February 18, 2020 Patient Education Call Transcription

Becky: Welcome everyone, I would like to thank you for being on the call with us this evening. Our Speaker today is Doctor David Fivenson. On the call today we will discuss treatments and side effects . First let me introduce you to our speaker this evening, Doctor David Fivenson attended The University of Michigan for undergraduate and medical schools. He did 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 1989-2002 he was in full-time academic practice at Henry Ford Hospital in Detroit prior to starting this practice. He is a nationally recognized specialist in autoimmune skin disease, wound care, clinical research and cutaneous T cell lymphoma, He has published over 125 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: Thank you all for calling in tonight. This is fun for me and I hope it's interesting and informative for everybody out there in IPPF land. We did come up with a list of questions that people submitted ahead of time and Becky was kind enough to give me a synopsis of them, and it was actually a pretty long list, a lot of different issues. One of the topics that we discussed was maybe a starting point and there were a lot of questions about people who have been suggested to use Doxycycline as one of the therapies for treatment of their disease. And since I can kind of lay claim to having pushed that therapy quite a bit over the years and published quite a bit on I will start there. So the tetracyclines are a family of antibiotics and when they are used in short term they are used to kill various infections in people who may be allergic to other kinds of antibiotics. But they can also be used as long term anti-inflammatory agents meaning that they help suppress inflammation. They can be used in acne for months on end and various other diseases. In particular in our autoimmune blistering diseases they seem to work by suppressing the ability of white blood cells to move in and out of tissues. So it suppresses inflammation by way of not suppressing the immune system so they are inherently safe because they are not considered immunosuppressants. Another term that you can use is an immune

modulator, meaning that they kind of downregulate. Side effect wise, the family of tetracycline can cause stomach upset problems. It has to be taken without milk because milk products bind to them. They have a special binding place for calcium right in the middle of the molecule. Particularly Doxycycline has an outcome that can make people have an increased sensitivity to the sun so if you are taking that medication you should be using sunscreen and avoiding heavy exposure to outside sunlight. I think those were the main things that were in the advance questions about Doxycycline. I know that somebody asked about a reaction versus is their pemphigus spreading? The allergic reactions that are typically seen with these medicines are more measel kind of blotchy rashes or hives and not tender crusty bumps or blisters that are typical of pemphigus or pemphigoid. There is not much testing that needs to be done before taking these and like I said they can be used safely for long periods of time. When I recommend it I usually also recommend it in combination with a form of vitamin D called Niacinamide which also has some similar effects on immune cells, slowing their ability to move and again it's not an immunosuppressant. These are relatively weaker therapy so it doesn't work for everybody and often times it takes a good 2 to 4 weeks to know for sure if these are starting to work. Typical scenario, they are introduced as someone is slowly tapering off steroids, as a long term steroid-sparing medication. And you will hear me use that term over and over again tonight. The goal of all of these drugs to manage in managing blistering diseases is to suppress the immune system and to keep the disease under control without causing a lot of drug-related side effects. And the first line therapy in most people when they are initially diagnosed is oral steroids so maybe that would be a good segway to go back to the top of your list Becky to where people were wondering about steroids?

Becky: Sure. Absolutely, so how do steroids work with pemphigus and pemphigoid to control the disease.

Dr. Fivenson: Well systemic steroids do a number of things on our immune system and in high doses they can actually kill white blood cells that's why sometimes steroids are used in chemotherapy protocol. In high doses they slow the ability of cells to move. They also slow the growth of cells. So when someone is developing an immune reaction a number of cells in the body start rapidly growing and expanding then these would typically be the B cells which make antibodies which then attacks the skin. So we are suppressing their growth, trying to keep them in a more dormant state. So steroids work rapidly but they are not something that is necessarily

considered durable, meaning that when you stop often times the patient has only had them for short periods of time, the disease can come right back. So there can be a lot of rebounding, or ping ponging, or yo-yoing of the disease if they are not used for long enough initially.

Becky: So when you say they work rapidly, is it within a couple days that a patient would see the results? Does it usually take a week or so or more like two weeks? What is the general time frame when you start to see relief with steroids?

Dr. Fivenson: I would say that for people with an acute flare of pemphigus or pemphigoid, if put on an adequate dose of steroids that should control their disease, they should begin to see responses in 2-4 days and typically within 1-2 weeks there are no new blisters forming and things should be starting to heal. The problem is a lot of people are not given high enough doses at the beginning and they end up taking a little dose and then a little bit more and then a little more and their doctors incrementally increase it rather than “hitting it with a big stick” and getting it under control quickly. Now steroids certainly have side effects and probably everyone has heard of the things, agitation and irritability, I have heard it called “roid rage”. It can also make you gain weight, it can make you hold on to sodium so you have swelling. If you are diabetic it can make your sugars go up. If you’re prone to high blood pressure it can make your blood pressure go up. It can make you really want to eat a lot of unhealthy fried food so I always advise my patients those are the things they have to avoid the most. Certainly one can do things to help prevent some of those side effects by approaching it proactively, ensuring you exercise. Long term use of steroids can cause bone thinning and cataracts, so taking calcium and vitamin D supplements to help your bones work and stay stronger. Having regular eye exams if you are going to be on them long term. I think that other than monitoring those common side effects there is not any specific testing that has to be done on someone that is going to be on steroids for a short to medium amount of time. When I say those terms I’m talking a matter of several months but if someone is going to be on them for six plus months then they adrenal gland is no longer working properly and when they come off the steroids they have to come off a lot slower so that the adrenal gland which makes natural cortisol wakes back up properly.

Dr. Fivenson: Somebody asked the question about hemoglobin A1C levels in association with virulence of pemphigoid? I am not really familiar with any direct relation to the hemoglobin A1C levels and bullous pemphigoid however pemphigoid is a disease of people who are older in

general and often times there is higher incidence of diabetes in the population. There has been some association of pemphigoid being triggered by some of the oral diabetic medications that are out on the market these days.

Becky: We also had another question Dr. Fivenson about, can hormone treatments affect the ability for Prednisone to work in either pemphigus or pemphigoid?

Dr. Fivenson: I'm not exactly sure what hormone treatment was referred to, one can certainly take thyroid medication and it doesn't have any impact. If a woman needs to take birth control pills or estrogen replacement around menopause there is no reason that they can't take steroids. There is maybe a little evidence that birth control pills might be as effective in someone that is taking oral steroids. So for their birth control function, we usually recommend that a second form of birth control be used just in case to prevent an accident.

Becky: Great, another question has come in and they say that they have been on Prednisone for PV and are a photographer and their eye's keep getting a gooey discharge. Could this be a side effect of Prednisone?

Dr. Fivenson: That sounds like it would more likely be a form of conjunctivitis or either an allergic or infectious conjunctivitis. The one thing that can happen is blurry vision with steroids and the cornea swells when people are on more than 20-30 milligrams per day so that side effect, blurriness of vision but not a discharge, but that goes away when the steroid level comes down. That reminds me another side effect is in people that are more prone to glaucoma, high doses of steroids or even medium doses of steroids can increase the eye pressure.

Becky: Great, thank you. Another patient has written in and it is a common thing that I hear with a lot of our patients is that high dose steroids keep them awake. How do you counter this effect or what are some tips and tricks that you generally share with patients to help them be able to sleep when they are on the high dose Prednisone?

Dr. Fivenson: I try and make sure that the patients take the steroids in the morning. There is sort of a split amongst the people who treat autoimmune diseases about whether there is an advantage to split the daily dose, by taking half of the Prednisone once in the morning and then half at night works better on the immune system versus the more suppression of the natural

sleep cycle. So people who normally sleep at the night time, unless you have a midnight shift working, taking a dose of steroids can make you wired and make it hard to sleep if you take it later in the day. In fact our bodies' natural cortisol levels are highest first thing in the morning which is why we have energy when we wake up after sleeping and being well rested because we have higher levels of steroids in our system naturally, it's not just that cup of coffee.

Becky: Great, well thank you. Another question has come in and the person says, "My mom got an injection of steroids during a big flare up, is this more effective or should it be given with pills as well as having an injection?"

Dr. Fivenson: Injectable steroids, generally depending on the compound used are in lieu of oral steroids, if it's a dose equivalent sometimes the injections will be given because they work a little faster and then subsequently lower doses of oral are given because it is an additive thing. If I give you a shot of 40 milligrams of Kenalog that's about equivalent of me giving you initially 30 milligrams orally but a 40 milligram shot tappers over 40 weeks where if I give you 40, 60, or 100 milligrams or oral in one day, it's gone by the next day. So it's a more prolonged way of treatment. There are other shots that are used by injection that are less known but that is a common one and lasts in the system only about 2 weeks. Personally I do not like to give people injectable steroids only because, once it is in it's in, you can't take it out. Where if you are on pills and you have a complication or side effect you can stop taking them. Any other steroid related questions?

Becky: Yeah, so there was a question that someone submitted that states, "When I take Prednisone I feel great but when I start to decrease my medication I get a lot of body aches, especially in my knees and in my hips, why does this happen?"

Dr. Fivenson: A very good question. So what happens is as you're withdrawing from steroids is every single thing in your body, any inflammation is suddenly not had it for a long time. So if you were prone to a little bit of arthritis suddenly it gets unmapped again. If you've been on steroids for more than a few weeks, you can start to have a breakdown of muscles and can have what's called steroid myopathy or atrophy of the muscles and the muscles actually get smaller and you become weaker. I saw somebody today who has pemphigoid who just had an extremely high dose of steroids for a very serious player and she was, she couldn't get out of a wheelchair, but

she was walking last time I saw her. It can be quite a serious problem that requires time and exercise to gradually recover. Other things that can happen is when people are tapering from steroids, there can be serious outbreaks of acne-like rashes on the body called steroid acne. There can be depression because steroids give you sort of a little high sensation and when you come down off of them, your brain is suddenly withdrawing and you feel down in the dumps and it can give you a form of steroid related depression. Then very rarely there's something called steroids, psychosis, which mainly in older people when they're on higher doses of steroids, it can make them act out in ways that are not normal for their usual behavior, put it that way. They can say things, they can be sometimes very aggressive when the, you know, sweet little grandma was the nicest, kindest lady. And then she's on steroids and she's a Holy terror. So those are all things that potentially can happen. And you know, we try to advise patients as much as possible, but obviously but you can't list out everything to every single patient or nobody would fill a prescription one time.

Beky: Great. And if we could just take a quick step back real quick. There's been quite a few questions asking what is considered a high dose? Is it 40 milligrams, 60 milligrams, 80 milligrams of prednisone?

Dr. Fivenson: The best way to look at it is not an absolute number but to measure it in relationships to someone's ideal body weight. So if the ideal person weighs supposedly 70 kilograms, we're about 145 or 150 pounds, the weight for the average woman combined average with an average man. Obviously nobody weighs that but if we go a half a milligram per kilogram, so 35 milligrams and in an ideal body weight person is up to that, it's considered low to medium dose and high would be more on the order of over a half, one milligram per kilogram. So somewhere in the 60 to 80 range is what we would consider high. And then very high would be 100 to 150 milligrams of Prednisone or its equivalent on a daily basis.

Becky: Great. Thank you. And then we're also getting quite a few questions about what is a safe tapering schedule to decrease their prednisone. And I understand like all doctors are probably a little bit different and have their own opinions and patients should definitely talk to their doctor before tapering.

Dr. Fivenson: Right. I think that the advice is something that's low enough to not trigger the disease flare but fast enough that the patient begins to feel better. There have actually been some standardized published papers used in some of the clinical trials that have been done for pemphigoid and pemphigus. And oftentimes what they do is they decrease by about 10% per week. So if someone's on a hundred milligrams a day for a severe flareup of pemphigus they go down 10 milligrams a week until they get to about 40 or 50. And then more like five milligrams a week because 10% of 50 is five. And then when they get down to 20, they may go down by only two or two and a half milligrams. So it's sort of like three phases and it's actually the same rough percentage of the starting point going down in tweaks. So that's kind of a published, accepted way. Everybody has their own way of doing it obviously that's one that's out there, you can find if you look in the medical literature.

Becky: Great. Thank you. Our last question involving Prednisone that has come up says that a patient was diagnosed with PV around 2008 and was treated with coricoid therapy. They relapsed in 2016 and at that time was treated with rituximab and cortisone. But since the beginning of 2008, his nails, especially his thumbnails are completely dented. Is there a link between PV and nails becoming dented or between the medication and his nails becoming dented?

Dr. Fivenson: Temporary, horizontal dents ones that parallel your cuticle can occur in anybody who goes through an acute illness and those are called Beau’s lines. And those can be even from a bad cold. Denting that’s permanent and not going away usually indicates some damage to the nail bed. And there are some people that actually get pemphigus involvement of the cuticle and the nail bed itself, which can sometimes cause the scar issue, which would make a nail grow abnormally or look permanently dented. I'd have to know if it was a linear dent or a horizontal dent or if it was a bunch of little polka dots. If there's a bunch of little polka dots in the nail those dents you can see in someone who has nail psoriasis.

Becky: Yeah, they didn't explain any of that. So I thank you for taking a minute and talking about that. So how about if we move on to immunosuppressants? Would you explain what they are and how they work?

Dr. Fivenson: So immunosuppressants, steroids are part technically immunosuppressants. Immunosuppressants are drugs which suppress our body's ability to mount an effective immune reaction to something. Probably the simplest thing that most people are familiar with is poison ivy. That's called the delayed hypersensitivity immune reaction. So you get your skin to get exposed to something that are allergic to and then you react to it. In the skin are white blood cells called T-cells, they cause itching and blistering. The steroids suppress those. Both white blood cells from moving into the tissues. Immunosuppressants generally work a little bit farther upstream. They don't directly make the cells slow their movement they work on preventing those white blood cells from expanding in response to some stimulus. So when you get poison ivy, it's a good example to use. You have a bunch of cells that are programmed to react to poison ivy oil that started growing and expanding and then go to the skin where the poison ivy oil is at start attacking. So drugs like Methotrexate, Azathioprine, Cytoxan, Cyclophosphamide, Mycophenolate all of them suppress those white blood cells from expanding and getting ready to make the new reaction. So that's another reason why steroids work quickly because they are already working on the cells that are preformed and whereas other classes of immune suppressors work farther upstream. They're suppressing the cells from expanding in the first place but the ones that are already preformed are what the steroids are kind of taking out first. It's sort of like the steroids take out the first wave and these drugs work more on all the deeper lines of defense. If you use the analogy of the old civil war kind of reenact group with wave after wave of soldiers marching towards each other and shooting. I have a bit of an imagination for example, so I come up with some interesting things.

Becky: That’s great, you can see it. It's a good thing so you can picture it.

So in general, we have other kinds of immunosuppressants like Rituximab or Rituxan, which has become very popular for the autoimmune diseases that specifically kills a very particular target, it kills a specific cell type. The more broad spectrum immunosuppressants like Azathioprine, Mycophenolate, cyclophosphamide, they're kind of broad effectors of T cells or the T-cells that help the B-cell grow up and become antibody producing cells. They're more working upstream and they work more on the bone marrow itself. And that's why all of those cells have an increased risk of other infections because both, it's not just targeting cells that are reacting, they're more broad spectrum they target everything. It's also why some of those medications

have increased risks for white blood cell related cancers like lymphoma or leukemia over a lifetime with use. There may be a slight increased risk because they're continuously sort of beating on those cells to prevent them from growing while you're taking those medications. Anybody who goes on one of these, for a short period of time, there's not too many complications, but generally we're looking at three, six, nine months, a year or more and therefore it's good practice to make sure that person doesn't already have an active infection. A lot of times screening for anyone to make sure they haven't been exposed unexpectedly to tuberculosis or maybe a silent carrier is important. Most of these have one effect or another on our ability to make white blood cells and red blood cells. And so monitoring of those counts called the CBC or complete blood counts. Some of the medicines in his family can be toxic on the liver. So the liver test has to be done and monitoring is, there's no standard perfect set guidelines that generally when patients are changing doses, the monitoring is done more frequently, maybe every two to four weeks. And then they're on stable doses that may be and they're doing well, they may be less frequent even like every two or three months. And also another question that somebody had submitted ahead of time was how long they take our work. And, I kind of alluded to that a little bit earlier and that because they're working more upstream it takes a while for their effects to kind of trickle down to the disease activity level. And so they may take anywhere from three to six weeks to see significant effects, some of them even longer. Methotrexate, sometimes it can take even up to three months to see it's true effectiveness when it's used in some of them and the same is true for a lot diseases not just blistering diseases but even in things like rheumatoid arthritis or in psoriasis. It's been around for years for that too. So in differentiating between the different ones is Azathioprine and Mycophenolate are similar in how they work on the B cells. Azathioprine is a little bit more directly toxic to cells and less oppressive the function then is Mycophenolate. Neither of them is by themselves will wipe out large numbers of the patient's blood counts normally. Although rarely it can happen to anybody. Cyclophosphamide or Cytoxan is a little bit more specific for B cells and it's used intravenously or orally. It has a much narrower basically window, which in English means that it has higher risk for side effects. Things like bleeding in the bladder can occur and quickly lower your blood count. Also can cause a lot more GI side effects with those. We don't see too many people treated these days with Cytoxan like 15, 20 years ago it was used a lot more common.

Becky: Thank you. Are there immunosuppressants that work better for patients with pemphigus and another one that works better for patients with pemphigoid or is it just really kind of dependent on the person?

Dr. Fivenson: There's not a perfect study that I can quote, but there has been a formal clinical trial with Mycophenolate in pemphigus and since it has a little bit wider safety window, it's probably a preferred first line cell toxic immune suppressor, as the steroid sparing agents. Whereas Azathioprine is an older, cheaper medication but it hasn't had as rigorous with study. In pemphigoid it seems like Methotrexate across the board may be a better firstline drug in those patients. Although many of them also will do better on mycophenolate. There's a lot of individuals, there's not an easy things, but I know for me, I usually reach for mycophenolate first after steroids in pemphigus. Usually somebody who has failed doxycycline and niacinamide in pemphigus or pemphigoid, in pemphigoid I would more commonly, possibly consider going to Methotrexate. Now in between those is one drug that we haven't talked about called Dapsone. Dapsone is an old fashioned antibiotic, mainly developed for treating leprosy so used to suppress leprosy in people who've been exposed in rare places. It works on slowing the movement and then, and the growth of your white blood cells called neutrophils. It is a sulfon. It's not in the same family as sulfa drugs but it has the sulfur molecule in its structure. But it doesn't cross react to people who might be allergic to sulfa antibiotics. And it does not suppress the immune system. So you're not at increased risk for infection with that medicine but it lowers everybody’s red blood counts. Sometimes a little and sometimes a lot. And that can be the limiting factor because it can make you tired and weak and short of breath if you don't have enough red blood cells.

Becky: Okay. Well thank you. We have a question, is there a difference in the efficacy of Mycophenolate Mofetil (CellCept) versus Mycophenolate Sodium (Myfortic) in the maintenance of immunosuppression?

Dr. Fivenson: I don't know the answer. I'll have to beg ignorance. I think the latter one is primarily the form that’s available in Europe and the Mycophenolate Mofetil is the form more commonly available in the U.S. That’s as far as I can speak on that, sorry.

Dr. Fivenson: Okay. Another patient says that they're currently on 2.5 grams of CellCept per day. Are canker sores a common side effect of CellCept? She's been on this for two years now.

Dr. Fivenson: Yes, they are a fairly common side effects of Cellcept. Any of these medicines can because they slow the growth itself. And so anything that slows cell growth even a little bit causes the tissues of our lining of our GI track, which means from your lips all the way to the other end, those tissues are rapid growing tissues and if they have their growth slowed but you can get sores. Methotrexate actually has a higher incidence of canker sores than Mycophenolate, but it is a not uncommon side effect. Sometimes people are not sure if it's their pemphigus beginning to flare in their mouth or if it's a canker sores. But usually we can tell the difference and canker sore are usually very tiny pinpoint grey dots with red rings around them where the larger blisters and ulcers you get in the mouth from pemphigus or mucous membrane pemphigoid are larger irregular ragged red looking things. So good thing is steroids work for canker sores too.

Becky: Great our next question is, what if a patient is going onto immunosuppressants but they're flaring up right now. Do you continue to take the Prednisone while you're taking an immunosuppressant?

Dr. Fivenson: Yes. You can think of Prednisone as the bridge because it’s what works quickly and usually as soon as the patients start to have their disease slow down, they have no new blisters forming or very few. That's when typically a steroid sparing agent is started most protocols anyway. So somebody who walks in the door, new diagnosis, they get put on 60, 80 or 100 milligrams of prednisone. And it's like I said earlier, if five to seven days later, they're no longer making new blisters,that's the time to introduce the steroid sparing medication and then give that a couple of weeks to start working and then slowly start weaning the steroids down over many weeks to months. That's kind of the combination of approach that's used with most medicines and most steroid sparing drugs are meant to gradually get you off the steroids. One so you don't have an immediate rebound of the disease and also to give the other medication adequate enough time to work. The International Autoimmune Bullous Disease Advisory Group, which is people from all over the world who specialize in rare diseases actually even come up with some sort of definitions and one of the goals of therapies is to be on what's called minimal

therapies and which also means low risk and minimal therapies include less than 10 milligrams of steroids per day. Dapsone or Doxycycline and Niacinamide, and not on high dose steroids or on oral, more broad immunosuppressant drugs. So that's just kind of a defined target. And what we're trying to do with treating patients is to get to that point where we're, in other words, a relatively safe combination to keep the disease in check. So finally by an intermission person can be off therapy altogether.

Becky: Great. Thank you. Linda says that, “I use Methotrexate for PV and I have outbreaks at least once a month, so I'm put on 60 milligrams of Prednisone for four days and then taper off and then it starts to come back next month. And my doctor doesn't give me a higher dose because I have Osteoporosis. What else, if anything can be used?”

Dr. Fivenson: In short courses of steroids, I kinda said it earlier in my discussion, was oftentimes are only temporary fixes if people rebound quite significantly. So if your Methotrexate isn't holding, then you may need a higher dose to be more effective. Some people don't absorb Methotrexate very well from their GI tract and it is better to be given by injection where it can be injected just inside the belly fat, like insulin injection, so a very tiny needle. And much higher predictable blood levels of Methotrexate can be achieved that way or switching to another steroid sparing agent. Maybe Methotrexate is just not the right thing for your disease.

Becky: Okay, our next question says, “I have bullous pemphigoid for two years with prior blisters only on my feet and toes. I have been off steroids for nine months and have just begun reducing Cellcept from 2000 milligrams daily down by 250 each month. If a blister or two appears during this time, should I continue with the tapering or go back to back to full dose of 2000 milligrams?”

Dr. Fivenson: This is a good question cause I can refer back to those standard definitions that were published by that advisory group, the Bullous Disease Advisory Group and they defined something called transient leave, which meaning short-lived or a few spots that come out and either go away on their own or respond to just the topical steroids. Those don't indicate that somebody has to immediately go back on their therapy. And that's what I tell my patients, one or two lesions that over a course of a week that is not a big deal back. In fact I made a little rhyme up, my last name is Fivenson and a lot of people call me Doctor Five, so I said, if he gets more

than five call Doctor Five. And that's a good guide because if you get more than five in a week, that might be a sign that those are not just those transient ones or even get several lesions that are lasting more than five days, other rhymes with five, so it's a good, easy way to remember if you've got several spots or your few that just are not going away. Then that may be time to call your doctor and ask if you should be medication changing. But if it's just a couple that come and go within a short period of time and need some strong topical steroid on them, then that should not overall change the effect. And most people have a couple of mild blisters that develop with each step down of almost any therapy that's there winning.

Becky: Great. Thank you. Our last question on immunosuppressants says that if I'm allergic to Mycophenolate, does that mean I'm allergic to all immunosuppressants?

Dr. Fivenson: Absolutely not. It's just like if you're allergic to penicillin, you can still take other antibiotics like Erythromycin or Bactrim or Clindamycin. If it's a true allergy, it should be very specific to the drug itself. Now if you are allergic to Mycophenolate Mofitil, you might be allergic to the other form that was in the earlier question that they have in Europe. They're almost identical chemical structures.

Becky: Great. There's another question on immunosuppressants. This man's wife has worked through Prednisone and the doxy routine, has gone on to Dapsone and now onto drugs like Methotrexate. Is there any consensus on which immunosuppressant is better, his wife has a bullous pemphigoid?

Dr. Fivenson: There's probably not consensus, but I tend to like Methotrexate especially in, it could be very good in older women. Women tend to respond to lower doses of Methotrexate. And across the board the average woman is smaller than the average man so might be just the body weight thing. There's the disease, rheumatoid arthritis, which affects women far more than men. Oftentimes older women who have long standing rheumatoid arthritis, very effective disease control, very low dose for Methotrexate, 2.5 or 5 milligrams once a week. And I see that regularly. And in women who have bullous pemphigoid, a disease typically of people who are in their sixties, seventies, and eighties and beyond, very low doses of methotrexate sometimes are

effective. So I go to that first and if it doesn't work or I can't get to a high enough dose for to be effective without side effects, then I would go to something else maybe like Mycophenolate.

Becky: Okay, great. Thank you. Our next question just talks about a side effect in general, have you heard of tinnitus as a side effect for any of the PV medications?

Dr. Fivenson: Tinnitus or rain ears is that's actually with Minocycline is it's fairly common thing. And also a form of vertigo can be seen rarely with the the Minocycline and the other drugs, I'm not sure of any of the other ones specifically causing it. I know that sometimes people can get a little bit of balance problems from high dose steroids, just like the cornea swell, sometimes the inner bones of the ear swell and it can mess with your balance, but not that, not a ringing sensation in the ear.

Becky: Carol says, “I am a bit nervous about prednisone because I have muscular dystrophy and can't afford muscle weakness or wasting, what are my options for treatments?”

Dr. Fivenson: Well, if you have severe disease, sometimes you have to take steroids because they are the only thing that works fast to get ahead of the game and disease control. In patients that absolutely cannot ever take steroids occasionally other fast acting medications are used like Cyclosporin which is a transplant probe which is a little more selective for the T helper cells in the body. So it's still an immunosuppressant, but those work fairly quickly but not as reliable in the blistering diseases. The main thing in somebody who has a disease like MS or MB is to try to limit the time that they're on steroids so they don't get the muscle damage. But if you're only on steroids for a fairly short period of time, a few weeks, muscle atrophy can be fairly minimal. Plus trying to maximize, you know, good protein intake and good exercise will help keep your muscles intact while going through the steroid therapy.

Becky: Okay. Well thank you. This was a really quick hour and we have some time left. So let's try and cover as much Rituximab while we can. How does rituximab control pemphigus or pemphigoid?

Dr. Fivenson: Well, that's a pretty easy one. It kills the B cell in your body that would eventually grow up and be the plasma cells, which make the antibody so it sort of cuts down the population by going in and killing the grandparents. So it doesn't actually affect the cells that are producing antibodies already, it gets the ones that were eventually going to grow up to becoming antibody producing cells. And that's also why it takes a little while to work because it doesn't affect the cells that are already there doing it. They have a natural life cycle individually. The cells may live for one, two, or three weeks, so every few weeks portions of cells are replaced by the ones that are growing up. So that's how it works and that's why it takes a bit of time to kick in, so to speak. So most people who go on that, they'll have to go on something more short term acting first like prednisone or some kind of steroids to get rapid disease control. There are certainly, there is a push actually in Europe to use Rituximab immediately upon diagnosis. You're in this state that's hard to do because the drug has to be obtained and insurance has to be a lot more clearance and hurtles compared to some of the departments in Europe where they have it readily available and that can literally treat the patients the day of diagnosis.

Becky: So it sounds like Rituximab can be used in combination with other medications and other immunosuppressants.

Dr. Fivenson: Exactly, and it actually just like the steroid-sparing medicines we already spoke about the immunosuppressants, it usually needs something to bridge until its effect kicks in. And so I tell people, you know, up to three months to see full effectiveness from a dose and typically like the speed and getting better, but, and maybe starting to slowly wean down on certain other means of suppression. But I wouldn't want to take somebody off completely as soon as they got their dose with Rituximab because of the delay in this effect. The flip side is that Rituximab's effect on those cells is quite prolonged. The protocols that are out there typically talk about treatment, an initial treatment and then a followup treatment at six months to a year. And because the cells that it targets the effect this prolonged, it can be 18 months to 2 years until the B cell population actually comes back to normal after a single dose of that medication.

Becky: Thank you. So it kind of sounds like, at least in the with the Europe group that Rituximab would be considered the best option to try and reach and achieve remission with pemphigus vulgaris or are there other options that would work equally as well?

Dr. Fivenson: I think it's by far the best supported by data to induce remission, meaning disease in complete control and off of all therapies. Now, because the effect of that drug lasts so long, you can't say that you're in remission because you have no, no lesions, and you're not taking any pills two months after Rituxan but 6 or 8 months, 10 months, a year down the road, if you're in the same situation and we know your blood cells are starting to repopulate back to normal after the insult from the Rituxan then that's when you can safely say, yeah, this must be a remission and not on anything else and the effect of that is it's wearing off.

Becky: Great. What tests do I need to have before taking Rituximab?

Dr. Fivenson: There aren't really any required tests. It's practical because it’s an immunosuppressant to make sure that the blood counts are relatively normal, if the liver is okay and if there's not a late infection like tuberculosis. Those are kind of standard for almost anything that suppress the immune system, but there's not anything that's uniquely specific for Rituximab. Most of us that use it like to follow our patient's lab work for their disease, so we'll follow desmoglein 1 and desmoglein 3 levels. And people with pemphigus, they should come down over time as the cells that are making that antibody are gradually reduced. Unfortunately in the pemphigoid group, the blood levels of the pemphigoid and target antibodies have typically called BP230 or BP180, those are more variable and they don't always correlate with the disease activity or in a lot of people, they may not even be detectable. So but monitoring and then the other thing that's monitored after the dosing is some people will monitor the B cell counts to see if the body is starting to recover from the effect of the dose of Rituxan.

Becky: Okay, great. Our last question is what is the success rate of remission with Rituximab and how does IVIG after Rituximab treatment increase remission rates?

Dr. Fivenson: I don't know the statistics right off the top of my head, but I believe that the paper that led to definitive approval by the FDA, which was based on work mainly out of Franch, initial dose disease control in I think it was about 70% of patients. With the single dose and then dosing beyond the first year needed in, was an additional 20%. So upwards of 80 or 90% of

people will respond to Rituximab as primary therapy. IVIG works on a completely different mechanism. It actually floods the body's system with normal immune globulin so it gives a feedback signal to the immune globulins that are being produced that they don't need to make all of these other ones because they got plenty on board. And in combination with Rituxan, it's been used in patients who have particularly difficult disease control or to gain control over, where there's an alternating cycle of giving IVIG and getting Rituximab to more effectively block production and the effectiveness of the antibodies that are still there. So you're blocking it on one end from being made and you're also blocking them from doing their bad job because there's so many good guys there that the bad guys get booted out. And some of the newer drugs that are in clinical trials now are working on kind of similar mechanisms of getting rid of the so called bad or targeting the production of these antibodies that are detrimental by decreasing the antibody production or antibody numbers directly rather than killing the cells that grow up eventually to makes antibodies because it's a longer cycle there until full effectiveness.

Becky: Well that was a quick hour Dr. Fivenson. Thank you for being on the call with us today.

Dr. Fivenson: My pleasure.

Becky: It was extremely educational, always talking to you and especially having you on the call today. I'd like to also give a huge thank you to everyone on the call for joining us and a big thank you to Genentech for today's call possible. Just to close up, I have a few announcements. I know we have a lot of questions that have come in and we didn't get a chance to answer them, but our next patient education webinar will be on March 3rd with Dr. Janet Fairley for more questions and answers about treatments and side effects. If you didn't get your question answered on the call today, please email me your questions, send us your questions and we hope that we can answer them in two weeks. I'd also like to remind you that we're raising funds for this quarter's IPPF research and advocacy programs with a goal of raising $15,000. Your tax deductible donation enables the IPPF to advocate for patients and collaborate with stakeholders for the development of research of pemphigus and pemphigoid. We provide the most current information to clinicians treating these diseases, researchers investigating potential cures, and patients. With your support, we maintain relationships with congressional representatives and

other rare disease support organizations who provide the IPPF with the opportunity to advocate for those affected by pemphigus and pemphigoid. Your tax-deductible donation will help the IPPF continue the promise of new therapies, improved access to treatments, and a better understanding of these diseases through our advocacy efforts, research grant program, clinical trial support, natural history study, and biobank.

I am very excited to announce that the 2020 IPPF Annual Patient Education Conference will be held at the Treasure Island Hotel in Fabulous Las Vegas from August 21st through the 23rd! Our host this year will be Dr. Janet Fairley and Dr. David Woodley. Registration will be opening soon. We hope that you will join us this year for an educational and fun weekend!

If you have not heard, the IPPF has a natural history study! If you have not registered for the IPPF Natural History Study, we encourage you to do so. The IPPF Natural History study is a new 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 e-mail Becky Strong, at becky@pemphigus.org, or call (916) 922-1298 x:105, and we would be more than happy to help.
This call recording will be sent out with the survey following this call. Thank you everyone for joining us today, goodbye.