Anti-Inflammatories: May 3, 2023 Patient Education Webinar Transcript

Becky: Welcome everyone this webinar is now being recorded. I'm Becky Strong and I'm the IPPF Outreach Manager, and I'll be your host for today's webinar. Thank you for joining us. I'd like to thank you for being on the webinar with us, and for the support provided by Sanofi and Regeneron for making today's call possible. As we start, I'd like to kick off with a quick poll. You will see that come up now. Please let us know if you are currently taking an anti-inflammatory for your treatment of your disease, and which one you're taking. And while you're answering the poll, I'd like to introduce our speaker for today. 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 1989-2002 he was in full-time academic practice at Henry Ford Hospital, prior to starting this 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 150 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 175 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.

Becky: And if we could pull up the results of the survey. It looks like about 47% of our viewers today are taking an anti-inflammatory. It looks like 10% are taking Dapsone, 40% are taking doxycycline, tetracycline or minocycline. It doesn't look like anyone is taking a sulfa drug and then ones that are not listed is about 53%. So thank you for taking the time to answer the poll for us. As we start this webinar, I would like to go over a few housekeeping items… (Reviews Housekeeping Slides/Rules). Now it is my pleasure to hand things over to Dr. David Fivenson.

Dr. Fivenson: Oh, that was a very nice introduction. Thank you. I kind of have the, I'm not worthy sort of response to that. But I have been doing this for a while, and even though I didn't truly invent the doxycycline and niacinamide regimen, I'm certainly the one who's popularized it and done the pivotal clinical trials to get it to a point where it has become a standard of care, especially for mild to moderate disease patients. So it's

sort of my claim to fame. Thank you all for taking my medicine. It's cheap, and it works, for most people. All right, with that I'm going to give an overview. Some of this is a little technical and I won't belabor some of the higher level immunology of the way these medications work, and I'll point out some interesting tidbits about where they are used in other situations.

Dr. Fivenson: So, starting with the tetracycline family, most people would be taking either doxycycline or minocycline. But there also is the older fashioned medicine that maybe you might remember, was used for treating acne a lot is a classic tetracycline. These are anti-inflammatory medications used in low to medium dose as well as antibacterial or common skin bacteria, and rarely for other infections. They have a variety of things that they may do for inflammatory diseases of the skin and joints such as inhibiting this thing called matrix metalloproteinase which is released when you get a blister, and that's what makes the blister spread. It's one of the enzymes that kind of dissolves away at the basement membrane zone. They kind of help prevent further dissolving of the connective tissues that hold your skin together. That's another reason why they're used in various inflammatory things. Even minocycline has an approval for as an anti-inflammatory in rheumatoid arthritis.

Dr. Fivenson: Niacinamide or nicotinamide which is a precursor of nicotinic acid, or what we commonly think of as the vitamin Niacin but has a side chain which is chemically different, so it doesn’t cause the horrible flushing that high doses of niacin can. So again, we have nicotinamide and niacinamide are interchangeable names as well as niacin and nicotinic acid, which are interchangeable names. They are two different chemical structures that share identical structure except for this amide side chain and that's what makes the difference as far as side effects. It's been shown that very high doses of niacinamide might really have very little effect on the vast majority of patients and it can be taken up to as high as 5, 6, or event 7 grams per day.

Dr. Fivenson: And this is a critical cofactor in a variety of enzymes in our body to help keep energy systems flowing properly, help prevent cell aging. In fact, nicotinamide has become a popular additive or niacinamide has become a popular additive to cosmetics these days to help with aging. Orally, it also can help prevent skin cancers, it's been shown, from chronic sun damage.

Dr. Fivenson: There's a variety of specific things that are related to inflammation in the skin that are important. Phosphodiesterase is an enzyme that's involved in turning on inflammation. Some of the newer medications that are out for psoriasis and eczema target this enzyme. IgE which is involved in allergic reactions, causing histamine to release from mast cells, and which is what causes severe allergic reactions as well as hives. Its release mechanism seems to be slowed down by niacinamide or nicotinamide. Other mediators of inflammation are turned down by this drug as well as a host of other intracellular cycles are suppressed and/or alternatively up regulated to help keep the person in a kind of state of good repair rather than progressive inflammation which can be destructive.

Dr. Fivenson: I'm going to skip over this slide because it gets into some fairly sophisticated immunology. But suffice to say that this proposed mechanism has to do with how some of the regulatory enzymes that help keep DNA and its products from breaking down. If you are low in Niacinamide some of these things chew through the system and kind of eat up the reserve very fast. So by taking this, it kind of slows things down and helps stabilize, and maintain a better homeostasis.

Dr. Fivenson: This is just a partial list of some of the things that it's been used for, besides our autoimmune blistering diseases. The second bullet point here, erythema elevatum diutinum is a form of vasculitis, necrobiosis lipoidica is a chronic scarring condition in the lower extremities often seen in diabetics. Polymorphous light eruption is an allergy to ultraviolet light and a host of other things. Pellagra is actually a disease caused by chronic lack of niacinamide or vitamin B3 in your diet.

Dr. Fivenson: Outside of it, it’s been used in general to help with side effects of these medications. The niacinamide since it is a drug that helps prevent sun sensitivity in skin cancer, the combination helps mediate a little bit of the sensitivity of the sun, that that the tetracycline family have. Very rarely there are cases of people who have had flushing or liver abnormalities from taking niacinamide by itself. Minocycline we know can cause irregular pigmentation, sometimes vertigo, ringing in the ears, and even rarely some swelling in the back of the brain or trigger a form of autoimmune disease that simulates lupus.

Dr. Fivenson: When we look at the combination of the tetracycline family and niacinamide in all of the autoimmune blistering diseases, when I put this talk together and summarize data the year before last, there was close to 250 bullous pemphigoid patients that had been reported throughout the literature who showed a good responses in three-quarters of them, 197 out of 242. Aso it's 80% of cicatricial pemphigoid patients that had been reported so far and surprisingly even to me was that 80-90% of pemphigus patients, which I think of is usually a little harder to treat, have reported good responses at some stage of their disease. There's a small series of linear IgA disease patients that I and others have reported, as well as a few patients with dermatitis herpetiformis that have all shown sustained disease control with this combination.

Dr. Fivenson: The first report of this was out of the University of Chicago by Dr. Berk and Lorincz, this was back in 1986. This was when I was in residency, and that's what got me kind of turned on to this idea, and then led to the data accumulation between my work and others over the number of years since then. There have been some oddball cases, I don't know if any of you have heard of radiation therapy inducing bullous pemphigoid but there's a few cases of that out there, and this combination has been used in that. It’s been used in different formulations to treat mucous membrane, cicatricial pemphigoid and even in herpes gestationis. We generally don’t use tetracyclines during pregnancy, because they can affect the formation of bones and teeth. So that was probably a study done somewhere outside the United States.

Dr. Fivenson: This is again a little more detail into these diseases, and the different combinations that have been used in pemphigus and pemphigoid, but suffice it to say that there has been really a broad range of presentations. I can't tell you if these 66 patients all had oral disease only, or had limited disease. I would be willing to guess that they probably didn't have extremely extensive disease, because as I'll show you in a minute, this preparation takes a bit of time to work, and is just not robust enough for the really severe patients.

Dr. Fivenson: Niacinamide is used in a host of other diseases now, and in history. Even used in schizophrenia treatment and in the in the sixties, because high doses of niacinamide increase the level of serotonin in our brains, which we know is the calming, relaxing hormone. And more commonly these days if you have depression, most of the antidepressants we have that are in modern day use are serotonin reuptake inhibitors,

which means that they increase the levels of serotonin in the tissues. Not that I recommend niacinamide to treat your depression but it might make you feel a little bit better if you're on it while you are fighting your autoimmune bullous disease.

Dr. Fivenson: Now, shifting gears to that Dapsone. I'm gonna kind of quickly go over how Dapsone came into being as far as a drug for our bullous diseases, it's effects and side effects, and then we'll get to the fun part of the questions. So this was originally a drug for treating leprosy. It's a derivative of sulfa, but it's a sulfonamide, so it does not cross-react with other medications like bactrim, which, if you are allergic to sulfa because it has a different backbone structure. It's used in every inflammatory skin disease there is, all the blistering diseases, all the forms of vasculitis, many of the connective tissue diseases, even things like granuloma annulare, which, if you haven't heard of it don't worry about it hopefully you won't get it. And it is also used in common diseases, in the old days it was used for severe acne particularly because it works on neutrophils and the pus forming cells. It is used in anything that has severe allergic reactions. So eosinophils which are the allergy cells involved in histamine release in hives, as well as oftentimes the early inflammatory cells that come into sites of bullous pemphigoid and pemphigus but it is a drug which can have significant side effects. It can lower our blood counts, increase a form of hemoglobin in our bloodstream, which doesn't release oxygen, which makes your functional hemoglobin even lower. It's important that a glucose-6-phosphate dehydrogenase, our body's natural antioxidant, that this be tested before treatment because if this is very low, then even small amounts of Dapsone can be devastating. Long-term, there can be neuropathy, meaning numbness and tingling of fingers or toes. This is usually seen only after many, many years of therapy and some unusual allergic reactions that are almost like mononucleosis with liver inflammation and swollen glands. Very, very rarely it can knock down our white blood cell count to the point of being 0, which is what a granular cytosis means, it means no circulating white blood cells.

Dr. Fivenson: This is kind of the hit list of things that I was able to pull up in aggregate of the number of patients who have had good responses to Dapsone when I did this review 2 years ago. Again, you see a good percentage of the patients who were reported, had favorable outcomes. Now you have to remember that those of us who do publications in medical science, we don't publish our bad results so these may be

skewed, and but at least it's not 100% response within every single column. So you know that the doctors who are putting together these papers are giving a fair view of their experience and they're not just saying I had 10 patients that all got better and this is the wonder drug because that's not how you know clinical science works. We do lots of clinical trials and testing on new medications, and these days new drugs, particularly our new drugs for the blistering diseases have to go through very rigorous clinical trials, including placebo controls and comparators to standard of care. These historical reports that this data would come from reports based on the last 10 or 15 years, 20 years, 30 years worth of publication may not have been studies that were done as rigorously as what new drugs go through these days.

Dr. Fivenson: This is kind of an overview of what I do for my patients, and I have a handout that goes over the lab work that I recommend for baseline, and then monitoring as we gradually increase the dose of Dapsone Dapsone is a drug that you have to go up slowly because of this effect it can have on your blood count. So we gradually work up, making sure that the person doesn't get too anemic with blood work every week or 2. Then when they're on a stable dose you can back off and not have to do it quite so frequently. During the first couple of months it helps to take extra vitamin E because Dapsone is a strong oxidant and vitamin E is a good antioxidant. There's a little bit of data that the old fashioned drug for stomach acid and ulcers known as cimetidine or Tagamet is an inhibitor of one of the breakdown products of Dapsone that causes a lot of that damage. And so for the first couple of months I try to have patients take this too. I started a patient this this morning who was having rapidly progressive, mucous membrane pemphigoid. And believe it or not I forgot that this is the abbreviated version of the talk. So that's the whole presentation. I had a longer version so that's why I was rushing through it. I was thinking I had my longer version pulled up. This gives us more time for questions.

Becky: Well, if there is anything else you would like to throw in here we are happy to listen to that too.

Dr. Fivenson: As sort of as a sidebar commentating on these types of therapies, I think that if you are being treated by someone who has experience in using medications, most of us don't want the patient to be on the most toxic drug all the time. So the goal is always to get the person under disease control with the least amount of side effects and

the least amount of morbidity in getting to that disease control such as weight gain, stomach ulcers and all these lovely side effects you can have from steroids or or stronger immunosuppressants. I think it's reasonable to try these kinds of medications in mild to moderate disease patients. If somebody is very severe, they need to be more aggressive. Oftentimes these are started after an initial steroid is used to get rapid disease control because they don't work super fast. So if you present to me or one of the other doctors who specialize in this if you're having a big flare or a new diagnosis, you're still going to have to be on prednisone for a period of time to get initial disease control. And starting one of these medications while tapering, because these take a few weeks to kick in while the steroid is slowly coming down. There's a sort of an art to managing these. Generally, if you are on something like doxycycline and niacinamide, if your doctor can get you down below 20 milligrams with complete disease control that's a good checkmark, then if you can get below 10 that’s a good check mark and then gradually work off of it. If you end up staying on a very low dose, that's a sign that the medications are working. If you can't get below 20 milligrams without rapid recurrence of blistering then you know you need something stronger, the what we call “steroids sparing” medication. That’s really what, when we talk about anti-inflammatory medications that is what the goal of these are, they are steroid sparing. You can think of them as immune modulators or anti-inflammation meds, but they're not immune suppressing. So unlike the older fashion medicines like cytoxan, methotrexate, mycophenolate or Cellcept, they broadly suppress the immune system so you're at increased risk for infections. Our new secret weapon, Rituxan, that is used a lot in blistering diseases and that is a profound immune-suppressor. It selectively turns off only part of our immune system, but yet its effects last for months to years after a single dose potentially. So I guess that's the other art of medicine side of these medications, knowing how to use them, and “when to hold them, and when to fold them” so to speak in the art of managing complicated patients. I always try to get my patients off steroids if I can. I hate steroids, but I use them all the time, and I'm always trying to get patients to the lowest possible dose. Likewise with anti-inflammatory medicines like these, if the person is doing great and they have no disease activity I'm going to try and wean these off. It may take a couple of years, but if they stay in remission wonderful. So I want to go ahead and start going through some of the questions. Now Becky did give me a list

ahead of time that I thought I could just kind of quickly go through some of the patients' questions that were sent in, some of them were already answered by my presentation.

Dr. Fivenson: I talked a little bit about how Dapsone and tetracyclines work. I talked about what a good candidate is, meaning somebody who's got good disease control or moderate disease rather than severe disease. Also how and when it might be weaned, I talked about that. Somebody asked, are they strong medicines? That's a very subjective term. Their targeted medicines for inflammation that are strong in their normal disease states. Like it's a strong medicine for treating leprosy if you take Dapsone but it's a milder medicine if you're treating bullous pemphigoid or pemphigus. Doxycycline is an antibiotic that's used to treat many different kinds of infections. It's also used to treat acne so it's not super strong but yet it can give you a wicked sunburn if you're on doxycycline. In fact, I had experience with that myself last summer, because I actually got lyme disease and had to take 3 weeks of doxycycline in the middle of the summer. No matter what sunscreen I had on, I got sunburned a couple of times real bad.

Dr. Fivenson: Someone asks about kidney disease and minocycline and doxycycline are okay in mild kidney disease. Tetracycline can often be harder to clear from the kidneys if they're not functioning well. In more severe kidney disease, all of these medicines particularly doxycycline is not cleared by the kidney, so sometimes the dose has to be reduced. Minocycline is mainly metabolized by the liver, so that kind of goes by a different mechanism. Somebody asked about liver scarring. Most of these medicines are okay to take, the only one you might be to avoid is minocycline because if you have severe liver scarring and poor liver function, but our liver has a remarkable redundancy and ability to kind of overcome insult. So people can have liver scarring from 5 or 10 years of taking methotrexate, let's say, or maybe they had a history of heavy alcohol use, and got some liver damage younger in life. But if it's not ongoing, the liver has a lot of reserve, and kind of repairs some of itself to a certain extent.

Dr. Fivenson: I mentioned how long the medicines take to start working. Somebody asked if they are better in pemphigus or pemphigoid? I lean more towards pemphigoid, only because I have more experience with that and that's what I did my studies on. The data shows that they work in pretty much every autoimmune blistering disease because of how they work on inflammation. Someone also asked if they've been used in pemphigus foliaceus and the answer that is, yes, for sure.

Dr. Fivenson: There's 2 forms of doxycycline, someone asked, which is better? They both work the same, it's just that doxycycline monohydrate is sometimes easier on your stomach, but it usually cost more so usually your insurance won't cover it unless you've already had stomach upset from doxycycline hyclate which is the more common form of it.

Dr. Fivenson: Going down the list, I hit all the side effects already. I talked about what you have to do, whether someone would be able to take it. Someone asked, is there a reason you couldn't ever take these? If you have the G6PD deficiency, that glucose-6 phosphate dehydrogenase enzyme that I said has to be tested before you take dapsone. If you don't have a minimal amount of that, and small percentage of people go around not knowing that they are genetic carriers of a defect, they shouldn't take it. Or somebody who already has severe anemia, say hemoglobin under 9, probably wouldn't want to take dapsone because everyone gets a little bit more anemic when they take dapsone. Tetracyclines, as I said, are contraindicated in pregnancy. There's a little controversy about taking doxycycline if you have an inflammatory bowel disease. There's people that say it might flare it and others that say it won't. I usually have a frank discussion with the patient, and say, look, if it flares it up we'll stop it, but it's not absolutely convincing that it's going to happen to everybody. I've asked gastroenterologists and gotten the same response. If the person is doing fine, they don't care about it. If the person is flaring up, they don't want to make it worse.

Dr. Fivenson: Somebody asked, how long can you take these medications, and I've had a couple of patients with pemphigus who've been on it for more than 20 years with disease control. But yet, if they go off, they start having mild disease, so it's not curative, like some medications. But many, many years though. The same thing for dapsone, you can be on it for many, many years. People who get exposed to leprosy will be on dapsone for their entire life to help prevent the disease from becoming active.

Dr. Fivenson: Long-term side effects, not really any but I did mention them in my talk. There is somebody that said they are on dapsone for MMP, is there any data that indicates that the following regimen on similar drugs, the blood cells currently cease to produce antibodies? So this question is, are these medications curative? That is definitely a no. There is no evidence that these medicines target B cells which make the antibodies that cause our diseases and kill them like Rituxan potentially can. So they

suppress the production and they suppress the function of the antibodies. But if you stop the medications, in theory the disease process is still lying there in a dormant state, and will come back to life.

Dr. Fivenson: Somebody talked about itching on doxycycline, and wanted to know if they could take to Dupixent while on doxycycline? Dupixent is an interesting newcomer to the field, originally being developed for treating asthma and atopic dermatitis or eczema because of its effect on IgE function and on the itch mechanisms, Dupixent can certainly be taken with a lot of different medications. It's very specific in what it targets so it's not really an immune suppressor either. It's pricey though, it can be $7,000 to $10,000 a month if you don't have the right insurance, and you don't have the right doctors office that fights for your medications. Which also usually means you have to have the disease that it's approved for by the FDA. You need to have one of the diagnoses, or your doctor has to find evidence that supports you have some degree of eczema besides your bullous pemphigoid to be able to get it as a potential additional therapy.

Dr. Fivenson: We talked about the anemia parts in Dapsone and how people get it. Somebody asks, can you use it in IgA pemphigus and yes, there's a couple of case reports in IgA pemphigus for doxycycline and niacinamide. For linear IgA disease, I presented there were 7 or 8 cases of that. Several of those were my cases from when I used to be a Henry Ford. Recently, in the last 3 months I've seen a couple of new linear IgA bullous disease patients that have been started on it, and seem to be doing pretty good so stay tuned for that.

Dr. Fivenson: Does Dapsone make you more susceptible to sunburn? No, but doxycycline certainly can and tetracycline but minocycline does not increase your chance of sunburn. Can you drink alcohol while taking Dapsone or tetracyclines? It's okay in moderation, but very heavy alcohol use is obviously hard on your liver and some of these drugs are metabolized by the liver. Like they say, everything in moderation is okay. Does Dapsone come in a cream or a gel, is it effective in treating pemphigus? So it is approved as a gel for treatment of acne rosacea, which is adult acne. There are a couple of case reports of using it in the mouth for treating mucous membrane pemphigoid or for localized or persistent oral pemphigus. I've had a couple of patients I've tried it in, I'm not sure if it's something I would regularly do. It is a little hard to get

covered by insurance, even if you have acne. But there are some places, specialty pharmacies that have the drug for a modest price that your doctor's office may be able to get for you. And the last one I have on the questions that were submitted in advance is, somebody asked about their mother who is in her 90's and is it okay to take Dapsone. That really depends on her other medical problems. If she's a spry, feisty 90 year old, with a pretty good blood count, sure. If she's already got multiple other medical problems as somebody in their 90's who no doubt would more likely have, probably she's already anemic, then she might not be the greatest candidate. So that kind of is the calculus that you and your doctor would have to make to see if that was a good choice for somebody in their 90's. So with that I'm going to turn it over to Becky, for a little help with moderating other questions, and I'm going to stop sharing my screen.

Becky: So we have gotten a lot of questions in, and a lot of other questions that have been submitted since we sent those to you. Just to reiterate, we've gotten a few questions on how long doxycycline and Dapsone take to start working? I know, in the presentation you'd mentioned a while. But how long should it be before somebody expects to see results?

Dr. Fivenson: 2 to 4 weeks minimum and maybe even out as much as 8 weeks. With Dapsone, you're gradually increasing the dose. So there's a threshold for when it starts working, and that's kind of individual to individual patients. Sometimes you have to get up as high as 200 milligrams before it's fully effective. My way of doing it is I go up 25 milligrams a week, so that means it's 8 weeks to get there. For other patients, like if you have dermatitis herpetiformis, oftentimes 50 milligrams will give complete disease control, because it's so specific for that subset of patients with blistering diseases. The doxycycline and niacinamide is a little more reliable in the 2-4 week range that it starts kicking in. But again doing it while the person's on a steroid taper allows the majority of the disease gets suppressed in the short term by the steroids, while the other stuff kind of gradually kicks in.

Becky: Great, we've gotten quite a few questions on the doses of tetracycline and niacinamide that you usually put patients on.

Dr. Fivenson: So I usually use 100 milligrams twice a day of doxycycline and I usually start with 500 milligrams 3 times a day of niacinamide. I found that if the patients are not

quite fully controlled that sometimes I'll actually double the niacinamide to 1,000 milligrams, 3 times a day. If they're like 85% controlled and I'm sort of like, well do I want to give up on this medicine, or can I push it a little bit more? Because like I told you in the beginning with niacinamide you can take buckets full of it and it's safe and it's very cheap. I think you can buy 1,000 capsules on Amazon for 5 bucks. There is a lot of latitude there. It hasn't been published that I know of, to go to higher doses, but I've done it a bunch of times. So it's inherently safe. So it's one of those things that it's not quite working but the standard dose and with minocycline it's the same thing, it's a 100 twice a day with 1,500 total per day of niacinamide.

Becky: Then we've gotten a few questions as well asking if niacinamide by itself can control pemphigus or pemphigoid?

Dr. Fivenson: There's a couple of cases that are in the literature. There's a bunch more the other way around tetracycline by itself, or a tetracycline drug by itself controlling disease. I wouldn't use it as my only therapy. I just don't think it's strong enough to get disease control. For some of the other things I listed at the beginning, diseases that you can use niacinamide for as an alternative therapy, yeah, they're not as aggressive disease, they're slower to come on and to come off then I'd give it a try, but not with a bullous disease patient especially if they were severe. Now, if they were really mild and they were just using topical steroids and spot treating here and there sure, why not give it a try and see if it worked.

Becky: Okay, Brenda is asking how effective is sulfasalazine for MMP?

Dr. Fivenson: Sulfasalazine is an anti-inflammatory sulfa medicine that's been used in rheumatoid arthritis for years. Versions of it are also used to treat inflammatory bowel disease. I have very little experience, maybe a couple of patients in my entire career. And because it's in the sulfa family that does have more significant sulfa allergies so I generally avoid it. There are some really bad allergic reactions that have happened even with the antibiotic bactrim. Long term sulfa medications make me a bit skittish, and I'm a pretty aggressive clinician when it comes to giving out medication.

Becky: I completely understand that. We have also gotten a couple of questions. Are there infusions of anti-inflammatory medications or are they mostly systemic pill medications?

Dr. Fivenson: They're all pills, as far as I know, there's not any intravenous anti-inflammatory, meaning non-immunesuppressing drugs. That's kind of the beauty of it., you don't have to get it pumped into you and go through the infusion center experience, and need to have good veins. Short answer is no.

Becky: Jean is asking if you are on Dapsone and doxycycline for MMP, which drug should be weaned first.

Dr. Fivenson: So if your disease is completely controlled and it's been controlled for a long time, my preference would be to wean the Dapsone first only because it has more toxicity and your blood system. With Dapsone being like the first step on the ladder of immune suppression or immune modulation, it's got a better safety profile. So if you can get rid of Dapsone and step back to step one and still have your disease completely control that's how I would do it but it's a very subjective thing for other doctors.

Becky: Frank is asking, how long does it take to go into effect but you already answered that. You said 2 to 4 weeks. But Frank also asks, how long must a patient remain on these drugs?

Dr. Fivenson: Well, I kind of alluded that in my presentation that you need to have long-term disease control, so I look at it as 6 to 12 months after all symptoms are gone before I try to take them away and do it very slowly. But I also said I had a couple of patients who have been on it more than 20 years, so you can be on it for forever.

Becky: Okay. I think you mentioned this in the talk too but just to reiterate, because we've gotten a few questions about it, how long can it take to wean from the steroids and doxycycline medications?

Dr. Fivenson: So with steroid weaning, it's inching it down 5 or 10% of the dose every couple of weeks. That's the usual regimen that most people go by and typically you want to get the steroids either off or almost completely off, let's say 5 milligrams or less, before trying to take down some of the non-steroidal medications like Dapsone or doxycycline or whatever other one you are on. There's even a few people out there that still get treated for either MMP or pemphigus with hydroxychloroquine, Plaquenil, is still occasionally used for some patients. It's a similar drug. It's something that you can take for a really long time. Patients with lupus are on it for decades but if you are weaning down, you'd rather get rid of most of the steroids first because they have more toxicity.

Dr. Fivenson: This next question I think, is a pretty interesting one. It was pre-submitted, and I don't have a name for who did it but it says, I've read that blistering and peeling can be a side effect from taking doxycycline. How do I know if I'm experiencing this side effect, or if my disease is returning?

Dr. Fivenson: Oh, that's a good question. It's not hard for me to answer, because most of the blistering and peeling that people get from doxycycline are from sunburns because it is a strong sun sensitizer. Occasionally people have medication side effects where they get peeling of their fingertips which is definitely something we don't see in most of the blistering diseases. You don't get tiny, and I don't mean blistering where the whole skin layer comes up, but I mean just the outer layer of skin like I burned it 3 weeks ago, and now it's peeling kind of appearance. Then you can also actually see that in children who've had strep infections. It looks totally different if you know what you're looking for.

Becky: So you need an expert.

Dr. Fivenson: Or at least somebody who knows their stuff.

Becky: Our next question is, are there any natural medicines that can be complementary when taking these anti-inflammatory medicines? Maybe like a complex vitamin?

Dr. Fivenson: At this point, no. There may be things coming down in the next 5 to 10 years with specific modifications of the gut microbiome with certain supplements because there's some evidence that that can be drivers of autoimmune processes. We know, has Dr. Werth done the presentation where she talks about some of the supplements that have been known to even cause autoimmune diseases?

Becky: Not yet.

Dr. Fivenson: You should get her to do that one, because I think spirulina that has been actually known to cause dramatomyocytes. And there's a few other high levels of some of the other Chinese herbs that have been shown to cause autoimmune diseases. So while they're natural, my favorite thing to tell my patients is poison ivy is natural too, and you wouldn't want to eat that.

Becky: Well, great.Then this is, I think, an interesting question. We have a couple of questions about vitamins so I'm going to try and kind of get these together. If you are taking a calcium tablet or an iron tablet, can you take them when you're taking anti-inflammatory medications? And what should the timing be like?

Dr. Fivenson: So if you have Dapsone as your main medicine that's your anti-inflammatory then there's really not any problem with taking any of those supplements. But calcium and tetracycline and doxycycline and minocycline bind to each other very well. So if you have calcium-containing products in your stomach when you take any of those medicines in that family, they'll bind to the calcium and not get absorbed, and just pass through in your stool. So that's why you should take these medicines an hour before or 2 hours after a meal, particularly if it's a meal that has a lot of cheese, yogurt, milk or calcium-containing foods. Or if you take a calcium supplement, and a lot of our patients are taking calcium supplements because they're on steroids, and they're trying to prevent osteoporosis. Iron is not as big of an issue. In theory, it could bind a little bit to the tetracycline structure, but it's not as vigorous as what calcium is. I usually tell the patients to take it on an empty stomach, first thing in the morning, and last thing they do before they go to bed. If they really have a stomach upset from the doxycycline in particular, then I'll say have a cracker or a piece of dry toast just so there's something in your stomach, and be sure to take it with water not with juice or not with milk obviously.

Becky: Great. Does Dapsone affect the TSH (thyroid stimulating hormone) levels?

Dr. Fivenson: Not that I know of. I don't know where that would have come from. Interesting one. I guess I would have to look it up to know for sure, but I've never heard that before.

Becky: And is there any interaction with taking synthroid and Dapsone? I know you said that the calcium binds with doxycycline but I didn't know if there was anything with synthroid and Dapsone?

Dr. Fivenson: Only that, in theory you're supposed to take all thyroid supplements separate from other medications for the optimal absorption. So, having any other drug in your stomach is supposed to interfere with its optimal absorption. There is nothing special about Dapsone or doxycycline or anything else we're talking about. It's just that if you're on thyroid medicine, you're supposed to take that separate from everything else, and it's a pain.

Becky: Great, thank you. Joan is asking a really interesting question, does taking doxycycline or the tetracyclines for a lengthy time contribute to antibiotic resistance?

Dr. Fivenson: There is certainly evidence that there is a change in susceptibility of some bacteria. It's mainly going to be the bacteria in your gut. So a small percentage of people have bacterial overgrowth or things like that. But the vast majority tolerate really well. The whole concept of antibiotic resistance is, for infections that are in the community that you might use these drugs for. Doxycycline is a second or third line drug for MRSA, Methicillin-resistant Staphylococcus. If you're allergic to the penicillins and the Keflex and clindamycin you might take doxycycline but it's not a first line medication. That is why in the whole field of dermatology there has been a lot of angst about chronic use of antibiotics, especially in the acne population, because that's really where the lion's share of the drugs are used, and they don't want their acne bacteria to become resistant to it so they try to limit it. Yes, there is this possibility, but it's a lot lower risk and a lot milder side effect to have to deal with compared to how powerful some of the other drugs that need to be used are, and how toxic they are. It's an overall risk-benefit ratio that still leans way in favor of an anti-inflammatory non-immunesuppressing drug versus the potential to have some antibiotic resistance. That goes away fairly quickly if it's an innate bacteria that lives on you normally anyway, that goes away within a few weeks or months of stopping it.

Becky: Well, great answer. Thank you so much for that. Joan is asking, can you take doxycycline with Dapsone? Are they ever prescribed together?

Dr. Fivenson: Sure, I don't do it a lot, but occasionally, and they are working on different mechanisms. There's some overlap. They both work on neutrophils and eosinophils movement into tissues. There's some complimentary stuff that I said at the beginning, the doxycycline and tetracycline family suppress these enzymes that make blisters worse and break down tissue. Dapsone doesn’t do that, Dapsone really just makes it harder for those white blood cells to march into areas to attack. So, yeah, the 2 things could work together in that sense. And they both have been used as acne medicines for years in varying combinations and together for acne as well.

Becky: Great. You were talking a little bit ago about the gut biome and the doxycycline affecting that. Is there anything that we can do to protect our gut biome while we're taking these medications?

Dr. Fivenson: Do you want me to say maybe you should take a probiotic?

Becky: Just saying like maybe could it help?

Dr. Fivenson: Becky and I have known each other for a while, we could almost do a standup routine together. So yes, there certainly is a potential to do prebiotics as well as probiotics if you are one of those people who, and for more practical reasons,

ladies oftentimes will get yeast infections if they take doxycycline or any of the tetracyclines just because in that area of the body if you change the bacterial content of the the vagina then you get a yeast infection. And using a probiotic orally, helps keep the vaginal bacteria in balance and in check as well.

Becky: Great, along the gut line, can doxycycline or minocycline affect the appetite? This person is saying that they never feel hungry during the day, and they don't want things to worsen.

Dr. Fivenson: They don't want things to worsen?

Becky: I think probably they don't want their disease to get worse, but they don't want to have any ill side effects for not feeling hungry either.

Dr. Fivenson: Well. I can be a little sarcastic in these, and say that if you've just come off of 6, 8, or 10 weeks of steroids you probably put on 20 pounds, you kind of don't want to eat, you want to lose some weight. But to be a little bit more serious. Yes, they can sometimes suppress the appetite a little bit just because of this low-grade nausea that you can have. You don't want to get to the point where you're not eating enough protein nutrition to repair. So that's kind of the real serious part of being almost like anorexic which is very, very rare. You just have to kind of force yourself to make sure you get some adequate calories, but if you're really finding yourself chronically losing weight, because you're not getting in 800 or a 1,000 calories a day total then that's something you need to talk with your doctor about and and probably change medicines.

Becky: Is there any relationship between doxycycline and hair loss and weight gain?

Dr. Fivenson: I don't think so. Hair loss is very common in patients with severe medical diseases in general. It's a form of stress, it's called the telogen effluvium, which is very common where people lose a lot of hair when going through a serious illness. Often it lasts for 4 to 6 months after the initial insult, then gradually the hair comes back. It's not this kind of hair loss, this kind of hair loss has taken many years and I can blame it on my grandparents.

Becky: Okay. I think there is one more question. If the blistering in your mouth is in remission should you still stay on the medication for worries of ocular pemphigoid forming over time?

Dr. Fivenson: If it's been in remission for a long time, 6 months or year or longer, that's something you can talk with your doctor about gradually going off. It isn't necessarily

something you stop abruptly, especially if we're talking about the doxycycline or tetracycline family there's a lot of evidence that even really low doses can have prolonged anti-inflammatory effects. In rosacea there is a medication that contains 20 milligrams of slow release and 20 milligrams of rapid release doxycycline that's been on the market for years for disease control. So it's 40 milligrams a day total. Whereas we are talking about initially starting out at 200 milligrams a day. So yeah, you can get down to pretty low levels and still have that anti-inflammatory effect in place when it has no effect on your gut bacteria, no effect on your diet, and no effect on sun sensitivity.

Becky: Just a couple of last questions, is the niacinamide, tetracycline combo the preferred frontline drug for patients with pemphigus and pemphigoid? Or where does it fall in the scheme of treatment for bullous pemphigoid?

Dr. Fivenson: It is one of the preferred steroids sparing products. I want to make sure we know we're not saying frontline treatment, meaning it's the very first thing you've taken and it’s going to make you better. If you're covered in blisters and you can't eat., no, it's not going to work fast. Prednisone is like the only thing that really works fast until maybe some of the new drugs that are in development get a little bit closer that they might actually be things that work in a couple of days. But right now prednisone is our first gun. I like to try it with anybody who I can easily get control of with prednisone. Even if I got to give them a lot of prednisone, I like to see if I can wean and try that as a first line as a steroid sparing agent and emphasizing that term steroids sparing. And if it doesn’t work, you can always go back up on the steroids and try something else.

Becky: Okay, and I know you've answered this question a couple of times, but we're getting requests again about what were the doses for niacinamide and the tetracycline?

Dr. Fivenson: So the doxycycline is a 100 twice a day. If somebody uses the old-fashioned tetracycline that is probably 500, 2 or 3 times a day up to even 2,000 milligrams. Then the niacinamide is 1,500 a day, or 500, 3 times a day.

Becky: Great, well thank you so so much. You have provided a lot of insight and answered a ton of questions for our community. And I can't believe how quickly the time has gone. So thank you for joining us, Dr. Fivenson.

Dr. Fivenson: It's been my pleasure, and if anybody has other questions, I am happy to entertain them by email. Or if they pour into the chat, you can just dump them into an email and send them to me, and I can answer them later.

Becky: We will do. Thank you so much for that as well.

Dr. Fivenson: Thank you for listening in and have a great evening.

Becky: Thank you. We'd also like to say thank you to Sanofi and Regeneron for the support for making today's call possible. Our next patient education webinar will be held on June 7th, with Dr. Kyle Amber, Assistant Professor and Director of Dermatology Infusion at Rush University, Chicago, Illinois to discuss another treatment, IVIg. Registration is now open, and you can register online by using the QR code on your screen. We also want to thank all of those who participated in the Externally Led Patient Focused Drug Development meeting that we hosted on January 25th. If you didn't get to speak and share your story we are still looking for people to submit written comments. Please submit your written comments to pfdd@pemphigus.org. Written comments should cover either your disease and how it impacted your daily life or the treatments for your disease, the side effects of the treatments and how to improve them. Written comments should be no longer than 500 words and all writtens will be published in our Voice of the Patient Report and shared with the FDA and industry partners and will be used for future decision making when developing drugs for our diseases. Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! Visit www.pemphigus.iamrare.org and join today. The IPPF needs your help! Your financial support is crucial to allow us to continue to provide free programs and services like

today's webinar and our Peer Coaches. Your support also allows us to continue pushing forward research and educate doctors and dentists about pemphigus and pemphigoid. If you are interested in supporting these efforts you can become an IPPF Healing Hero. Healing Heroes make 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 and your monthly donation goes a long way. Scan the QR code or visit www.pemphigus.org/hero to support our community today. The IPPF has a number of upcoming virtual support groups across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting. Also, we are always looking to expand our support network. If you are interested in starting a support group in your region please contact Becky Strong at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients. This call recording will be sent out with the survey following this call. Thank you all for joining us. Good night.