

Dr. Korman: The people listening on the phone, certainly some other much rarer autoimmune blistering diseases that we sometimes see and need to manage. So typically for most of these diseases we want to make a diagnosis these are immunologically mediated diseases. And, we need to take a skin biopsy, we need to take a blood test and we need to make a definitive diagnosis of these diseases, which, is critical before we embark on therapy. But we'll make an assumption that the diagnosis is properly made by the physician managing these conditions, and then the question is how does one go about managing these diseases? Typically, the large, enormous majority of patients will end up on systemic steroids. Prednisone typically, and because steroids have lots and lots and lots and lots and lots of side effects. If you stay on them too much for too long, we often add a second agent or perhaps more than one agent. And those are agents that are so called immunosuppressants. Probably the two most common agents that we add our aids Azathioprine or Imuran and Cellcept or Mycophenolate mofetil. And the way that we decide which one of those agents is often based upon, we get baseline blood tests, make sure that the patient has normal kidney function, liver function, normal blood counts, not any other major issues going on. A lot of times the decisions are driven by the individual practitioners preference. Side effect profile of these two drugs usually, pretty well tolerated, Both of them usually. I mean, there's lots of potential side effects and that's the reason why we routinely do blood tests and we're typically putting people on these medicines. And typically I do blood tests about once a month. If you guys who are on the call have listened to other dermatologists, give analogous talks to what I'm giving, you'll undoubtedly hear a lot of very similar themes, but we're all different. Every physician, every dermatologist is different. So we don't all do things identically and that's, thank God, that's a good thing. You know, we're not computers where people, and we have different opinions and opinions are how we make decisions whose opinions are based on our experience they're based on facts, they're based on medical literature studies, but they're also based upon our experience. And those of us who do this a lot, those of us who are typically people that get on the telephone and talk to you guys, are people who are very experienced in this doing this for a long time.

Dr. Korman: Where was I, I was talking about how different physicians make different decisions. And I was talking about choosing Cellcept versus Imuran, the two major immunosuppressive medicines. In general I would probably say most of the time that I prefer Cellcept as long as I can get it. About three, four, five years ago, I started noticing that it became harder and harder to prescribe Cellcept. It turned out that, certainly pemphigoid patients are typically older and if you're over 65 and you have Medicare as your primary insurance, a lot of times insurances will deny Cellcept. They will say well, what kind of an organ transplant has your patient had? And if you haven't had an organ transplant, which thank God the enormous majority patients with pemphigus and pemphigoid have not had, then your Medicare insurance will deny Cellcept. And, so I've had a major problem with that until more recently, somebody helped me and enlighten me that there's this program, this is a company called Good RX. And so a lot of my patients I prescribe Cellcept through Good RX. Basically you're going through a separate insurance and you're not using your Medicare insurance. And it can be, instead of, you know, a thousand or \$1,500 a month, they can be \$50 a month. So with that in mind, I'm using a lot more Cellcept again, but certainly I use a Imuran a fair amount. Also in terms of side effects of these two drugs, the major side effects that I see and most of the see with Cellcept is it can cause some GI upset. So when we put people on it we typically slowly titrate up the dose. We don't put them on their full dose right away. We started a low dose and add more in because of gastrointestinal side effects, whether it be nausea or loose stools, those kinds of things. And people tolerate it much better and they minimize their side effects if we slowly build up the dose. We checked blood counts and kidney and liver function usually once a month and the enormous majority of patients are totally fine, but occasionally we'll notice something and we certainly pay attention to it, if we notice changes. For Azathioprine, Imuran same kind of story. You can't get upset stomach as well. I think it's a little less common. We monitor lab tests as well. Probably a slightly higher incidence of a lab test, abnormalities around the liver. So a fair amount of the time I will need to stop the Imuran because somebody's liver tests has gone up. For Imuran we actually do a blood test before we start that guides us to how to dose the Imuran. So some blood test that measures how much enzyme you have that will metabolize the Imuran and if you have a of the enzyme then you got a high dose of the Imuran

and if you have a smaller amount of the enzyme get less of the Imuran, and if you don't have enough enzyme, we actually then it's actually contraindicated, so you will not take Imuran at all. The purpose of Cellcept and Imuran is to steroid spare. It's to minimize the amount of steroids that you're on and allow us to gently taper you off the steroids while controlling your disease. And as I said, I'm talking about both pemphigus and pemphigoid and the variance that I mentioned that these are my approaches in general for patients. We're going to concentrate today on these agents cause I understand that you've had other calls with other physicians who've talked more specifically about Rituximab (Rituxan) and IVIG although occasionally or maybe even more than occasionally these days we are using more of those agents and sometimes in combination with these agents. But I'm going to mostly concentrate on using prednisone and Imuran and Cellcept and minimize my discussion about adding these other agents in and when we do it and when we don't and what are the scenarios under which those things occur.

Dr. Korman: I'm just gonna look over some of these questions so I capture some of the things that people want to know about. So how long does it take to get the disease under control? Everybody's different. There's not a right answer. If I put somebody, if somebody has brand new onset disease and I get them on some prednisone and some of the Cellcept or some of the Imuran, I'm hopeful that within several weeks to a month or two that we're going to see an excellent response in helping to shut down their disease, but everybody's different. Some people have milder disease and it's easier to get it under control and some people have more severe disease and it's harder to get it under control and harder to get it under control might mean a longer time on high dose steroids until we can start to lower them. The goal of adding these two immunosuppressive drugs is to allow us to successfully taper the person off prednisone. There's no set way to do it. The way that I do it is I don't say to the person, here's the list of how and here is timeframe of when I'm going to change your prednisone. I say, well, we're going to see you again in a few weeks and then we're going to see how you're doing and then I'm going to assess how you're doing. Then I'm going to decide what do I do. Should I and can I safely lower your prednisone, how much do I lower your prednisone? So, you know, I have

a question here. How do we decide which immunosuppressant you'll be taking? So to some extent it will depend on your other conditions. If you have any conditions that might make it a problem. But if most people don't usually have other things. And as I said, I typically prefer Cellcept over Imuran as long as I can get it. I feel that Cellcept is probably a little less immunosuppressive than Imuran. In terms of what do I mean by that, I mean immunosuppression means that your immune system is being suppressed. These are all diseases where your immune system is revved up and what we're doing with prednisone and these immunosuppressive agents is trying to suppress that revved up immune system. If a normal immune system, let me make an analogy, let's say that people on the phone who are on the phone cause their loved ones have a disease and they don't have a disease. Let's make believe a normal immune system is a fifty, on a scale from zero to a hundred. Zero means you don't have any immune system, so that's bad. And hundred means you're really revved up. Fifty means you're normal. Revved up, like you have pemphigus or pemphigoid for example. Our goal is to take that person with a hundred and get them down to 50. But there is some risk if we're not cautious about how we use the medicines that we might take their immune system down to 30 or 20 or 10 or five or two and that's where the risk comes in and that's where we manage things closely and that far we're monitoring blood counts regularly and we're listening to symptoms. We're listening to how the patient is doing and do they have a fever, do they have a bad cough, do they have belly pain, do they have the other infection somewhere? Those are potential signs that we might be immune suppressing them too much and then that needs to be managed. We need to take care of whatever that problem is that's occurred and then we need to think about do we need to adjust the medicine as a function of that.

Dr. Korman: Somebody wanted to know if Cellcept is toxic to the liver? Typically that's a very rare phenomenon. I think I just recently about a year ago saw one patient who actually have toxicity from Cellcept but the only time I've ever seen it. The liver specialist that I talked to said he had never seen it. So it's a super rare side effects. The inverse, for Imuran it's quite common. 10 or 20% of people will have problems with liver issues or when on Imuran such that I actually have to stop. Somebody wants to know, do immunosuppressants always need to be

given with prednisone? Well, the issue is if you just do prednisone alone and you don't add an immunosuppressant, you will have a much harder time getting a patient off of prednisone.

What are the side effects? I said there were a couple of side effects of prednisone that was, that was sarcasm, a couple. So weight gain and diabetes and high blood pressure, the cataracts and Glaucoma and increased risk of atherosclerosis and increased risk of stomach ulcers and thinning the bones and broken bones and need I go on? That's a bad, long, long, long list. So the reason for the immunosuppressant is to be able to allow us to minimize the dose of Prednisone so that we don't see any of those side effects, hopefully. That's not always the case.

Unfortunately, some patients will end up getting some of the prednisone side effects, so it's always a balancing act when I managed patients and try to minimize their dose of prednisone. Sometimes I will tell people, well, oh, you're getting a few blisters, how bad are they? You know, can you tolerate it? Maybe we should lower your dose even though you're getting a few spots just as long as it's not taking off because for the long term it'll be safer to you for you to be on the little less prednisone. The way that I typically manage all of these patients is that when I can get there, my goal is to taper the prednisone. When I get somebody on what I call, the full dose of the immunosuppressants of Imuran or Cellcept, and then there are the maximal amount of steroids then and they start getting better, I start lowering their steroids and I continue the lower their steroids and I keep them on the full dose of the immunosuppressant and I can keep regularly checking blood tests and seeing them and making sure that they're doing well and if their diseases under reasonably good control. As I said, we don't necessarily always aim for 100% clear, depends on the patient and what they can tolerate it, how bad it is. We certainly would like to have 100% clear, but occasionally we will balance that with the need to taper because of side effects or because of other issues. So overtime I continue to lower prednisone and often I try to go to every other day prednisone. Because every other day prednisone minimizing the side effects of prednisone. So often when I get somebody down to maybe 20 milligrams every day or so, I will start a tapering and maybe do 20 milligram one day and 10 the next. And then they reach 20 milligrams one day and five milligrams the next. And then 20 milligrams every other day and then continue to lower from there, maybe down to 15 every other day and 10 every other day, seven and a half every other day. I often go very, very

slow towards the end of tapering just to make sure that they're not going to get worse because there's not a lot of good information for how, you know when disease is coming back.

So I'd rather go too slow and not have the disease come back, certainly not come back badly.

But that's a style thing and many of my colleagues who do a lot of this don't do it exactly that way.

Dr. Korman: Somebody wants to know how do you know if your medicine is working or you're in remission? Well, pretty simple are getting blisters or you're getting raw areas? Are you itching, are you having spots that heal instantly? So I think it's pretty obvious to patients and their doctors whether or not the medicine is working and they're in remission. And sometimes if one medicine is not working, if I can't continue to taper somebody's prednisone it makes me think that maybe I have the wrong immunosuppressants. I will sometimes switch them, that's the point where I might switch them to a different immunosuppressants or in fact, even though I just said I wasn't going to talk a lot about it, that might be a time where I would say, let's go straight to Rituxan. Rituxan is approved actually for Pemphigus Vulgaris and we can often get it for Pemphigus Foliaceus. So a lot of times I go straight to Rituxan from the get go, maybe put somebody on a little prednisone until I can get Rituxan approved. But that's much harder to do for pemphigoid diseases. But for pemphigus diseases in the last several months since Rituxan was FDA approved for pemphigus it's a lot easier to do.

Dr. Korman: Somebody wanted to know about what to do about Cellcept and the insurance coverage. As I mentioned, Good RX. Somebody wants to know how long does it take to be immunosuppressed to put you into remission? I don't know, we'll have to see. Each person is different. Typically months many months, four, six, eight months would be a minimum. So usually when I start somebody on prednisone and a steroid sparing agent, immunosuppressive agent, I expect they will be, depending on how severe their diseases so everybody is different, right? So there's no cookie cutter answer to everybody's tough questions. But everybody's different and the answer is we work together, patient and doctor work together. So, I think it's hard to know how long it'll take until you're in remission. It could be a minimum of six months to a year would be probably my low level of prediction but it could be much longer. Somebody

wants to know when immunosuppressants shouldn't be used? Well, if somebody has cancer, for example, along with an autoimmune disease, well then I would be talking to their oncologist and more often than not the oncologists would be not in favor of using Cellcept or Imuran for fear that those drugs would worsen their underlying cancer. So, and then certainly other disease states where that can be the case. So it's always critical when you see your doctor that they know all of your history so that we can do the best job we can of taking care of you.

Becky: Dr. Korman, I have a question. As you are starting your dose of immunosuppression with a drug like Cellcept or Imuran, how often do you typically see a patient? Is it monthly or is it weekly?

Dr. Korman: It varies depending on the patient, depending on the state of their disease. So, you know, somebody relatively stable and I'm building them up, I might see them every two to four weeks, certainly. Typically not every week. That's overkill in my experience.

Becky: Okay and then you were talking about having blood work done to monitor the immune suppression. How often is that typically done when you're on a medication like Cellcept or Imuran?

Dr. Korman: Once a month for most of my patients. I would say the enormous majority of people once a month and as people have been on it longer and longer, if they're stable. You know when people are doing really well and they're in remission for example, and they're all done with prednisone and I'm very, very slowly tapering their Cellcept or Imuran, maybe lowering their dose a small amount every three, four, six months, I might be doing blood tests less often, even every two months for example.

Becky: Great, there is a question that came in and they're asking what type of lab work do you typically draw on a monthly basis? Is it just the white count or an ESR or?

Dr. Korman: No, it's a complete blood count, which measures the red count, the white count, the platelets. And we also get what we call it differential, which allows us to look at the subtype of white cells that are there. And that's particularly important for pemphigoid where this cell type called the eosinophils can be elevated and sometimes you can get a clue if somebody might be starting to flare if their eosinophil count is elevated. So it's called a complete blood count with differential. And then I also get what's called a comprehensive metabolic panel, which measures kidney function, liver function, most of most of the things. There is no place for a sedimentation rates or you know, you really don't need most of those. So those are the two major tests that I'm doing once a month.

Becky: Okay. Well thank you. There is a question, Wendy is saying that her husband is on a medicine like a methotrexate and that he has a low energy and is in kind of a low state, a low mood I guess she's saying. Is reducing the dose helpful with relieving those symptoms, because they are fearful of having a relapse?

Dr. Korman: You know those are the kinds of tough questions that are impossible for me to answer well on a phone call like this. So the concept is that they want to know what do we do now? And I'm not there, and I'm not seeing them and I don't know the whole story. So I can't really give a good intelligent answer that's well thought out. That takes into account everything that's going on. The answer could be that methotrexates related to the reason why this person doesn't have any energy. And the answer is it could be something else going on that is the reason for that. So what I always recommend and those kinds of scenarios is that the patient shares that with their physician. And I think that there's one really important point about your question, which is that you must, and I can't emphasize this enough, everybody must, who has pemphigus or pemphigoid and is on prednisone or on immunosuppressive agents must have a primary care doctor managing them with us, with their dermatologist. It's critical because in this kind of scenario, if I get that phone call, my answer is going to be let's get your primary care doctor to see you and evaluate you and see what they say. And then maybe the two of us put our heads together and we talk about the pros and cons of should we lower your methotrexate,

what will happen? Yes, that's true, if the methotrexate working. And methotrexate is another drug that is an immunosuppressant that's kind of steroid sparing that we use somewhat, much less but somewhat, typically for the pemphigoid diseases less for pemphigus disease, but so it's in some ways analogous, it has different side effects. We don't need to go into all of that, but the concept would be the same. Is the methotrexate the reason for these new different symptoms as or is there something else going on in? And the answer is, again, I have no idea and I can't give a definitive answer, but the key is that that it's very critical that everybody has a primary care doctor who helps to take care of them because these, you know these drugs are potent and they can cause weird side effects and dermatologists are not always going to be aware of every potential side effects or it can just be a coincidence. You know this is one thing I preach to everybody every day. Just because "A" happens and then "B" happens, you as a patient are sure "A" caused "B". I as your doctor, I'm not sure. Okay. So just as I'm on a medicine and then something happens to me, that does it mean the medicine is the reason something happens to me. So it's very, very, very important that we try to assess that. Not that we always figure it out for sure, but we certainly want to put some energy into trying to figure it out and that's where having a primary care doctor can come in handy and they can help us assess these things.

Becky: Great. There was another question. Pam is asking, does an immunosuppressant like Cellcept or Imuran make somebody more vulnerable to cancer then Rituxan or as Rituxan a drug that would make somebody more vulnerable to cancer?

Dr. Korman: Yeah, that's a great question. I don't think anybody actually knows the answer. And so let me take it one step at a time. Let's ignore the Rituxan for the moment and just talk about the risk of cancer with these diseases first, alone before we even add in the medicines and then the risk of cancer with somebody with these diseases for taking these medicines. So for many years, people talked about bullous pemphigoid which is the most common oral of these diseases and it's typically a disease of the most older people. So it's like a disease of people of average age, mid to late seventies. So, uh, there was a lot of information over the

years that say bullous pemphigoid must be associated with cancer, cause look how many people who have bullous pemphigoid get cancer. But endless studies have demonstrated just because you have "A" doesn't mean it caused "B". Just because you got cancer doesn't mean it was from your bullous pemphigoid. And the answer is if people who are old get cancer and people who are old get bullous pemphigoid and the two or unrelated. I think it's very clear that that's not the case. So then let's add in the drugs, now. What about a drug like Imuran or Cellcept? What's the risk of cancer with those drugs? Well, the diseases, these autoimmune blistering diseases are quite uncommon. They're quite unusual and there's never been any big studies of thousands and thousands of patients on these drugs to look at their risk of cancer. So there is some literature, there's some information in the medical literature about these drugs and the risk of cancer. The problem is it's in using these drugs in other disease states. And probably the biggest, most common one is the disease state of transplants. Like people who have a kidney transplant or a heart or a lung or the liver transplant. And there is an increased risk of cancer in patients on these immunosuppressive drugs when they've had a transplant and they follow those patients over the long term. The challenge is that those patients are on many other drugs that suppress their immune system at the same time. And so I don't know that that information is actually relevant to us. So my answer is I don't know. I don't think anybody knows. I am not confident that there was any increased risk of cancer. Certainly in my 30 plus years of taking care of people with autoimmune blistering diseases, I don't have the sense at all that I've seen for people with cancer who are on these drugs. I do not have that sense at all. And as I said, there's no real data about it because these are rare diseases and you'd have to follow people for a very long time. And so we don't have any actual facts, but we have my experience and other people's experience and I think most of us do not believe that any of these immunosuppressive drugs increase the risk of cancer. Although you might see that if you read it in the package insert, lots of things are written in package inserts of medicines and a lot of times they're written there because it was seen in one disease that that drug is used for. Like I just said, for patients with transplants, there is that literature. So that's why that information might be in the label, or so called package insert about these medicines. But I don't actually think it's relevant for our patients with a autoimmune blistering diseases.

Becky: Great. Thank you. Some other questions that we've received are, is it okay to get a flu shot while taking a Cellcept or Imuran?

Dr. Korman: That's a great question. So typically, so there's two kinds of, when flu season comes around, usually there's two ways to be vaccinated. One is the flu shot, which is a killed vaccine. So no one will be able to get the flu from a killed vaccine. And then many years there's also the availability of a different kind of flu vaccine that is like an inhaled one. And that is actually alive, but they call a live attenuated vaccine. So we would certainly never want to give a patient who's on steroids, prednisone and immunosuppressive agents, Cellcept or Imuran a live vaccine, even though it's a quote unquote attenuated. So a person with a normal immune system not on these drugs that are suppressing their immune system will be perfectly fine a healthy, you know, 20 or 30 or 40 year olds with no diseases can absolutely use the inhaled live attenuated vaccine with no issues. But a patient who's on immunosuppressive drugs should never use the live vaccine. As far as the killed vaccine, again, they haven't ever really studied it, but I routinely recommended to my patients and again, I've never seen any issues. I think the bottom line is, you know, you can get really bad flu and if you have risk factors for increased risk of getting flu like being immunosuppressed, I think it's probably better to get the vaccine than to not get it because you're worried that maybe it won't work as well. So I always recommend people get it.

Becky: What are your feelings on the pneumonia vaccine and the shingles vaccine as well?

Dr. Korman: So the issue with the shingles vaccine is that, there were two shingles vaccine. There was one vaccine that used to be around for many, many years, and that was actually a live vaccine. So, that was called the Zostavax, I believe is what it was called. And that one's pretty much gone and done. And we thought, we don't have to worry about it anymore, but people should double check and make sure if someone's talking to them about the shingles vaccine, that they're sure that they're talking about the new shingles vaccine, which is a killed vaccine and it's called Shingrix. So I think that's perfectly safe for patients to get kind of in an

analogous way. It's a killed vaccine in an analogous way to the flu vaccine, I would absolutely encourage people to get it. And I believe it's indicated for people over age 50 in fact. So like the large majority of people who have these diseases are going to be over age 50. So they're going to be candidates for the shingles vaccine. And I would absolutely recommend it. And then the pneumonia vaccine, the Pneumovax, same thing. It's a killed vaccine. So I don't think there's any issue and I don't remember the details of when that is indicated, but I think it's indicated also for people who are immunosuppressed. So again, I think most of our patients, if they are a candidate, I can't remember what age is, the Pneumovax is recommended, might be over 65, but I'm not positive, nobody should quote me on that. I think both of them, as long as you are sure that it's the killed vaccine for the shingles vaccine, that it's Shingrix then I think it should be totally fine.

Becky: Great. Thank you so much. That's really valuable information. There was another question about, what diet is adequate when you're either taking, immunosuppressants? Like with Prednisone, a lot of times doctors recommend to take vitamin D and calcium together. Is there any supplements that should be added or should be considered when you're taking immunosuppressants as well as any that should be avoided?

Dr. Korman: I have no idea, nobody has any idea. Patients love these kinds of questions because they think there's really some magical answer, but there isn't. So yeah, calcium and vitamin D are indicated, you know, when you're taking long term prednisone. And the other thing that may be indicated for a lot of our patients is actually prevention of osteoporosis by taking a drug like a bisphosphonate, like Fosamax or Alendronate. You know, each position and each patient there is an individual decision. But a lot of times most of our patients are going to be on long term prednisone. But you know, that's a good example of a place where the primary care doctor might be, you might want, depending on who your physician is and how comfortable they are, I will routinely put most of my, there's enormous majority of my women patients who are, you know, getting older who are postmenopausal, they are past menopause. Postmenopausal women already have a somewhat increased risk of thinning of the bones. And

if they're on prednisone that's going to do the job even more, that's going to thin their bones even more. So I will almost always put those patients instantly, right on a once a week Fosamax or Alendronate. Less so for men, because the data is not there as much and it can be a little more of a challenge. So it's sometimes it's a good question for the primary care doctor. The primary care doctor might be advised to do, for example, at bone density test to see if the patient has any issues to begin with, with thinning of their bones, so called osteoporosis. Generally these drugs are relatively safe so it might be reasonable to do it, but it's, you know, I think it's going to be different for different physicians taking care of patients. I think many dermatologists, again, who like are involved with the foundation and to do a lot of this work, most of us are very, very comfortable at least prescribing one of these agents like Fosamax, Alendronate but many dermatologists may be who are taking care of some of these patients who don't do a lot of autoimmune blistering diseases will be a little less comfortable with this and they may not do it. So that's yet another place where the primary care doctor will kick in and be helpful to allow the patient to be better managed and to make decisions that will improve their long-term health by minimizing side effects. So, I think calcium and vitamin D is a no brainer. I think anyone on prednisone should be in calcium and vitamin D. I usually recommend 600 milligrams of calcium and 400 units of vitamin D in a combo pill that you can buy at the drugstore. And I'd say take it twice a day cause you can't absorb a lot of calcium at once or you can take each of them individually. You could take the vitamin D alone once a day and you can take the calcium twice a day.

Becky: Great, a lot of great information. Thank you Dr Korman. Going back to talking about the flu. Stacy says has PV and MMP and she's on 2000 milligrams of Cellcept. She says her internist just prescribed Tamiflu since her husband has the flu. She currently does not. She's asking, could Tamiflu cause a flare and does her Cellcept need to be reduced or stopped to while she's taking the Tamiflu?

Dr. Korman: I have no idea. That's a great question. You know, if she was my patient, I would be talking to my infectious disease specialist and discussing it with them. But my reaction is, I don't

know. I mean, patients always ask tough questions and we don't always know all the answers. So I phone a friend when I don't know the answer. I have no idea what the right answer to that is.

Becky: That's awesome. And a lot of patients do experience a bit of trouble having their dermatologist and their internist talk with one another. How best do you see patients, kind of helping those conversations to happen to make sure that they get the best care possible?

Dr. Korman: Yeah, well that's welcome to health care in 2019. They're totally right. I know that. I experience it every day when I try to call people. You know, the good news for me is I've been doing this for a long time. I'd been in the same place for my whole career almost my whole career. I know people and I've built up a relationship so I can call people, but a lot of times they see new patients and then I need to call their internist and then they blow me off and they don't talk to me and they don't return my calls. And there's no good answer except for the patient to be a persistent or then to decide, well you know, this internist, if they like the dermatologist, but they feel like the internist is not helping them, then maybe it's time to find a new internist. Not easy, not easy in healthcare in the year 2019. Doctors, unfortunately, many of them are overworked and many of them don't feel like it's their job anymore to actually get on the phone and talk to a doctor. They say, well, you know, I've got an electronic medical record and you know, when I sent them a note, so leave me alone. And that's totally inappropriate in my opinion. I work very hard to get people on the telephone and talk to them and say, here's my issue. What do you think? What should we do? Can we put our heads together? And that's the way to maximize care. But well your patients to the people on the phone who are frustrated and can't get that to happen, they're right. I see it all the time and I don't have any magical solution except to be persistent and to say this is important to me. And you try to find somebody in the office that will be your advocate. Try to get to, be friendly with the physician's nurse or their front desk person and see if they can help you. When's the right time I can call maybe I can talk to the internist myself or maybe they'll return my call. These are all really hard things to do and everybody's overworked and many people feel like they can't do

it and many of them don't do it. So I absolutely agree with the observation and I don't have any brilliant ideas of how to solve it except to be a nice and persistent, which is hard to do when you're not feeling so well, especially if there's an actual problem. But the answer is that's the best that I can recommend. Sometimes the key, here's actually a good trick. Sometimes the key if you are, if you're being cared for at a major place, like at my institution at University Hospitals, Cleveland Medical Center in Cleveland, I do my best to have my patients seeing physicians that are part of my institution. Doesn't always work, people come from far away and they say no it's too far and I don't want to see that doctor that seems inconvenient. Can't I just say here and I don't want to drive. But you know, a lot of times people get the best care when they have all of their care at the same place. That's not possible a lot because a lot of people are not even in the big academic or big hospital system. They are just, this was my doctor and that's my other doctor and they don't even know each other and they've never met and they're not going to talk to each other. But sometimes the key would be to say, if it's not working, you may be asking, your dermatologist who's really sort of more the quarterback, primary care, leader of the pack here, is there an internist that you worked with more that maybe I could see? And then you and that person would have a better chance, especially if you're internist is, excuse me if your dermatologist is saying, well, I really need to talk to them, but I just can't reach them and they're not responding. Maybe today can help facilitate you seeing somebody else who will then be more on their team if they, you know, they have a relationship with them. I know this sounds in some ways unfair and not right, and why don't they do it? And I'm just telling you, I've been dealing with this my whole career and you have to get past the part where you're annoyed and frustrated that it's not right and you have to figure out how to make it better. And so that's what some of my little suggestions and ideas are all about.

Becky: No, thank you Dr Korman your insight and having that insider knowledge is definitely helpful for our community. So thank you. Somebody is asking, is Cellcept bad for my teeth? I was told by my doctor that my prolonged use and questioned me or whether I had continual need to drink and he's the first person ever asked me this and when I answered, definitely he blamed it on the Cellcept.

Dr. Korman: I have no idea. I've never heard of any issues with Cellcept and dental stories. So, I don't know. I'm not sure I have a clue what, what this person is talking about. When they say a continuous need to drink, that means drinking fluids or that means drinking alcohol. Is that clear to you?

Becky: I think it's probably fluids like non alcoholic beverages. More like water or something.

Dr. Korman: Okay. Yeah, I don't really understand this question, meaning that I don't believe there's any relationship whatsoever with Cellcept and teeth. So I mean I think the answer is doctors do a very good job when they are asked questions that they don't know the answer to, of making up answers and hoping the patients will take the answer and run with it. Okay. So my, my skepticism when I read and hear this question is it sounds like somebody who is not even taking the patient seriously and they're just saying, oh yeah, that's definitely related to that. To me it sounds like utter nonsense. It's Cellcept would have anything to do with one's teeth. Okay. So what I would recommend here is how about that patient go see a dentist and see if the dentist can find something wrong with their teeth and whether or not that can be treated and managed. And I doubt the dentists will have a clue whether it's related to Cellcept. That dentist probably can't even pronounce Cellcept or Mycophenolate Mofetil and is probably never heard of it. So my skepticism is, I doubt there's any relationship here. I certainly never heard of it. And my opinion is I doubt it. That's not the same as I'm positive there's no way that it could be. It's just I am very skeptical that that's my first reaction.

Becky: Okay, no, thank you. I'm Sheila said that she was on 2000 milligrams of Cellcept for three months and it looked like her symptoms were managed and she was clear. She said her doctor didn't have her taper the Cellcept but just rather stopped it. And within three weeks she had an extreme flare up, with symptoms on the bottom of her feet were much worse and she wants to know if that is common and if you should taper coming off of Cellcept.

Dr. Korman: Yeah, absolutely. So I alluded to this before when I said that we build up a dose of Cellcept. We typically put people just on a significant amount of prednisone at the get go with whatever's wrong. Whether they have bullous pemphigoid, they have pemphigus, they need a bunch of prednisone and we just put them on a bunch on 60 milligrams for example, if they have bad disease. But then the cellcept like I said earlier, we build it up slowly because it takes a while to work. And because I'm concerned about potential a GI issue so that it can cause, you know, bloating and nausea and diarrhea, that kind of stuff. So the inverse, when you're taking somebody off Cellcept, especially if you're taking them off for the reasons that Sheila is coming off it, which is she's doing well, why would you just stop it cold turkey? I don't agree with that at all. I typically taper it and I taper it rather slowly. So let's say and this doesn't talk about if she's on prednisone at the same time or not. I gather that she wasn't on prednisone because I have this question typed in front of me after steroids calmed her symptoms down suggesting that she was put on steroids suggesting that you wasn't previously on them. So I would, there's no way that if I was managing this I would have done things like that. The only time that I would stop Cellcept or Imuran was if I thought there was a significant important concerning side effects. A rare thing like the the would be kidney function was awful or the blood counts were going down or things like that that I found on the routine blood tests. So otherwise I would, I typically tape Cellcept. So a typical dose and Cellcept for most people is 1500 milligrams twice a day. So it comes typically in 500 milligram tablets so people are typically taking three tablets in the morning, three tablets at night. And if, let's say she was on four tablets, two tablets in the morning, I presume it to at night. And if she was doing well after three months, I would have said, okay, let's try to taper you down from 2000 to 1500. Let's take you from four pills to three. And then if she were doing well two or three or four months afterwards, I would have said, okay, let's take away one more pill. So I might have taken a year to taper this young lady off of Cellcept and she was taken off into all instantly. And that doesn't surprise me that she had a bad flare when she it was stopped cold turkey as I would call it.

Becky: Okay, thank you. Cohea asks, do you give a combination of cellcept HCQS? That's the combo her Dad is on for oral MMP and he's not taking any steroids anymore.

Dr. Korman: I'm sorry, what's the abbreviation? H what? Who?

Becky: H as in Henry, C as in cat. Q in quiet and S as in Sam.

Dr. Korman: Not sure I know what that is. Is that it's hydroxychloroquine even all the letters don't fit? And the answer is no, I don't use that combination. So I can't really comment on it. It sounds like something that somebody thinks it's helpful and I wouldn't tell them that it is, and I wouldn't tell them that it isn't because I haven't used it, but I'm also making your guess as to what the medicine. Hydroxychloroquine as a drug that is much more commonly used to treat things like a skin lupus. It's not typically used at all in the place of blistering diseases. So I can't comment on it.

Becky: Okay, and Trini says, are there any increased risk the longer that you're on Cellcept? I've been on Cellcept for over five years for PV, 2000 milligrams a day. The last time we tried to reduce the dosage, I had a major flare but I'm worried about Multifocal leukoencephalopathy.

Dr. Korman: Yeah, so the package insert for Cellcept talks about that mouthful, we'll call it PML. Okay, cause that's much easier to say. The first letter for P is progressive. It's progressive multifocal leukoencephalopathy. And that's in the package insert, it says that Cellcept might cause that. Fortunately the good news is that Cellcept has never caused that in a patient with an autoimmune blistering disease like pemphigus or pemphigoid. And so it's hard to stop people from worrying and when they read about a side effect, they definitely get worried about it. So I can't tell them that, you know, that it won't happen. I can only tell them that I'm not sure it's a relevant side effect. I think that it's in there because that has occurred to people on Cellcept, but it's occurred to people on Cellcept maybe two or three or four or five or six other immunosuppressive agents at the same time. And who had other diseases like Lupus and cancer and transplants and things like that. So typically, especially if she's on cellcept only or maybe Cellcept even with a little steroid, the likelihood that she's at risk for this PML I think is very, very, very, very, very low.

Becky: Great, thank you. Ashley asks, is methotrexate a downgrade from Cellcept? Which one is more effective for treating pemphigus foliaceus?

Dr. Korman: Yeah, so you know, in terms of like grading things, they're aren't good enough studies to say, "A" is better than "B" is better than "C" is better than "D". We don't use a lot of methotrexate to treat pemphigus. So there isn't a lot of information and I barely use it at all in that place. But I wouldn't really use the word downgrade. I would say if somebody were on Cellcept and things weren't going well enough or they had a side effect and they needed to stop it, I would actually consider, depending on how severe their diseases in April, April of 2019 with Rituximab approved, I would talk about Rituximab instead of going to a drug like methotrexate. But there's no right or wrong answer and I can't really answer her question of, is this a downgrade? The answer is, if they try it out and it works and it's a good idea and if they try it out, if it doesn't work, then maybe it wasn't a good idea. So I'm not saying she should not take the methotrexate and that she must go on. Rituxan, I'm saying if she's already embarked on the path on methotrexate, I think it's okay. Generally pemphigus foliaceus is a little less severe than Pemphigus vulgaris and so methotrexate might be a very reasonable choice and it might help. She would probably shouldn't give it a few months to see how it works. And notice I did not specify how many. I said a few. I would say on purpose more than three would be my answer.

Becky: Great, Ira says that they're on monthly IVIG infusions for MMP and taking mycophenolate and Cellcept as a companion drug. They don't really fully understand what the two drugs are doing together. Can you explain how those work together?

Dr. Korman: No, not really, but I can try. So we often do combine things. So that rituximab works. Is that Rituximab?

Becky: No IVIG

Dr. Korman: IVIG, Cellcept and Rituximab. I thought I heard that. No?

Becky: Oh, sorry. I might've misspoke.

Dr. Korman: Okay so I've told you how Cellcept works. That it's kind of a broad immunosuppressant. It's sort of knocks down the inflammation. Remember we talked about 50 being in the normal level of immune activation in a hundred would be a really revved up immune system and zero would be zero, might be dead. It might be like, well, you have no immune system, so you're not really actually able to function. So 50 is normal. The purpose of Cellcept is to take somebody who's sitting at 60 or 70 or 80 and try to get them down to 50ish. Okay. So when you add IVIG I, we don't really have a clue what IVIG does. It's a very, very broad commish or mix of a whole bunch of stuff. The way it's made is that tens of thousands of people's blood are combined to take out the good part. The so called the antibodies and those antibodies are they given to you in a infusion, once month typically or sometimes a little more often. And there's like endless amounts of studies to suggest that it works like this, it works like that, it does this. It overwhelms the immune system. It gives you new antibodies that are better than the old ones. It knocks out the bad ones, it blocks them. There's no really great understanding of it. That thing that's good about IVIG is that typically it's not considered immunosuppressive. So that's a very nice thing because prednisone is immunosuppressive cellcept as immunosuppressive. So IVIG can help and there's no question about it, there is reasonable data that it can be valuable in a pretty much all of the autoimmune blistering disease. Better data is in some than others. Probably best data for pemphigus and less great data for pemphigoid but certainly lots of clinical experience to suggest it's valuable, but I don't think we really have a clue how it's working. And I told you about the advantage that it's not immunosuppressive. What's the disadvantage? Well, it's an intravenous thing. It needs to be done regularly. It is outrageously expensive. And so a lot of times it's a good idea and then insurance laughs at you and says forget it, you can't do it. So it can be challenging to get people on it because of cost. But when I do it most of the time it can be very, very helpful. And, I like the idea of combining it with other things. I will often combine it to help somebody quote unquote, steroids spare. So somebody is on prednisone and Cellcept and I'm having a hard time

tapering their prednisone, one technique would be to say, well, Cellcept isn't working so I better get rid of Cellcept and I alluded to that earlier and I said, all right, well let's change the immunosuppressive agent to Imuran. But then another thing that you could do if you could get it approved in such a scenario would be to say, let's add IVIG and let's see if that will allow us to get the patient better and taper off the prednisone that we were having trouble tapering before. So I didn't entirely answer the question because I don't think anybody has a good answer for how does IVIG work along with and in combination with other therapies. But the answer is we do know that it does work. We have a good amount of experience that it works, but we're moderately puzzled as to why or how it works. If you brought in a panel of us and you asked everybody to talk about it, we would all yell and argue with each other. And when we're all done, you will not understand any more than you do right now.

Becky: No, that's, it's a great answer. It gives a little insight. This was a question when you're talking about how revved up your immune system is if you're at 50 or a hundred. The question is, are there tests to gauge and that would just be testing for your auto antibody level, correct?

Dr. Korman: No, I don't think that that really gives you the answer. It's not definitive enough. So when we're making a diagnosis of somebody we're measuring, typically we're measuring their antibody levels. We will also do this test called an ELISA, which measures how many pemphigus antibodies you have or how many pemphigoid antibodies you have. But the studies are not definitive enough so that if I had all the numbers of everybody on the phone who has these diseases and I had to know 60 people with pemphigus vulgaris and they're a antibody levels ranged from five, which would mean actually they don't have it because I think an active number is above 10 or 12 if I remember correctly, a up to 200. It wouldn't correlate that the people who have a 200 antibody are much worse than the people who have a 20 antibody. Okay, so the antibody number, the quantitative measure of how much pemphigus or pemphigoid antibody you have in your blood is not a direct correlation to how bad your diseases and how bad your immune system is doing. There isn't really a great answer because each person, this is high level stuff that we don't understand. How does, why is it that person

“A” has 20% of their body covered and I put them on medicine and they respond beautifully. And why is it that person “B” also has a different 20% of their body covered and I put them on the same medicine and they don't respond well at all. I don't know the answer, nobody knows the answer to that. And part of the reason that we don't know the answers to things like that is because these are super rare diseases and we don't have enough people to be able to do studies that try to answer questions like that. So again, people have opinions about how that works, but nobody actually knows. So there's really no way to assess the status of one's immune system. How badly hyped up your immune system, there just really is not any good number that's an objective piece of data of how hyped up your immune system is, how close to a hundred it is. If a hundred is the worst that can be, there's no tests that we can do that helps us figure that out. And the test of how good you are getting close to 50 is kind of just an obvious one of, hh, your disease diseases getting better. Oh, you're not getting any more blisters or erosions or itching or high flight spots and we're tapering your medicine and you're continuing to get better. So then I say, well, you're kind of getting back towards normal it seems, probably, hopefully. But there's no definitive answers to these things.

Becky: Well geat, Dr. Korman that was a quick hour. I'm sure that there's a lot of more questions out there that we could ask. But I just want to say thank you for being on the call with us today. It was extremely educational, having you here and I just want to give a huge thank you for you on behalf of everybody.

Dr. Korman: Well thank you, I'm happy to do it.

Becky: Just a few announcements here. At the end of the call, the IPPF awareness program has launched a new awareness campaign that stresses the importance of a biopsy when diagnosing pemphigus and pemphigoid to help accelerate diagnosis time. Your tax deductible donation this quarter, will support the biopsies saved lives campaign and that will educate and encourage dental professionals to consider a biopsy sooner in order to diagnose patients faster. We are counting on you to make a difference in the lives lives of pemphigus pemphigoid patients and

their families by helping us accelerate diagnosis times donate today and help us reach our goal of reaching \$15,000. If you haven't heard the IPPF has a natural history study, if you haven't registered for the natural history study, we encourage you to do so. The IPPF natural history study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the U.S. Food and Drug Administration, the FDA. You can register today at www.pemphigus.iamrare.org. This online data system collects, stores and retrieves patient data for analysis and research studies. The more data we can collect, the better information we can give to researchers like Dr Korman. The sooner we can find a better treatments, earlier diagnosis and one day even a cure. The IPPF is also pleased to announce the date and place of the 2019 IPPF Annual Patient Conference. This conference will take place in Philadelphia from October 11th to the 13th. It's our 25th year as an organization and we hope that you will join us for an educational and fun weekend in the city of brotherly love. More registration details or to come in the next few months but mark your calendars and we hope to see you there.

Our next patient education call will be on Thursday, May 16th from 10:00 AM to 11:00 AM Pacific Standard Time with Dr. Margaret Michalska, who is the medical director of immunology at Genentech to discuss rituximab and Genentech Access Solutions for patients. Registration details for the May call will be on our website. Lastly, if you have a question today that didn't get answered on the call or have additional questions, please email me the IPPF outreach manager, Becky strong at becky@pemphigus.org or call me at (916) 922-1298 extension 105 and I'd be more than happy to help. This call recording will be sent out after the call with a survey. Thank you for listening. Good night.