his Ph.D. degree in Medical Sciences of Immunology in 1986 from the same institution. Subsequently, he pursued post-doctoral research at Stanford University in the Department of Microbiology and Immunology. Dr. Sinha's subspecialty training in dermatology was completed at Yale University/Yale-New Haven Hospital. Prior to his appointment in 2011 as Chair of the Department of Dermatology at SUNY Buffalo/Roswell Park Cancer Institute, Dr. Sinha held faculty appointments at the Department of Dermatology, Weill Medical College of Cornell University and at Michigan State University, where he was the Chief of the Division of Dermatology and Cutaneous Sciences. Dr. Sinha is a board-certified dermatologist whose professional goals are aimed at bridging the bench to the bedside. His research is focused on understanding the genetic and immunologic basis of complex skin disorders. He has published extensively, over 150 peer-reviewed articles, including 4 in the journal *Science*, and received numerous honors and awards for his academic activities. Thank you all for taking the poll. I'm going to close the poll real quick. It looks like a good majority have taken Cellcept and then Methotrexate and Azathioprine at about 25%. So, this definitely helps us understand where most of our questions are coming from today. So, thank you so much and thank you Dr. Sinha for joining us today.

**Dr. Sinha:** Well, thank you for having me! Glad to be here. And what I thought I'd do is spend the first little bit, maybe 15-20 minutes giving an overview about immunosuppressants and some basic facts and reviewing some of the drugs that many of you are on. And hopefully that will give you some base knowledge or reinforce things that you've already heard and provide new information as well. Then I know many of you have submitted questions and believe you are going to be interactively sending additional questions and I'm happy to answer those. Hopefully, we'll be able to cover the topic in some amount of detail, and so again, I'm happy to be here.

**Amethyst:** Before we begin, Dr. Sinha, let me just go over some quick housekeeping slides and then we will switch it over to you. Does that sound okay?

**Dr. Sinha:** Sure, that sounds great.

**Amethyst:** (Reviews Housekeeping Slides...) I will now turn it over to you Dr. Sinha.

**Dr. Sinha:** Okay, I hope you can all see my screen there with the first slide, Immunosuppressant Therapy for Autoimmune Bullous Disease. I just want to mention that I have no conflicts. I'm coming to you, as was mentioned from Suny Buffalo, New York where it actually is sunny today. Well, what is Immunosuppressive therapy? So immunosuppressant drugs are a class of drugs that suppress or reduce the strength of the body's immune system. There are several of them, many of you on the call that are taking them one or more. It's a huge market. In 2018, it was roughly \$14 billion in the US healthcare system and it's expected to grow even more to 42.5 billion dollars in five years. So it really is a booming market. There is an increased need for these drugs because autoimmune diseases are increasing. Immunosuppressants are used for autoimmunity, but also organ transplant patients to suppress the host's immune system so it doesn't reject the organ. But of course, here we are talking mostly about autoimmune disease, where pemphigus and pemphigoid and the bullous disorders fall into that category. So what is autoimmunity? So, we're on the same page. It's a failure of an organism to recognize its own constituent parts for self, therefore, we start attacking our own cells and tissues. Normally we have this amazing immune system that is ready to attack all the viruses and pathogens out there but something goes wrong. Normally, we don't attack our own tissues. But in these diseases we don't know why the body attacks itself. We have some deeper understanding, but it really is a central issue of biology. How can we have this incredible system that attacks everything else in the antigenic, pathogenic universe that we might encounter, but we don't attack their own tissues. There are a number of mechanisms, the immune system has those self correct responses in check but when they break down you get what was described as "horror autotoxicus" by the Nobel laureate, Paul Ehrlich and he defined it that we have this horror that's attacking our own tissues. Collectively there are over 100 human autoimmune diseases that affect 5-10% of the population. Right behind heart disease and neck and neck cancer, it's a leading cause of morbidity and mortality. That's a huge healthcare cost burden to the health system, over \$100 billion annually.

**Dr. Sinha:** But here's the problem, there's not a single human autoimmune disease for which we have a cure. Why is that? Well, these are complex diseases, meaning that they are multifactorial. There are several factors, genetic factors, most of which we don't know. There are environmental factors, such as exposure to viruses and bacteria and certain medications, other things such as toxins etcetera, that may trigger disease and somehow these multiple factors inspire together and dysregulated the normal workings of the immune system so now

you don't have those checks and balances to keep your immune system from attacking its own tissues. Then they breach that self-tolerance and start creating new activities for our own tissues and cause problems. This happens in other autoimmune diseases such as Type 1 diabetes, MS or Multiple sclerosis which occurs in certain neurological cells self. In Rheumatoid Arthritis, which attacks the joints and in Lupus you have a lot of different issues. So there are a number of autoimmune diseases in the skin too including vitiligo which attack the pigment cells and there is alopecia areata which attacks the hair follicles. And then there are the blistering disorders, pemphigus and pemphigoid.

**Dr. Sinha:** But pemphigus is actually one of the diseases which we know a little bit more about how the disease happens. So how do you get a blister? You see this blister and it results from a split in the top layer of the epidermis of skin. That's caused by these antibodies, that you can light up the other amino reagents that are fluorescently tagged and you can see that the antibodies are lit up in green in the top layer of the skin. Those antibodies are produced, if we go backwards, to how the disease starts, by B lymphocytes which are a class of white blood cells that produce these Y shaped proteins or antibodies that attack certain key proteins that are important in holding the skin cells together. Two of these key proteins are called Desmoglein 3 and Desmoglein 1 or DSG 3 and DSG 1. There may be others, but these are the primary cells. But how do the B cells produce these antibodies? Well they need help and certain signaling factors and cytokines from another class, another class of white blood cells, the T Helper Cell. And those T cells themselves are activated when their receptors recognize a certain protein, or a bit of a protein that's presented on the surface of another type of immune cell that specializes in initiating an autoimmune response. So we have some basic roadmap about this and two important genes that I sequenced when I was at Stanford that are very important in initiating these immune responses in pemphigus, those genes produce those proteins that present the peptide to the T cell which then help the B cell make the antibodies which attack the cell adhesion proteins that then lead to the skin cells falling apart and causing a blister. There are many more details to fill in, in this roadmap but that's the basic idea. Nonetheless, we still don't know universally and comprehensively how to effectively shut down the immune response. But we have some options.

**Dr. Sinha:** So when we are treating pemphigus, what do we have to do? These drugs have to be effective at suppressing the immune system and ultimately reducing the production of a synthesis of those autoantibodies for their effectiveness. That's the basic principle that you have to carry on with for any therapeutic approach. Now before steroids, corticosteroids, which are known to suppress the immune system, pemphigus was a pretty fatal disease and the mortality rates really astounding, 50% after a few years and 85% at five years because usually the autoimmune would run rampant and you might get infection with open wounds. Then after steroids became more widely used in the 1950's, the mortality rate went down quite a bit but still significant, mostly from the complications of steroids because steroids are very effective in suppressing the new system, but they have a multitude of effects on the body and organs. So, therefore, there are a lot of associated side effects. Now, with additional drugs including

immunosuppressants, the mortality rate is much lower, closer to 5% at five years and getting better. So, that's the good news.

**Dr. Sinha:** So, let me place the treatment in our history and evolution of treatment on an arc for you and then we'll see where the immunosuppressants fit in. So we need to knock down the immune system, so we can do that generally, just knock down the whole immune system and that's with steroids and that's very effective but they have a lot of side effects. Then, later other non-steroidal steroids or steroid sparing immunosuppressants were utilized, and that's what we are going to be talking about. But I want to place this in a larger context. So if you remember our roadmap to disease, also a disease caused by the antibodies or the immunoglobulin molecules that we need for a normal immune defense, that are misdirected and attack our own skin tissue in pemphigus. We can try and get rid of those antibodies by other strategies, such as intravenous immunoglobulin, absorbing out those antibodies, those are therapies that are used as well. Again, to more targeted therapies, the antibodies are produced by those B cells, there are other drugs that target the B cells. A couple of different strategies including Rituximab which is anti CD20, a marker on B cells. Then we're getting to more antigen specific treatments that not just knock out and get rid of the immunoglobulins and not just target the B cells that make the anti immunoglobulin but target only the antibodies, the immunoglobulin and the B cells that are causing the disease. The ones that make the antibodies to the desmoglein 1 and 3 and there are some new strategies and emerging things therapies being studied. But nonetheless, the mainstay in the foundation of therapy still rests in general in immunosuppression, either steroids or nonsteroidal immunosuppressants. And that's what we're going to focus on.

**Dr. Sinha:** So, the foundation and the beginning of this arc of treatment is generally immune suppression, steroids and nonsteroidal immunosuppressants. But before we get into the nonsteroidal immunosuppressants, let's talk just briefly on steroids because I bet almost all of you were given steroids at the beginning after your diagnosis. So steroids are very effective, and the way they're generally used is to give them an initial effort to control disease at maybe 60 to 80 milligrams per day, then continuing to the end of the consolidation phase. That's when no new lesions have developed for two weeks and well over half of the regions have healed. And that control of the disease activity in the consolidation phase typically happens over 2-3 months but it varies among patients, that's a common thing in autoimmune disease, is that you can't predict exactly the disease. But that is a rough estimate of most people based on my experience. Then once the disease is under control, and the disease is in the consolidation phase we can start to taper down steroids because they have a very effective approach, but they have a lot of side effects and you don't want to be on them too long especially on high doses. So people had various regimens to decrease and taper schedules for steroids. That's where we go and ultimately we want to get down to a maintenance therapy of only 5 and 10 milligrams within a few months or less so the side effects would be less. If there's a flare because these diseases as I said, wax and wane, they go through periods of flares and remissions, we'll go back a couple of steps on the tapering schedule to a higher dose and then

eventually try and taper down again. So I won't delve more into steroids at this point because we are going to focus more on immunosuppressant drugs but the mechanisms of action of steroids are quite Freudian and they have a lot of different targets and they have a lot of different side effects. So as a second line, but sometimes shortly after steroids or sometime concurrent with them, we can start adjunct therapy or steroid sparing, immunosuppressive drugs. There are a number of them. In the U.S. we're particularly using mycophenolate mofetil also known as Cellcept or azathioprine known as Imuran. There are a number of different options that exist and have been used and especially historically, we'll review those. So let's get into it.

**Dr. Sinha:** Let's talk about Cellcept, what dose? Usually about 500 milligrams, 1-3 times a day. Some people can go up to 2,000 milligrams a day but usually I like to stay at a max of 1,500 milligrams a day, so 500 milligrams 3 times a day. This immunosuppressive acts on blocking the DNA and RNA synthesis which is important for the growth and proliferation of cells including immune cells but of course they have non-specific targets so that's why they are used for stopping the growth of cancers as well. When you are on Cellcept you want to screen and then monitor your CBC, complete blood count, liver function, and renal function. There is some debate about how often to monitor, but usually, a little more often the first 3 months, every week or two, and then monthly for 3 months, and then after that every 3 months. That is roughly a good schedule to go on. You might want to screen for a deficiency for an enzyme called HGPRT, but that's a very rare deficiency so most people probably don't screen for it but some people are born with an error of metabolism that causes problems with Cellcept. Side effects, the most common side effects are gastrointestinal, nausea, vomiting, diarrhea, etcetera. Sometimes it can cause leukopenia, that means the decrease in the white blood cell count. It can cause an increased risk for shingles and other infections, urinary burning, or urinary urgency, headaches, tinnitus or ringing in the ears, and a risk of cancer although it hasn't really been established. Cellcept is blocking the proliferation, so you are blocking the immune cells but it's a balance because you need your immune system to fight off infections and also cancers but at the same time you have this big problem in autoimmunity because you got immune cells causing damage to your soft tissue. So that's the immediate danger and it is a benefit versus risk consideration.

**Dr. Sinha:** Let's talk briefly about Azathioprine or Imuran because a number of you were on that as well. Usually the dose is 50 milligrams, 3 times daily. Again, it blocks some of the DNA and RNA synthesis pathways and therefore, what happens is that this drug blocks when your immune system is ramped up, the white blood cells are proliferating or growing fast and replicating but if you block the steps for that replication, the Azathioprine blocks that immune function. One thing you do need to do, when you are on Imuran is to get a test for TPMT, thiopurine methyltransferase, it is an enzyme. With this you have two types, you have the TPMT wild-type and you have the normal gene and if you have a decrease of this enzyme, because you have one of your genes or both those genes into both these genes that can code of this enzyme or variant gene then you can have increased levels and this is required to metabolize the drug. It occurs more in black individuals. But you definitely need to test for this

and if you have one of the variant genes, you can still get the drug, but just in a lower dose but if you have two of these variant genes you should not use Imuran because it can lead to an accumulation of some of the toxic analogs of this drug and then induce suppression of the bone marrow. And of course the bone marrow produces the red blood cells and the white blood cells.

**Dr. Sinha:** Azathioprine again, some basic screening and monitoring of your blood, liver, and kidney function and an annual skin exam because it's sometimes associated with skin cancer. Side effects, again, gastrointestinal, you can have fatigue, increased viral infections, myelosuppression which we talked about which is the bone marrow suppression with TPMT polymorphism and possible increase in squamous cell carcinoma and skin cancers. So those are things to watch out for on Imuran.

**Dr. Sinha:** Cyclophosphamide, or Cytoxan the dose is about 100 milligrams per day orally in this country. In places like India, they have really championed a different approach in using pulse dose intravenous injections monthly, along with intravenous steroids. So this is an alkylating agent that again affects the DNA and RNA and the growth and replication of cells and immune cells. We sort of see a trend of how these drugs are working. Similar screening and monitoring for lab tests as we talked about, complete blood count, liver function, renal function. Then what are the side effects to look out for? There can be a bone marrow toxicity, and then you can see a drop in the white blood cell count in a couple of weeks, but this usually within a few weeks. Again, gastrointestinal discomfort, diarrhea, anorexia, also a hemorrhagic cystitis or inflammation of the bladder or even bladder cancer. So you should take this with plenty of fluids and watch for blood in the urine. Hair loss can occur and there have been reports of infertility as well. You want to avoid using Cytoxan with certain other drugs, allopurinol, barbiturates, digoxin. Avoid pregnancy as it can cause fetal abnormalities in women of childbearing age unless use of 2 forms of contraception. Avoid using in breastfeeding women and in people with serious infections or who have bone marrow suppression. You probably want to avoid most of the immunosuppressives in this category of people although some have a higher pregnancy risk

**Dr. Sinha:** I know some of you were on methotrexate. This was used a little more commonly in the past for pemphigus and pemphigoid. There are various dosing schedules out there. It's available in 2.5 milligram tablets. Usually given around 22.5- 30 milligrams per week or sometimes spread over 3 days in a week. Methotrexate, this drug inhibits folic acid metabolism which is again associated with cell growth and replications and therefore inhibits immune cell growth and function. You want to screen for infections including Hep B and C, HIV, TB, and varicella. You should get a baseline chest x-ray, a liver function test, et cetera. The side effects are, again, GI, anemia or loss of blood cells, decrease in white blood cells and platelets, liver disease although it's not as common as we originally thought with Methotrexate but you still should be monitoring it. We don't do liver biopsies pretty much anymore, we used to do that.

Sometimes you can very rarely get a lung disease called fibrosis. Also again, a risk of infections, photosensitivity and sometimes rarely some people get diffused hair loss.

**Dr. Sinha:** I didn't see if anyone was on Dapsone. This is a little less popular now in the blistering disorders. This is a sulphone antibiotic used to treat leprosy. And again, we want to do some basic screening and monitoring of bloodwork. You sometimes may want to screen for an enzyme deficiency of G6PD, glucose-6-phosphate dehydrogenase, which increases the risk for the red blood cells attacking causing anemia. Again, the side effects as commonly with these drugs, GI symptoms such as nausea, vomiting, diarrhea. Also symptoms like dizziness, blurred vision, headaches, tinnitus, insomnia and sometimes something called methemoglobinemia and it's a variant of the hemoglobin where it doesn't carry the oxygen molecule very well so you don't get enough oxygen so you can get blue and discoloration of the fingertips.

**Dr. Sinha:** Cyclosporin, this is a drug that blocks a molecule that is an immune-mediator molecule, interleukin 2 that is very important for T-lymphocyte function which is a key white blood cell. And you can take this medication orally as a liquid. You want to monitor the cyclosporine levels and have renal function tests. Again, GI side effects, it can cause high blood pressure, kidney problems and hair growth. Sometimes you get this weird swelling of the gums. You want to avoid grapefruit juice because there is stuff in grapefruit juice that interferes with the metabolism of this drug.

**Dr. Sinha:** Then I am going to end with gold and this is just for historical purposes and it's quite interesting. Gold and silver were thought to have medicinal properties in ancient civilizations and gold was used up to a few decades ago. It was an intramuscular injection but it has multiple effects on the immune system but I just put it in here for historical completeness.

**Dr. Sinha:** So, let me conclude by saying, again, there's a whole roster of various immunosuppressive drugs. I think more often we use Cellcept because it has a pretty good safety profile, especially compared to the other ones. Imuran is also very popular. But some people are still on cyclophosphamide and methotrexate as well as Dapsone and cyclosporine. So, let me go back to this arch of pemphigus and pemphigoid treatment. Remember that this is a foundational importance of steroid and nonsteroidal immunosuppressants. The general immunosuppressants they're good at stopping the immune system but the problem is, again, that they are non-specific and they are exposed to the entire immune system and large parts of it. So therefore, there are some things to worry about such as risk of infections and cancers because you need your immune system for those things. It's a risk versus reward balance but they're effective, especially in the early stages of disease. But they're often combined with other types of therapies that are focused on riding the body of immunoglobulins and the antibodies that cause disease or the B cells that produce or just the very specific B cells or antibodies that cause the disease. So we have a range of different types of strategies and options to mix and

match to try to control the disease. The problem is that everybody's disease is a little bit different. Disease waxes and wanes and there's variability across and among patients. Everybodies diseases course is a little different and we want to tailor things to each person and monitor and adjust as we treat each individual patient. So I'll leave it there. I know we have a number of questions, and I'm happy to take them now.

**Amethyst:** Great, thank you, thank you so much for that overview on a lot of those immunosuppressant medications. We are going to jump right into all the questions that we received. Dr. Sinham does pemphigus or pemphigoid respond better to immunosuppressant?

**Dr. Sinha:** So throughout the presentation I talked about these medications but everything that I was saying really can be applied to pemphigoid as well. The general strategy for these diseases is to start with a steroid and then add on immunosuppressives and you might have to try various combinations. So I think they both respond well but currently at this stage of science, we don't know who responds or who responds well and who doesn't. Some people respond very well to different medications for pemphigus and pemphigoid and others do not. We don't have the genetic or other biological immune markers to tell us who might respond and who might not. So we can't personalize therapy yet but there is a lot of research being done for that. My lab is focusing on that. We want to identify based on certain genes or the combinations that are expressed, the exact composition of patient's T and B cells and other immune markers so we might be able to say, "you have this, this, and this, you are more likely to respond to this drug because we want to match responders to the what drug will be the best fit.

**Amethyst:** That would be great, looking forward to the future. Are immunosuppressants considered to be slow acting or fast acting? Or does it just depend on which immunosuppressant you're taking?

**Dr. Sinha:** So, yes it goes a little bit. So steroids work the fastest and they work pretty much on everyone but not everyone tolerates them equally. For most immunosuppressants I would say they start working within a couple of months, and sometimes a few weeks. How they are working is to block the growth and proliferation of the function of those immune cells. So by the time the B cells are making the antibodies and the T cells are helping the B cells, you still have antibodies out there causing the disease. So now you have to stop the factory. So the "cars" are already out there and they are kind of running amuck on the highway and these drugs are working on shutting down the factory so you don't produce the antibodies that affect the skin cells. But in general, I would say it takes at least 3 weeks for them to start working. Now again, it's variable. Some people might respond better than others, some may not respond at all so therefore we have to adjust. There are some studies where the data is not that solid because it is a rare disease and it is hard to do these kinds of studies. But there is some data that shows Cellcept works a little faster or gets people to a remission on drug, on medication, faster than others. But again it varies.

**Amethyst:** Great, thank you. I know you talked about prednisone being used in combination with other immunosuppressives, are other immunosuppressants used in combination together and if so, which ones?

**Dr. Sinha:** Sure. You can mix and match. It's not uncommon to be on Imuran and Cellcept but it really depends on how fast someone is responding and if we are getting their disease under control. Very often we use the steroids as I mentioned, but they are often used in combination with others and some other categories of drugs that we talked about like IVIg, Rituximab. There are not exact algorithms, some attempts and some general rules that we all use but it really depends on the patient and the aggressiveness of their disease and how they responded to medication or combination of medications. So you really have to work closely with your specialist to fine tune your therapeutic regime and adjust along the way.

**Amethyst:** That makes sense, great. Are immunosuppressants considered a frontline treatment for pemphigus and pemphigoid?

**Dr. Sinha:** Yes, usually you start with steroids for anywhere for a couple of weeks to a month and then add the immunosuppressants. Sometimes I go right into it depending on what stage I see the patient and what else they have been on. So I would say it is a second line treatment, but often used very early.

**Amethyst:** Great. Thank you. Marilyn just wrote in and she says, how effective are topical steroids when taking Mycophenolate?

**Dr. Sinha:** So, I'll answer this first for pemphigus and then pemphigoid. For pemphigus, it's not clear that topical steroids help that much. Some patients seem to report some relief for a topical gel that is put in the mouth and this may have some protective effects and some local effects but remember, the problem is by the time you get to the skin the problem has already happened. The antibodies have already been made in the blood and then they are transferred to the skin and then they cause the disease. So what you really need to do is shut down production of these antibodies in the blood, systemically. So locally, there may be some benefits but usually not but there may be some local relief from the pain or to just cover the wound and have a symptomatic effect. Bullous pemphigoid, it's a very similar mechanism to pemphigus with similar principles in the basic roadmap to the disease, but there are also a little more inflammatory components you see in the eucinapils so steroids can help to knock down those inflammatory pathways and there have been some reports where high-dose steroids have been used, especially in elderly patients that did not take a lot of systemic steroids where they may not tolerate systemic steroids and immunosuppressants and there some reports of efficacy there. But really, really high amounts of topical steroids and high potency steroids you

really need to slather it on. But ultimately what you need to do is shut down the production of these antibodies quickly.

**Amethyst:** Great. Thank you. Isabelle also just wrote in and she said she was prescribed tetracycline antibiotics with her immunosuppressive. She didn't say which one she is currently on, she said, is there any useful information that demonstrates the benefit of using the tetracycline, with immunosuppressants?

**Dr. Sinha:** My guess is Isabelle has pemphigoid and tetracycline and sometimes niacinamide has been used in combination. Again, sometimes an anti inflammatory is used for to help with the anti inflammatory pathway so sometimes these antibiotics can be useful but are not commonly used and not so much in pemphigus which has less of an inflammatory pathway.

**Amethyst:** Great, thank you. Sue wrote in and she said that she heard that you cannot take methotrexate if you have a liver disease, and I know you touched a little bit on that. Of all the immunosuppressants, which one can she take with liver disease?

**Dr. Sinha:** Sure. So yeah, absolutely, methotrexate can be toxic to the liver and you have to monitor very closely if you have existing liver disease then you have to look for other options. You should still monitor for liver toxicity and sometimes there are some idiosyncratic things that happen to the liver (...Inaudible), I think if it would be reasonable to try Cellcept, or Mycophenolate Mofetil or Azathioprine, Cyclosporine maybe even Dapsone. But you want to monitor for how the liver is doing, especially if there is existing disease. But there are some other options.

**Amethyst:** Great, thank you. Ken said that Mycophenolate seems to upset his stomach. Do you have any tips for taking Mycophenolate and hopefully relieving some of those symptoms?

**Dr. Sinha:** Yeah, absolutely. Pretty much all the immunosuppressants there is a risk of some GI upset, especially I think in Cellcept. There's some things you can do. You can take it with food that may help. The other thing is, there is another form of the drug called Myfortic that is usually given twice daily that should help. The other thing is don't take antacids to relieve your stomach upset because it has phosphates and other ingredients that do not combine with Cellcept. So, maybe decreasing the dose if you can get away with it or maybe trying the Myfortic and taking it with food. If it's severe and not tolerable you might have to switch to a different immune suppressant.

**Amethyst:** Great, thank you. How do patients know that the immunosuppressant is working for them? And if they're heading towards a state of remission?

**Dr. Sinha:** Well the good thing about the skin is we can just see what's happening such as are they developing any new lesions? How are you feeling, are the blisters going away? So you will know within a few weeks and you will work closely with your specialist to monitor your disease with a certain scoring scale the disease activity. You will be able to visually see and be able to track and you can keep track of how many lesions you have in the mouth or on your body. You can also take photos and you will know within a few weeks if it is getting better. If it's not, hopefully you are in regular contact with your specialist and you are adjusting every few weeks if the medication regime that you are on is not helping to decrease the lesions on your skin and in your mouth. So you'll know within a few weeks but you have to give it a few weeks. Don't expect it to work in a week or two. But as long as you are in close contact with your specialist and together you can work things out. You can help by really keeping a good journal of your disease and writing it down. How many lesions do you have, did the old ones get smaller, did they start to heal? Take some photos or have a family member take some photos for you, that can be very helpful. If you are truly managing the disease together with your own documentation and then also with what your specialist see

**Amethyst:** Thank you. Should a patient just stop their medication of immunosuppressants rapidly or are there any issues associated with stopping quickly on immunosuppressants?

**Dr. Sinha:** Yeah, that's a good question. With steroids we know, you don't want to stop abruptly because when you give external corticosteroids, it stops the production of one's own corticosteroids which are needed for many, many normal functions. So you want to taper slowly, to allow your body to begin production of its own corticosteroids again... (Inaudible) but, again, I would caution against that. Always work in conjunction with your specialist and come up with a strategy to taper you off of one immunosuppressant and then put you back on a different one. And you don't want to be without any coverage especially if you have active disease. So I don't think there is any direct harm except that your disease might rebound even if you think it was having an effect but maybe it was holding it at bay. So I think it is a wiser thing to make those decisions with close communication with your specialist.

**Amethyst:** Great, thank you. This touches a little more on Rituximab and we do have an upcoming call about that. So I'd like to suggest that you also listen to that call. Karina wrote that she was treated with Cyclosporine and Dapsone and they didn't seem to be working so her dermatologist recommended that she get Rituximab. She received that in February of this year, but she's still getting lesions. Do you recommend that she gets a second dose of Rituximab or that she does Rituximab in combination with IVIg?

**Dr. Sinha:** That's a tough question to answer. I guess I'd like to know how many lesions she's having. How long ago was the first dose, did she get what I call the first dose of two cycles. You get a gram of IV on day one and then you get another gram the next day and then you then

repeat that in six months. Sometimes people get a maintenance dose of 500 milligrams every six months. So if there's been an overall improvement, you might want to continue with Rituximab, but continue to have low dose steroids and maybe another immunosuppressive. So all those options and combinations are on the table. It really depends on the history of disease for this patient and of course what's been happening and the relevant improvement or exacerbation of the disease. So those are the subtleties into the specifics of the treatment regimen so really there is no clear answer. There needs to be again, a consideration and direct communication with your specialist and you can map things out. It really gets at the heterogeneity or the variability of these diseases. There's no one exact rule but there are some general therapeutic steps or a therapeutic ladder. But we really have to adjust to each patient and again, there are a number of factors that play in. Some people might have not just this disease but they have other aspects to their health or comorbidities. These are good questions that this patient asked, and those are questions that need to be directed at their physician so they can work out a schedule and adjust the schedule as needed.

**Amethyst:** Great, thank you. Isabelle wrote in and said they seem to accompany Rituxan with immunosuppressive medications, particularly I think for her case methotrexate. Why is that?

**Dr. Sinha:** Again, hard to know exactly, it certainly can be used that way. Methotrexate is being used a little less than Cellcept and Imuran in this country. So, I don't know the specifics of her case and why Methotrexate was chosen. Some people respond very well to Methotrexate and you might want to keep that going to some degree while the Rituximab is kicking in. Rituximan really has been a game changer for pemphigus, a little less for pemphigoid. So, in about (inaudible) of people respond and achieve some sort of remission with Rituximab but not everybody. And within a year or two, half or more do flare, so not everybody responds. A lot of people do, but not everybody responds and not everybody responds equally. So other medications or combinations of medications are often given and you just have to see how the response is and then adjust accordingly. There are different options you can use in combination with Rituximab.

**Amethyst:** Great, thank you. Well, it is such a hot topic and I know a lot of patients are curious about the COVID vaccine, so we're gonna wrap it up with that. How do immunosuppressants affect the covert vaccine?

**Dr. Sinha:** Sure, nobody knows exactly but there's a good chance that immunosuppressants and the disease itself, may affect your response to the COVID vaccine. But the reliable, Dr. Fauci himself said, absolutely get the vaccine even if you have an autoimmune disease and are on immunosuppressants. Maybe your response won't be that high, it's hard to predict but you want to get the vaccine so your immune system is primed up and ready to go to take on the coronavirus if you happen to be exposed. But you will probably get at least some response and some response is better than nothing. But again, the science isn't exact. These are rare

diseases, especially pemphigus and pemphigoid. But in general in other autoimmune diseases, immunosuppressants are used a lot. Nonetheless, it's been hard to study for the blistering disease community about the vaccine. So I would say, definitely get the vaccine. The other points to make about COVID are, are people with autoimmunity and on immunosuppressants more at risk for getting COVID? And again, we don't know for sure. Possibly, yes, and so I would say, especially people with autoimmunity and people that are on immunosuppressants or anything that compromises your immune system that you should be extra vigilant about distancing and masking and just be extra cautious. But it's not clear, there's no clear data that this group of people are at much higher risk. There was some good news in a study from John Hopkins that showed that people on immunosuppressants did not get severe COVID any more than expected. But again the science isn't all there. So I would say, go ahead and let's get the vaccine, be extra cautious... (Inaudible). Discuss it with your doctor and they might want to lower the medication dose for a while or pause your medication for a while before you get the vaccine. It's always a risk benefit ratio calculation. So you have to have a heightened bit of awareness and vigilance. But there needs to be a balance and you want to keep the autoimmunity under control. I think what we are not seeing is that people with autoimmune disease and on immunosuppressants with very severe COVID. But nonetheless, stay cautious.

**Amethyst:** Great, good advice. Last question on the vaccine, and there might not be any research on this, but do you know if there's any research if the Pfizer or the Moderna or even the Astrazeneca or the J&J vaccine is better for a patient's to take who have pemphigus or are on immunosuppressive?

**Dr. Sinha:** Well, it's a question for the general population and as it applies to people with autoimmunity or on immunosuppressants. I think it's the same equation. Vaccine data show that all are pretty good. I wouldn't think that there would be a big difference in the autoimmune and immunosuppressant taking patients theoretically. As most of you have probably heard, the Moderna and Pfizer are RNA vaccines. But the basic idea is to get some of the coronavirus the, the critical spike protein in infecting cells, if an individual is exposed to that so you make a response and you attack those spike proteins. So I would say whichever vaccine is available first just get it.

**Amethyst:** Great, thank you! Well, that was a very quick hour and very educational. Thank you so much Dr. Sinha for joining us today, and thank you, everyone for being on the call with us. And I'd also like to give a huge thank you to our sponsors, Genentech, Principia Biopharma, a Sanofi company, Argenx, 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 next Tuesday, March 16th to discuss Rituximab with Dr. Victoria Werth, Chief of Dermatology and Professor of Dermatology at University of Pennsylvania, Philadelphia. I know we had many questions come in today as well about Rituximab so if you are interested, please join us for the call. Registration will open tomorrow.

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 and continue to provide valuable resources like today's webinar. 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 [www.pemphigus.iamrare.org](http://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 like Dr. Sinha, and the sooner they can find better treatments, earlier diagnosis, and one day a cure, hopefully!

Lastly, If you have a question that didn't get answered on the call, or have additional questions please contact one of the IPPF's Peer Health Coaches on our website by visiting: [www.pemphigus.org/peer-health-coaches/](http://www.pemphigus.org/peer-health-coaches/) or you can call (916) 922-1298, and we would be more than happy to help. This call recording will be sent out with the survey following this call. Thank you so much Dr. Sinha for joining us. We look forward to having you again soon.

**Dr. Sinha:** My pleasure. Thank you.

**Amethyst:** Have a great day, everyone. Thank you so much. Bye, Bye.

