March 23, 2021 Patient Education Webinar- Back To Basics: Treatment # 5 Anti-Inflammatories

Amethyst: Welcome everyone, to the final webinar in our Back to Basics Series to discuss anti-inflammatories. This call is now being recorded. I would like to thank everybody for being on the call with us this evening 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. The IPF reminds you that any information found on the internet or during the 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'd like to take a quick poll to see how many of you on the call with us this evening have had anti-inflammatory drugs, such as Dapsone and Tetracyclines for treatment of your pemphigus or pemphigoid? I'm going to launch that poll real quick, so if you could take a quick minute to answer the poll. And while you're answering that, let me introduce you to our speaker for this evening.

Amethyst: Dr. Fivenson attended the University of Michigan for Undergraduate and Medical schools. He completed his Dermatology Residency at the University of Cincinnati, and Immunodermatology Fellowship at the University of California, San Diego. He is board certified in Dermatology and Immunodermatology. From 1989 to 2002 he was in full-time academic practice at Henry Ford Hospital prior to starting his practice. He is a nationally recognized specialist in autoimmune skin disease, wound care, clinical research and cutaneous T cell lymphoma. Dr. Fivenson has published over 140 peer-reviewed articles, has lectured extensively at national and international medical conferences and has been repeatedly listed with Who's Who in America, Best Doctors in America and Castle Connelly's Top Docs. Dr. Fivenson is on the editorial board of the Journal of the American Academy of Dermatology as well as a peer reviewer for several other dermatology journals. He has been an investigator on more than 150 clinical trials for both common and rare skin diseases. Dr. Fivenson is part of the St. Joseph Mercy Health System Dermatology Residency Program and is Program Director for the Complex Medical Dermatology Fellowship which is supported by St. Joseph Mercy Health System Dermatology Graduate Medical Education.Thank you for joining us today. And thank you all for taking the poll. I'm going to share the results real quick. Wow, it’s about 50/50. So half of you have and half of you have not been prescribed and tried anti-inflammatory drugs. So that's great and that'll help us with answering a lot of the questions for this evening. So before we begin and get into our questions, I'd like to go over a few housekeeping items… (REVIEWS HOUSEKEEPING RULES)

Amethyst : It is my pleasure to introduce Dr. Fivenson to answer your questions about anti-inflammatories for treatment of pemphigus and pemphigoid. And I will go ahead and switch the screen over to you, Dr. Fivenson.

Dr. Fivenson: Great. Thank you very much. It's really a pleasure to be doing a presentation again for this group. I have a lot of warm fuzzy feelings for the IPPF, for many reasons, but most of it has been the support of you guys, the patients and the educational information that they provide as well as help with research down the road. So what we're going to do tonight, we're going to talk about things that are considered steroids sparing, non immunosuppressive, anti-inflammatory agents that are used in autoimmune bullous disease. For most presentations, you're supposed to start out if you have any conflicts of interest, which I don't, other than the fact that I am an investigator on one of the Principia trials but I am not going to be talking about their medications. So there's no conflicts. I want to talk about an overview of the tetracyclines, an overview of Niacinamide or Nicotinamide and then an overview of Dapsone, as well as highlighting some of the pros and cons of taking it and things that might happen if you happen to have it prescribed. This will probably take only about 15 minutes or so, and then we'll have the rest of the time to try and go through some of these questions. I will couch this in the terms that it's a little technical. So, some of it may not be super on everybody's level. It's from another presentation. So, it's not at everybody's level because there's just no way to really present the information. But, I think you'll get a good jist anyway from it.

Dr. Fivenson: Starting out with tetracyclines, they are anti-inflammatory, you know them as antibiotics. But they're also anti-inflammatory by blocking some signals that are used to turn on inflammation. Signals that turn the lymphocytes, or the white blood cells into production of antibodies moving in and out of tissues, especially neutrophils and eosinophils which are the bad actors in many of the blistering diseases. They also regulate some of the protein and the proteins that break down some of the connective tissue or the stuff that's in between all your blood vessels and then in your skin, which may help prevent some of this side effects that we see with the active blistering disease because the blister has to form by kind of dissecting its way through tissues to make a big bubble, so if you can turn off one of the enzymes that helps the blister forming, that's what this MMP 13 is. And then trying to turn off some of these other ones that would normally also chew up tissue that may be activated over and above what they should be, all as part of the inflammatory process within the site where blisters are forming.

Dr. Fivenson: Niacinamide or Nicotinamide, this is an active precursor of nicotinic acid or vitamin B3. Nicotinic acid is part of the energy cycle of all cells. So, it's important in what's called electron transport, that's how the energy charges move from one molecule to another in cells, kind of like the wheels that keep the cell going. And we need a certain amount of it, from our diet, around 50 milligrams a day. When it's used as a pharmacologic drug for its anti-inflammatory effects, oftentimes it's being used in 10 to 50 times that dose. In very low doses, you can take Niacin or Niacinamide and you'll see this in some of your multivitamins. But in high doses, nobody wants to take a larger dose than maybe 100 or 200 milligrams of Niacin without having gotten used to it because it causes pretty significant flushing, but Niacinamide doesn't do that. So, “amide”, means no flushing, no passing out, no turning, bright red. You can see down here, safe up to 6 grams so that’s 60,000 milligrams per day.

Dr. Fivenson: This is a picture that was from one of my talks years ago and it just shows all these different pathways where Niacinamide may play an important role either in promoting healthy metabolism shown more towards the left, or helping to turn off some of these inflammatory pathways that lead to tissue damage, shown more towards the right and towards the bottom. Other things that it does that we've seen its use in, beyond just the blistering diseases that it blocks histamine release from the mast cells, which is what causes people to get hives an itch. It blocks phosphodiesterase, which is one of the key mechanisms of asthma. So it helps relax smooth muscles like with some of the other more common drugs for asthma. It blocks a number of other inflammatory cytokines. These are all things that tissues release that signal inflammation cells to come on in and do their damage. So, if you can block the signal, I like to use an example, it's like when you turn the switch off on the wall. So the power doesn't get in. Final thing it does is it works on this pathway called cyclic AMP. This is very important in the balance of how our white blood cells work and by increasing its efficiency, it makes the cells less likely to be migratory and not going in and out of tissues. So it's a relative decrease in this system that seems to be a driving force for tissue inflammation. This applies to any tissue in the body but obviously, in our situation, we're dealing with the skin and mucous membranes primarily.

Dr. Fivenson: In autoimmune diseases, it's felt that, because of all this activation, there's a relative deficiency. I mean, you can test a blood level, and people have normal vitamin B3 levels but there's a relative deficiency and it has to do with this IDO pathway that you really need to understand everything about, but it's involved in a lot of primary inflammation pathways that date back to very primordial development. I think there's even some of these pathways expressed in fish, so long before mammals ever even developed. When you replace this NAD, which is what Niacinamide or Nicotinamide is metabolized to, then these aberrant pathways get the whip taken to them and they calm down. So it is really important, in not only controlling inflammation, but also controlling some of the effects of aging, effects on cellular repair, there's been some recent good evidence that taking Niacinamide helps prevent skin cancer because of that helping too repair the damage that ultraviolet light does.

Dr. Fivenson: In dermatology, this is just a list of some of the diseases that this has been used in either by itself or you'll see, I have it says +TCM and that means plus a tetracycline, not necessarily the drug tetracycline, but tetracyclines include: doxycycline, minocycline, cycling, and old-fashioned tetracycline. We also have some new ones that have come out, there's soframycin, which recently was approved for acne. All these different inflammatory diseases, though, have shown effectiveness with, either by themselves, or in combination with Niacinamide. In acne, which a lot of us suffer from, at not so young ages anymore, either, just because of their luck, their medical history, their family history, or some of the drugs that we dermatologists give our patients. There's even a very elegant pathway that I bullet pointed on the right hand side there, of how specifically works on this activator of inflammation called NF kB and that seems to be a unique thing for acne and for aging. So a lot of products these days are having topical Niacinamide in them in the beauty world and as a cosmetic anti inflammatory

type, not really an anti-oxidant but sort of in that same way that you might see other things appearing in some of the higher end cosmetics.

Dr. Fivenson: The common side effects we deal with with tetracycline either by itself or combined with niacinamide, Doxycycline primarily, but also old fashioned tetracycline can cause photosensitivity or sun sensitivity, and sometimes upset stomachs. I know one of the questions was someone had a severe upset stomach when they ran doxycycline. There are different forms of doxycycline. Some are more likely to cause an upset stomach. Some are slow release and they're less likely to. So the dosing schedule and the dosing formulation can make a big difference with tetracycline. Minocycline as you see down on the bottom, there are other more unusual things including dizziness or vertigo, increased pressure in the back of the skull, that's called pseudotumor cerebri, where there's some inflammation that makes your eyes bulge in the back and so that's an urgent/ emergency but also a very rare side effect. And it can even trigger autoimmune diseases. There's an autoimmune syndrome, a form of lupus that's very rarely associated with Minocycline. Minocycline on the other hand, actually has FDA approval as a drug for treating rheumatoid arthritis. So it's been around and acknowledged as an anti-inflammatory medicine for a long time. Then you see for Niacinamide, we call it NAM, just because it's too long of a word to say and too long to write on slides. Very rarely, do you see any flushing or stomach upset. There are isolated cases of people having liver enzyme problems, but it's hard to know if it's even related because the incidence is less than one in ten thousand, so it may be something else that happened to those few cases.

Dr. Fivenson: Now, I'm going to kind of quickly go over some of the results of using these in the autoimmune blistering diseases. In aggregate, this combination of some kind of tetracycline these days, it's usually doxycycline, but it can be any of them. In bullous pemphigoid there's a total of 197 out of 242 that have been published to date, that were responders, so about ⅔ . In cicatricial pemphigoid, ¾ of patients, although it's a small number, over 43 total cases that I found, I just recently did a review article on this so this is fairly up to date as of maybe four months ago. In pemphigus, initial responders and the definition of a response being able to get lower off of steroids for a minimum of three months time, that's the criteria that I used when I was pulling this data. 90% of pemphigus patients had at least a partial response to this combination of a tetracycline and niacinamide as a way to get off of or to very low doses of steroids. There's a few cases of linear IgA bullous disease and a few cases of dermatitis herpetiformis that have also shown responses.

Dr. Fivenson: If you look more carefully at bullous pemphigoid, the very first cases that I ever came across were published in 1986 and I was still in residency. The article that first got me interested in this and eventually led to my first grant, which was to do a blinded clinical trial of Tetracycline and Niacinamide versus prednisone in bullous pemphigoid that we did at Henry Ford and also had Dr. Korman at Case Western was also a site. It was very hard to do that kind of a study all on your own, even with some money from the FDA because these were considered orphan drugs. No drug company is going to want to put a bunch of money into

something that's already out in common use and in generic form for several decades. There's been good responses throughout the literature of combinations of doxycycline or tetracycline or minocycline up to this 180 out of 225. There's also some cases of using tetracycline by itself and having good responses. Some of these more unusual forms of pemphigoid such as radiation induced, herpes gestationis, pemphigoid gestationis that's associated with pregnancy, then I already mentioned a little bit earlier the outcomes with patients who have had cicatricial pemphigoid. This was actually a surprising number, when you look at these in aggregate, you've got 34 out of 42, so about ⅔ of people, on a disease, that is oftentimes more limited, but more damaging to the quality of life because patient's mouths are so sore, that you can get away with a good effective therapy like this.

Dr. Fivenson: The other cases that have been published in dermatitis herpetiformis, there's just a few cases and a couple of these were ours from Henry Ford back in the mid1990s. Linear IgA disease, similarly I have a couple of patients right now that are on that as their primary therapy. There's also one case where somebody had Dapsone combined with Niacinamide to help a patient. Then, also a pretty weighty amount of data in pemphigus vulgaris as well as pemphigus foliaceus, which I hope you can see on the slide. It might be a little bit below the screen. I wish there was a way to make this smaller. In pemphigus foliaceus there's about a dozen cases that have been published and ¾ of them have also shown. All of this again, is using the criteria of minimal therapy with the responses that were published by the Autoimmune Bullous Disease Consensus Group, by Dr. Werth and Dr. Murrell, showing what is a good response and minimal therapy, meaning less than 10 milligrams of prednisone, or some other non-immunosuppressive therapy. In that big category of non-immunosuppressive, this has been used a lot. And now, this is used by people really all over the world as first line, steroid sparing. Get the patient on some steroids and get them under control and try this first because it's safe. It's not gonna suppress your immune system. Other than maybe stomach upset and it's easy. If it works great, and if it doesn't work, you can always go on to something else. And nowadays, during COVID this is one of those medicines that you can take COVID vaccinations with and not have to worry about it interfering with your vaccination response. When we get to Dapsone, the same thing applies to Dapsone. So those are another advantage to those while people are working to get vaccinated.

Dr. Fivenson: Just a list of other diseases that you'll see Niacinamide use for schizophrenia, actually there's research using it back in the 1960's, in very high doses. It used to also be used to help with radiation therapy for tumors. It seems to help make tumors more sensitive when high doses of Niacinamide were given before someone goes to have radiation treatment. And even potentially has some impact on how cancer can spread. So, because this is involved in so many mechanisms of how cells work, grow, develop, et cetera it has many, many uses.A lot of it doesn't get studied because it's such an old thing that anybody can buy on a vitamin store on Amazon. All right, that's it for the tetracyclines and Niacinamide either separately or together. The next thing I am going to go over, a little more quickly, is what is Dapsone and how it works.

Dr. Fivenson: And Dapsone was originally developed as an antibiotic to treat unusual infections, particularly leprosy. It's still used worldwide as a suppressive therapy for people who've been exposed to leprosy and need to take something, lifetime to prevent the disease from becoming active. It's considered a sulfonimide, there are other sulfonamides that you may have experience with. Some of the diuretics are in that family but this one is unique in that it doesn't cross react with other sulfonamides or other sulfa allergy. So if you're allergic to Bactrim, which is a sulfa medicine, you can still take Dapsone without any cross reaction or risk of allergic reaction. It's been used in all the autoimmune blistering diseases as well as has a lot of use in other diseases like vasculitis, severe hives or urticaria. It's used in lupus as well as, in other inflammatory skin diseases like granuloma annulare and also used in severe acne. And there's a topical version that's used for both acne and rosacea. Very similar to Niacinamide, it is working on slowing the movement of your white blood cells, the neutrophils, and the eosinophils into an area of inflammation to help prevent the damage that those cells can cause when they release all their toxins. You can think of, inside these cells, normally there for killing bacteria. When we have an autoimmune disease they get pulled in as if there was something they're supposed to attack and all they know how to do is attack. They don't know how to distinguish or delineate between good and bad tissues. The side effects of Dapsone are it is a strong oxidant so anything that is susceptible to an oxidant damage will be potentially injured. Old red blood cells are more sensitive to strong oxidants. So there's hemolysis or the rupture of the older red blood cells. Everyone gets a little bit anemic when they first start it. I usually recommend that it gradually be increased so there's not a problem with too much loss of the hemoglobin level or too much weakness or tiredness that may come along from it. We have to carefully watch the blood counts. There's something called methemoglobinemia, which is a form of hemoglobin that doesn't work very well that everybody has a little bit in their system. And sometimes people on Dapsone, that can go up quite a bit. It's very important that we make sure that everyone has normal levels of our most important antioxidant in our system called glucose-6-phosphate dehydrogenase or G6PD. There are some people who, this tends to be a little bit more likely to be a genetic deficiency and they can't handle even a single 25 milligram tablet of Dapsone without severe blood loss. The blood cells rupture there, rupture of the red cells, which is the term hemolysis. Then these other rare, long term side effects from use. There's a rare peripheral neuropathy where people can numb toes and fingers who've been on it for a very long time. There's an allergic reaction syndrome, that's almost like mono, that can occur and very, very rarely, it can damage the bone marrow. So it is a powerful medicine that deserves respect but doesn't suppress our immune system and does require monitoring closely when the dose is being increased and then periodically when someone's stable on it.

Dr. Fivenson: These are just some of the outcomes that I found in Dapsone aggregate studies. Again, high percentages of patients who were reported seemed to have good responses, at least for some period of time as a steroid sparing agent. Not overwhelming and most of these people probably didn't have to stay on this drug for long periods of time, but there's subsets here. One of the subsets on the bottom, you see in red that says, “drug of choice” for dermatitis herpetiformis and linear IgA disease. Oftentimes, very low doses of Dapsone can completely control the disease and people may stay on it for lifetime. Cicatricial pemphigoid, even though

the numbers are small, amongst the bullous disease specialist community, everybody knows Dapsone is one of the goto things for mucous membrane pemphigoid or cicatricial pemphigoid. There has been a clinical trial that a number of us on the Advisory Panel participated in several years ago actually. A randomized trial studying Dapsone efficacy in pemphigus and while not a lot of patients were recruited, it did show clearly that control compared to a placebo that it was an effective therapy.

Dr. Fivensone: This is just some of the things that I regularly have my patients get for monitoring of Dapsone: blood counts, the liver function, watching to make sure things don't drop too fast. Also, I like to have people start out on an extra amount of antioxidant, that's vitamin E. Then cimetidine, the old-fashioned tagamet which was for gerd or stomach ulcers. When it's metabolized one of the it's breakdown products neutralizes some of the bad breakdown products of Dapsone. This is a weird thing in chemistry that happens, but I always put people on that for the first few months, too. So that's the last slide, and I hope I hit at least the majority of the questions that were submitted in advance. I wasn't kind of trying to check them all off, but I'll pause now, and then we can start dealing with how we want to deal with the rest of the questions that I'm sure people have.

Amethyst: Great, thank you. That was very informative. I definitely learned a lot. Like we said, if you do have any questions that you thought of during the presentation, please feel free to either type them into that question box or you can press the raise your hand button and I'll unmute you when it’s your turn to ask your question. One question that we had is, do insurances usually cover these medications for pemphigus and pemphigoid?

Dr. Fivenson: Oh, yes, these are old-fashioned inexpensive medications that are covered almost universally. Now, for Dapsone, there's only 1 or 2 manufacturers, so sometimes it gets a little bit harder to get. But, since there are very few specific disease indications and it's not super expensive, it's usually not a problem. The older tetracyclines are less than $0.50 USD or a dollar a day at most. Niacinamide, I usually have my patients buy it on Amazon. They can get 500 milligram tablets or capsules, 100 of them, for $5.00 USD. So I just have them get it that way. Also, that way I know they're getting the right thing. It's happened to me many times that if you have a patient go to a pharmacy, the pharmacist's automatically give them niacin. They don't seem to understand that 500 milligrams of niacin is not a good thing to give somebody who hasn't ever taken before, and they think it's the same thing. So, I always warn people, don't go ask your pharmacist which one to buy. Also most of the chain pharmacies only have enough to have up to 100 milligrams, even in the vitamin section. So you would have to take dozens of pills every day to get up to the adequate response, which typically I start with Niacinamide, 500 milligrams three times a day for blistering disease patients.

Amethyst: Wonderful. A question that I was actually thinking about as you did your presentation is, before a patient decides that they need to take Niacinamide, should they be

consulting their doctor versus, like you said, going on to Amazon and buying it and just taking it without consulting their doctor?

Dr. Fivenson: I think that any therapeutic change targeted at a specific immune disease should be in conjunction with your doctor. I will say however, if somebody wants to take 100 milligrams or even 500 milligrams, once a day because of these other effects that maybe helping prevent skin cancers and whatnot, it's so safe that I don't think that that's a problem. It doesn't really have any medication interactions so it's not going to mess up something else you're taking. But to get into the pharmacologic levels where, 1,500 to 2,000 or 3,000 milligrams a day, then that should definitely be in conjunction with your doctor.

Amethyst: Great. Thank you. Augustine asks, what's the big difference between tetracycline, and doxycycline?

Dr. Fivenson: It's just the chemical structure. They're very similar in their overall structure. Tetracycline is a little bit tighter, foursided molecule and it binds more to calcium than does doxycycline. If you have any calcium in your GI tract when you take tetracycline, it binds to it and then the tetracycline doesn't absorb. A similar thing can happen with doxycycline but not to the same magnitude. They both like relatively empty stomachs. That means it's a little more acidic for optimal blood absorption. Doxycycline only needs to be taken twice a day whereas tetracycline has a very short half-life and so it needs to be taken four times a day.

Amethyst: Is there a way that you determine which one you would prescribe to a patient?

Dr. Fivenson: I usually start with doxycycline. It's a twice a day medicine. In younger people, I may lean more towards minocycline but because of some of the other side effects, especially in older people who tend to have more blistering diseases, unfortunately, minocycline has a higher incidence of causing ringing in the ears and dizziness which are annoying side effects but you also don't want somebody who's a little bit frail anyway to be dizzy and then after they've been on steroids have a fall and have a compression fracture. So, that's why I kind of lean more towards that first. If someone can't handle it, they have some stomach upset and sometimes they have to take it with food. Sometimes we have to go from doxycycline hyclate to something called doxycycline monohydrate, which is a little easier in the stomach. That's one that was developed originally, also as an acne medicine. There are extended release forms, so you only have to take it once a day, instead of the standard twice a day. That's a little more expensive and some insurances don't want to pay for that unless there's a reason to, like you had a bad upset stomach with the shorter acting one.

Amethyst: Great, thank you and speaking of an upset stomach, Francis just wrote and she said, any tips for dealing with the nausea? She's on Cellcept and doxycycline.

Dr. Fivenson: Both those are drugs that are a little hard on your stomach. They both also say on the packaging from the pharmacy that they should be taken on an empty stomach. But a little bit of carbs in your stomach is probably okay. So a cracker or a piece of toast, not milk because of that calcium would neutral the doxycycline. Milk also raises the pH in your stomach. So the low pH, or the more acidic environment is why Cellcept is better absorbed. But they're both things that are rough on your stomach. So they may be a good person to talk to their doctor about one of the slow release forms of doxycycline so they don't have to take it at the same time as they're taking their Cellcept.

Amethyst: Great, thank you. How does a patient know if the Dapsone or the tetracycline is working? Should they see a significant decrease in the blistering? Is there a way to tell that? Do you do blood work to see where their antibody levels are at?

Dr. Fivenson: So we do blood work on everybody if they have high levels as a monitor. We have actually done some studies looking at levels and just like in the more powerful drugs for pemphigus patients, there is a correlation of lowering of the desmoglein levels. Unfortunately, the pemphigoid markers BP 180 and BP 230 are less reliable as a measure of disease activity in patients. But otherwise, it's mainly based on the clinical response and of course, if the person has any side effects that would limit its ability. But I would say that since I've been using these combinations for quite a few years, even though a high percentage of people will respond, there's also a good percentage that don't maintain that response. So it may work for six months or a year, but possibly there's going to be a relapse and then it might not work as well the second time and then they would have to go onto something else. But even if it's only a year or two that it keeps disease under control and it doesn't really go into remission that you might have to stop it, these are things that are safe enough that you can take for long periods of time. I have several patients who it's worked for decades and they just don't want to stop it, because they know that every time they stop it, I'm thinking of one guy who's has pemphigus who's been on this combination for about 26 years, because he was one of my patients at Henry Ford originally. He's probably on the call somewhere. He was on it for a very long time and finally went off, and within six months of stopping, he started to have the disease come back after being in remission for 14 or 15 years, from the last time we stopped it, with really no side effects. So, it's a good mechanism. This, again, is doxycycline and niacinamide not Dapsone. Dapsone is also safe for long term use but you do have to do a little bit more closer monitoring, and make sure people are not getting anemic or tired or other side effects from it.

Amethyst: Great, thank you. So patients can achieve complete remission on Dapsone and off steroids, in some cases, you've seen that?

Dr. Fivenson: Yup, definitely can occur. And that's the nature of some of these diseases, they do go into remission for long periods of time, especially in pemphigoid. All the textbooks say the average case of bullous pemphigoid is supposed to last 2 to 3 years and then goes into its

own remission. Now, be willing to bet that most people on this call are not average and probably have not had that wonderful experience of their disease just disappearing but it does happen.

Amethyst: Great, thank you. Robert asked, how long should you stay on the niacinamide and the tetracycline, after tapering off prednisone before, potentially weaning off? Do you have a standard of how long you'd like them to be on it and then say maybe we should get off of it or do you say, let's stay on it, it's working?

Dr. Fivenson: I think that my rule of thumb has been to go at least six months to a year of no disease activity. If they have measurable antibodies, it's nice to see them going lower, like in a pemphigus patient. But in a pemphigoid patient, if their disease is 100% controlled and it's been six months or a year, with no flare ups, then I start to take them off and I do it very similar to tapering prednisone. I have them decrease by one pill a month. So if they're on 3 niacinamides and 2 doxycyclines, that means that it takes a total of five months to gradually wean off. And in that period of time, if they're going to have a breakout, you can catch it and then get them back under control fairly quickly, hopefully.

Amethyst: Great, thank you. Shelly asked, what doses of vitamin E and the cimetidine that you recommend?

Dr. Fivenson: It's very easy to remember, 400 for both vitamin E. Cimetidine comes in 300 and 400 so you can just remember 400 of each. And really, that's most critical with Dapsone in the first couple of months. It's not something you have to have to stay on long term, because as the body is getting used to Dapsone that it gives you a little extra protection.

Amethyst: Great, thank you. Brian wrote in and asked dose niacinamide cause problems with liver enzyme levels?

Dr. Fivenson: So I mentioned it in reviewing things that very rarely there are cases of people having abnormal liver functions but it is so rare that it has been argued whether it's related to that or if it's something else they just happen to occur to that person while they were taking niacinamide supplementation. I personally haven't had a patient in all of them that I have treated that I've found. Now, I don't check liver functions regularly when people are on it, so it's possible. But also, there's so many other things that can make your liver functions go up temporarily. If you have 3 or 4 drinks the day before you go to have your blood drawn, your liver function can be up a little too. So hard to know.

Amethyst: Thank you. Andrea asks, do these medications lower the efficacy of blood pressure and diabetic medications like steroids do?

Dr. Fivenson: No, there's a little bit of evidence that niacinamide might actually help your diabetes drugs work better because it helps with a little bit more efficient use of glucose. It's one of those things that was studied in the early days, like in the 1950's and 1960's that never really pursued as a primary therapy.

Amethyst: Great. I know that you said that these drugs are typically okay for our patients who are worried about COVID. Are they okay to take while a patient is contemplating getting the COVID vaccine?

Dr. Fivenson: There's really no contraindications with either of the medicines that I talked about tonight, that would interfere with COVID vaccination. They don't have an effect on the production of new antibodies and even in the patients who have autoimmune blistering disease, if you have a good background in immunology or keeping up with me at the beginning, you heard me discuss about other mechanisms but there wasn't very much about changes in antibody levels or changes to the B cells. So this is a really nice opportunity for these, even if they only give you a partial response while you're getting immunized and it can allow you to get to the lowest amount of prednisone because we know that high doses of prednisone blunt your responses to the antibody production for sure.

Amethyst: Wonderful. That's good news for patients on these treatments. Sally asked, how successful is doxycycline and niacinamide in regard to ocular involvement with MMP? Are just the vitamins without antibiotics successful with ocular changes?

Dr. Fivenson: I couldn't find any good evidence for that and most people feel that with ocular involvement, you don't have a lot of wiggle room, so to speak. This is a disease where there isn't a lot of tissue to give and the outcome is really bad if you get scarring and you can't see out of your eye, which can happen fairly quickly. So, this is one of the diseases that most of us are pretty aggressive at the beginning. Maybe these would have a role in long term maintenance to help prevent low grade disease inflammation but certainly not as a primary therapy, because we want to get as much of it knocked out in a hurry so you don't get scarring and loss of vision.

Amethyst: Thank you. Can Dapsone or doxycycline affect the emotions? Somebody said that they felt like they were on an emotional roller coaster since their diagnosis and I was wondering if it has to do with the medication?

Dr. Fivenson: That sounds like prednisone to me. Probably, not these and I really don't think that there's any logical reason to suspect it. If someone was to become severely anemic, they might be a little bit more labile but mainly they'd be more tired. The same thing with the niacinamide, if for some reason you're having a side effect from it, it shouldn't make you more emotionally unstable, it just makes you feel cruddy. So I think that that's most likely a steroid thing.

Amethyst: Great, thank you. I know you talked about these drugs being pretty safe for the long term treatment of pemphigus and pemphigoid and typically, they don't have any long term side effects, bBut Joanne did ask if there are any long term side effects as it pertains to the resistance of antibiotics and the gut microbiome?

Dr. Fivenson: That's a really good question. Certainly, when anybody is on a high dose of antibiotics for a long period of time, there is a change in the gut microbiome and so the bacteria levels shift. Probiotics are really helpful for people when they have to stay on these long term. Probably the most common side effect in women is yeast infections. A lot of women have had that unpleasant experience even being an antibiotic for a short period of time. Doxycycline and tetracycline are kind of higher up on the list of potential things to cause yeast infection, which is also a microbiome change. So, I encourage my patients to take probiotics if they're prone to or if they end up having stomach upset. The good side of this is that these are antibiotics that aren't used for a lot of common infections anymore. Biggest use of doxycycline and tetracycline and minocycline is in the treatment of acne. There are kids and young adults who have to take it for long periods of time, weeks or months. There are reports of acne bacteria becoming resistant. The other things that we use doxycycline for is lyme disease and there's really been no incidents of people having resistant lyme disease. Doxycycline is like a fourth line treatment for people who are very allergic to all the penicillins and it’s used for some of the sexually transmitted diseases and also used a lot for staph infections. It's very rare to see doxy or tetracycline resistant staph infections. So, while it's a theoretical risk, it isn't a real practical thing that they've seen very often. And certainly, I can say that I haven't had it be a consequence that interfered with one of my patients or that they had some infection that came about because they were on these things for months or years at a time.

Amethyst: Great, thank you. Talking about some of the side effects, somebody wants to know will these medications cause them to gain weight like steroids do?

Dr. Fivenson: Nope. If anything, if they upset your stomach, they might make you lose a little bit of weight, just because you might not feel quite as anxious to eat. But usually people get used to that, and that's a temporary thing. But really no weight gain whatsoever, and that's one of the advantages of it being a steroid sparing agent. Most of the things we use are steroids sparing this family of diseases, things that don't make you gain weight because you're trying to get off the steroids but they have other, more significant immunosuppression so higher risk for

infections or cancer even with Cellcept or Methotrexate or Rituxan, the stronger meds that are used in these patients.

Amethyst: Great. That's good news. Augustine also wrote and he said that he's having dry and peeling skin, mostly on his feet, is that from the doxycycline or more from his disease?

Dr. Fivenson: I don't know. He probably should have his dermatologists look at that. It's really hard to know. It doesn't sound like a tetracycline related side effect if it's just chronic peeling like that. It's a good idea to show it to their doctor for sure. Things that are very common in people who are on other things that suppress your immune system are common infections like athlete's foot, which can cause dry flakey scaly feet.

Amethyst: Great. Thank you. George asked, will you repeat the usual dose and duration of the tetracycline that is safe for bullous pemphigoid?

Dr. Fivenson: It's 100 milligrams, twice a day of doxycycline hyclate, it's the most common. Then niacinamide, the other name is nicotinamide and that's 500 milligrams 3 times a day.

Amethyst: Great, thank you. Are these drugs used in combination with some of the other more common drugs, like Rituximab and IVIG?

Dr. Fivenson: Yeah, they can be and because they're considered minimal therapy under the definition and guidelines that have been published, they can be used to take the patient from the 95% improvement to get them over the hump, so to speak, to get them to 99 and 100% clearance without having to further immunosuppress them. So, if you've got somebody who's just about clear, they can be used as transition while you're waiting for something stronger to fully kick in. I always tell my patients to bridge it, don't just stop there doxycycline and nicotinamide. If they're still breaking out a little bit and I decided to put him on Cellcept, that doesn't mean you stop it tomorrow because the Cellcept is going to take a while before it starts to do its thing.

Amethyst: Great, thank you. Wonderful, just looking over and making sure that we got most of our questions answered for today. What about Doxy or Dapsone being used with topical steroids? Are there any contraindications to that or any side effects for topical steroids?

Dr. Fivenson: No, in fact, I can think of a benefit because topical steroids tend to often cause steroid acne and they're used for steroid rosacea. One of the more common things that

dermatologists treat all the time is rosacea and they use doxycycline as one of the first line therapy. Could be a benefit.

Amethyst: Could be a benefit, wonderful. Great well, I think we actually got most of our questions answered for today. I think we just had a question come in real quick. We've got a from Brian and he says, any advice on what you can do to get an effective response from a COVID vaccine for people on Cellcept?

Dr. Fivenson: The best response is if you're not on it, unfortunately. So you can ask your doctor if you're able to, what I've been advising my patients is, if they can get to whatever the lowest dose that they need to keep their disease under control. It's not the risk of their pemphigus or pemphigoid flaring to try and get that extra 5 or 10% response to the COVID vaccine. If they're on something that they can skip a week or two, most immunizations start to get a pretty good responses about 7 or 8 days after a dose. Like for my methotrexate patients, I just had them skip one dose and get their COVID vaccine 2 or 3 days after a dose. Give them a week to 10 days and then they start their methotrexate again. All my biologic patients for psoriasis, I just make sure that they get their COIV vaccine at the end of whatever cycle and then wait a week before their next dose. If it is something you take every day like Cellcept, you may not be able to stop, and there have been guidelines actually from the IPPF and the consensus has been to not interfere with stopping medicines to get vaccinations. It's more important to keep your disease under control and get your vaccine even if you might need to get a booster later on down the road.

Amethyst: Great, thank you. Yes, like Dr. Fivenson said, the IPPF does have information about that on our COVID-19 webpage that we've been working very closely with our Medical Advisers to gather information about. So if you guys have any questions about that, please reference that page as well. We've also had a COVID-19 webinars as well that you can reference in regards to the vaccine and COVID itself, so thank you for that. I know that you mentioned this in some of your slides about the effectiveness that you've seen, but can you re-iterate again, how effective the Doxy and the Niacinamide was for pemphigus foliaceus?

Dr. Fivenson: You've got to remember a simple number for almost all of the blistering diseases. It's about ¾ . If you look at those individual breakdowns, about ¾ seemed to have been able to get to minimal therapy, for at least three months, sometimes a year or two years. But like I said, the majority lose that effect and then eventually have to go on to something else, but it buys you some time. That's an easy thing to remember, 75% as a general rule.

Amethyst: That's great. Thank you. Last question here, somebody said that they were prescribed gabapentin for their pemphigoid is that common? I know it's not an anti-inflammatory.

Dr. Fivenson: I have never heard of that. Unless they were having a lot of pain or a lot of intense itching. Sometimes gabapentin is used for pain and for severe itching.

Amethyst: Great, thank you. Wonderful, well that was a very quick hour. Thank you so much for answering all those questions. I know I personally learned quite a bit about all of the drugs there. So thank you again for answering all of our questions today Dr. Fivenson.

Dr. Fivenson: It's been my pleasure. It's always good. The questions that come from the IPPF members are always challenging.

Amethyst: Wonderful, thank you. Thank you all for being on the call with us this evening, and for submitting your questions for Dr. Fivenson to answer. I'd like to give a huge thank you to our sponsors today, Genentech, Principia Biopharma, a Sanofi company, argenx and Cabaletta Bio for making today's call. Before you go, I do have a few quick announcements. Do you have bullous pemphigoid? If so, you are invited to participate in an interview as part of a research study to better understand the challenges of diagnosis, treatment, and everyday life of living with bullous pemphigoid. Contact Magnolia Innovation at ilymanscott@magnoliainnovation.com or call 914-414-6767 for more information.

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

If you have not registered for the IPPF's natural history study we encourage you to do so. The IPPF Natural History study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). You can register today at 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!

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/ or you can call (916) 922-1298, and we would be more than happy to help. Also, a recording of this call will be sent out following the call with a survey. If you could please take that and just let us know how everything is going, and what you'd like to see from us in the future. Thank you so much again for being on the call with us today Dr. Fivenson, we greatly appreciate it.

Dr. Fivenson: Thanks a lot. That was very fun. Everybody, have a good evening.

Amethyst: Have a great night. Thank you so much, everybody. Bye, Bye.