Bonus: Managing Systemic Therapy for Acne Across the Spectrum of Disease (Sponsored by Almirall)

Linda F. Stein Gold, MD, FAAD, interviewed by Jacquelyn Dosal, MD, FAAD

JACQUELYN DOSAL, MD, FAAD: Hi, welcome to *Dialogues in Dermatology*. Today's episode is sponsored by Almirall. My name is Dr. Jackie Dosal. I'm coming to you from Skin Associates of South Florida, in Coral Gables, Florida. And I'm here today interviewing Dr. Linda Stein Gold, from Henry Ford Hospital in Detroit. And today, our topic is Managing Systemic Therapy for Acne Across the Spectrum of Disease. Dr. Stein Gold is a Professor of Dermatology at Henry Ford. She's served as the Vice President of the AAD, as well as on the Board of Directors. And she has a special interest and expertise in acne. So we're thrilled to have you today, welcome.

LINDA F. STEIN GOLD, MD, FAAD: Thanks so much for having me.

JACQUELYN DOSAL, MD, FAAD: Today, we're mostly going to be talking about antibiotics, probably the most common systemic treatment we have for acne. And, of course as dermatologists, we love our tetracycline, so I thought maybe we could start there. Why do we love them, why are they so popular?

LINDA F. STEIN GOLD, MD, FAAD: Well, they are popular and they really are first line for systemic therapy. And when we think about it, we do know that there is a bacteria, Cutibacterium acnes. That is kind of at the center of the pathogenesis of acne. But we also know that antibiotics actually work two different ways. They have that antimicrobial effect, but they also have fairly potent antiinflammatory effects, so we really use them for both reasons.

JACQUELYN DOSAL, MD, FAAD: So obviously, we know that these are quite antiinflammatory agents and we'll use it even when things are not infected, per se, it's just sort of our mainstay of acne. But how about the dosing, because there's some doses that kill bacteria, there's other doses that don't. Can you guide us a little bit with how important that is?

LINDA F. STEIN GOLD, MD, FAAD: That's such an interesting question, because even though we use antibiotics so commonly, we have such a lack of data on what the best dose really should be. So when we look, for instance, at minocycline, we actually have a dose ranging study that was done with the extended release minocycline. So we're lucky here because they looked at a 12 week study, this was double-blind, placebo-control. And they looked at 1 mg, 2 mg, and 3 mg/kg versus placebo.—

--And what was really surprising was that more wasn't better. In fact, 1 mg/kg was equivalent to or better than the higher doses and there was less side effects, so that's why they went with the 1 mg/kg. And with doxycycline, we don't have any really great prospective studies that tell us what the best dose is. Often, people will use 100 mg a day, sometimes they'll use 100 mg b.i.d.—

--What's interesting though is we do have some small studies that actually looked at sub-antimicrobial dose doxycycline. And even though these were small studies, they actually found that, as you mentioned, antiinflammatory properties actually worked well and we saw a nice decrease in both the inflammatory and the comedonal lesions. So it's kind of interesting. I don't use generally a sub-antimicrobial dose of doxycycline, I tend to either use 100 mg or I'll go up to 200 mg a day for significantly inflamed patients. But I don't tend to use a low dose of doxy.

JACQUELYN DOSAL, MD, FAAD: Will you do minocycline 100 mg twice a day? Because it seems like that minocycline study with the extended release didn't seem to support it, depending on weight, of course.

LINDA F. STEIN GOLD, MD, FAAD: What's interesting about minocycline is when I was a resident, we tended to use minocycline as first line all the time. When we look at the side effect profile of the different drugs, we do find that minocycline, although it's a very safe drug, does

have a side effect profile with some unique side effects. So we know that all the tetracyclines have some GI upset. They can all cause resistance to Cutibacterium acnes.—

--They're all potentially not to be used in patients age 8 or under or in a pregnant woman. They can all potentially cause pseudotumor cerebri. But when we look at the unique side effects, we know minocycline more likely has the CNS side effects, the skin hyperpigmentation, and some of those kind of rare but more dangerous side effects, like autoimmune hepatitis, drug-induced LE, serum sickness. So kind of a long answer to your question.—

--I tend to prefer doxycycline over minocycline. And minocycline, we know the CNS side effects tend to be dose-related, so generally I stay a little bit lower minocycline. But we also have new options today.

JACQUELYN DOSAL, MD, FAAD: Just to spend another moment on mino versus doxy, this was a little bit of folklore when I was in training. But I was sort of taught that minocycline might penetrate the hair follicle and sebaceous gland a little bit better. So sometimes, I'll choose it for an acne or folliculitis patient. But I agree with you, I do like the side effect profile of doxycycline better and, of course, there are newer agents. But what do you make of that, is that folklore, the penetration of the hair follicle and sebaceous gland?

LINDA F. STEIN GOLD, MD, FAAD: I think overall minocycline is probably a little more efficacious for acne, although we don't have great data that show head-to-head trials. But I do agree with you, I think it probably works a little bit better. And I have used minocycline, but you have to spend a few more minutes probably consenting the patient. And you're really going over the headaches, if you get a headache. And you should do this with all of them. But if you get a rash or you just aren't feeling well, certainly stop the drug and let me know.

JACQUELYN DOSAL, MD, FAAD: I wanted to spend another couple of minutes on the lower dose doxycycline, because that was really interesting that there is some data for that sub-antimicrobial dosing. And some of those studies were done with 20 mg of doxycycline twice a day, correct, as opposed to the branded formulation?

LINDA F. STEIN GOLD, MD, FAAD: That is correct, they were. Especially some of the initial studies looked at that.

JACQUELYN DOSAL, MD, FAAD: And both of those treatment regimens should be considered sub-antimicrobial. So I know that sometimes when the branded 40 mg is not covered, they'll ask you to do a 50 mg tablet. But these are not quite equivalent, correct?

LINDA F. STEIN GOLD, MD, FAAD: I think that's really a critical point. Because I kind of feel like you should either use an antimicrobial dose or a sub-microbial dose, but not somewhere in between. And I think people are often, you know, think, "Well, it doesn't really matter. I'll just go ahead and use 50 mg or I'll use 100 every few days." First of all, we don't have to taper antibiotics, you can just use them and stop. They're not steroids, so there's no rebound that occurs necessarily with just stopping your antibiotics.—

--But I don't usually like, and in fact I don't use the 50 mg of doxycycline, mainly because when you're using the 50 mg, you're not staying below that minimum antimicrobial level or even the MIC. So what happens is sometimes you're killing bacteria, but most of the time you're not. And I do worry about the potential for bacterial resistance, especially maybe killing the weaker organisms. We don't have great studies on it to see what exactly happens.—

--But at least theoretically, it's not the best idea. So either go sub-microbial or go full antimicrobial. But I recommend usually not going somewhere in between.

JACQUELYN DOSAL, MD, FAAD: I was impressed with the findings of, I think you touched on it, there was the one study that compared the modified release doxy 40 mg to doxy 100 mg versus placebo in severe acne, and am I correct that the lower dose doxy did better?

LINDA F. STEIN GOLD, MD, FAAD: Yes, and this is not a widely publicized study but isn't it interesting that there was a study. And to be honest, it wasn't such a small study. When we look at this particular study and exactly what it was, exactly how you said it, it was a three arm study. They looked at full strength doxycycline 100 mg, they looked at the modified release 40 mg, and they looked at placebo. And they had over 200 patients in each arm, so that's actually a really big study, so it's powered fairly well.—

--And that's really what happened, they found that the modified release doxycycline worked just as well as the doxycycline 100 mg in the acne patients. So it's not something that we tend to think about for acne. It is FDA approved for rosacea. But if you're looking for something and you want something that's just antiinflammatory and not antibiotic, I think you could think about it.

JACQUELYN DOSAL, MD, FAAD: That's really interesting. I've tried it in a few patients, I've had mixed results, but certainly I haven't tried it in 200 patients, and that's why you need things powered, so I'm going to keep that in mind. So let's touch on those patients where they've used doxycycline 100 mg for a few months, you didn't get good results. And they don't want to go on Accutane because they're scared of Accutane. Is there anything else that can be done for them?

LINDA F. STEIN GOLD, MD, FAAD: Before we move onto what's new, I'll tell you I never really thought there was a major difference between the doxy 100 mg and the doxy 200 mg. But we actually did a study just in those patients that you're talking about. Those patients who had the kind of more severe acne that as they walk into your office, you're thinking, "I've got to start to get my isotretinoin paperwork together, because they really look like they're going to need more

help.” And in these patients, we actually used the 200 mg of doxycycline and we combined that with the fixed combination of adapalene 0.3 and 2.5% benzoyl peroxide.—

--First of all, it wasn’t nodulocystic acne, it was really the more superficial inflammatory acne. They were allowed to have a few nodules but it was not that type of deep, cystic acne. And what we found was a lot of these studies, over 90 percent of the patients at the end of 12 weeks actually got control of their acne, and they were using the higher dose of doxycycline. So this has kind of pushed me a little bit, when somebody comes in and they’re really inflammatory, I’m going to probably go to that.—

--I might start out with 100 mg twice a day, with a potent topical. And I think it’s worth a try, at least initially, although I’m still getting that paperwork together. Usually they have to fail some antibiotics first anyways. So I have been convinced that you’re really pushing the antiinflammatory properties a little bit higher, I think, with the higher dose.

JACQUELYN DOSAL, MD, FAAD: How long did you follow the patients? Were the result sustainable?

LINDA F. STEIN GOLD, MD, FAAD: That’s the whole key, absolutely the key. Because no, we didn’t follow them for a long period of time. And you know that when you put them on the treatment, you clear them up while they’re on treatment, and then you’ve got to maintain them. Once you get these patients under control, we’ve done other studies with the combination of oral antibiotics and potent topicals and shown that you can treat until you get those patients under control, and in some patients if you continue a good topical, you can maintain the efficacy, but you’ve got to do something.—

--Versus with isotretinoin, we can treat and potentially give them a holiday or maybe even not have to treat again once we receive clearance.

JACQUELYN DOSAL, MD, FAAD: Very exciting for our world is that we have new things, we have new things in the antibiotic toolkit which we haven't had in decades. So sarecycline is new and can you tell us a little bit about that product?

LINDA F. STEIN GOLD, MD, FAAD: We continue to evolve in our antibiotic development, just as we've evolved in the development of other drugs. Ideally, what we want to do is we want to go from a more broad spectrum antibiotic to a more targeted. And the reason we want to do that is really because of kind of antibiotic stewardship. If we have a narrower spectrum, that means we're targeting the bacteria kind of in our line of fire, as opposed to getting collateral damage.—

--Because when you take any antibiotic systemically, you're going to potentially be killing bacteria in areas other than the skin, for sure. So if we can get a narrow spectrum, and that's one of the things that sarecycline does, it looks like a tetracycline, it acts like a tetracycline, but it has some modifications that actually have enabled it to be more narrow spectrum. We know that it's more specific for the gram-positives and not the gram-negatives.—

--It tends to not have the same impact on the gut that more broad spectrum antibiotics have. And it has this modification that has actually allowed it to decrease the risk of bacteria becoming resistant to it. And we found that the mutation rate goes down dramatically with sarecycline. And you might say, "So why do I care?" Because we care about bacterial resistance and according to the CDC, this is one of the really major health problems globally.—

--And resistant organisms can kill people. So we want to be responsible. We want to use a drug that has the narrower spectrum of activity as possible. And some other interesting things about sarecycline, first of all, it has a really potent antiinflammatory property, and we already talked about that, that that's important. It has weight-based dosing, which is also kind of nice. And when we're talking about the side effect profile, we actually did a study in animals and looked at whether or not it penetrated the blood-brain barrier.—

--And we compared it to minocycline and we found that the minocycline was penetrating but sarecycline was not. So that might account for the fact that in the clinical trials, we didn't see the CNS side effects. We didn't see the gut side effects like we see with typical tetracyclines, mainly because of the narrow spectrum of action. But not having the dizziness is also I think a benefit for a tetracycline drug.

JACQUELYN DOSAL, MD, FAAD: When I was reading through some of the materials, I was pleasantly surprised that it did get some of the more common clear positive bacteria like MRSA and a few of the others that do cause problems even in our acne patients, so that was nice. And the side effect profile, while there were still some things, it was quite low. What were the most common side effects that people see?

LINDA F. STEIN GOLD, MD, FAAD: No drug is perfect. We definitely see some side effects. But when we look at it, the things that we would expect, like the GI side effects: nausea, diarrhea, actually not that much different from the placebo pill. Diarrhea, in fact, was even greater in the placebo than in the active. And abdominal pain, also fairly low. In most studies, nasopharyngitis or the common cold is usually the most common thing that we see, and that was up there.—

--Again, in one of the studies, it was more common in the placebo than the active. And the things that we worry about, like photosensitivity, very, very rare, 0.2 percent. Sunburn, less than 1 percent. Candidiasis, which we certainly worry about, less than 2 percent. So no drug has no side effects, but I think very manageable side effect profile. So it doesn't take quite as long a conversation with this particular drug than with some of the other antibiotics.

JACQUELYN DOSAL, MD, FAAD: Which is nice. And then how about the efficacy, is it similar to the other tetracyclines? Does it work, a similar rate, effective onset?

LINDA F. STEIN GOLD, MD, FAAD: One of the things I think that we carry around that's a little bit of a myth is when you put a patient on an oral antibiotic, we always feel like, okay, we're pulling out the big guns now. We're putting you on an oral antibiotic. And it's true, that definitely helps. But when you look at the efficacy of our traditional tetracycline antibiotics, first of all, you don't see great efficacy until 12 weeks. And the efficacy is not that great, it's pretty moderate often.—

--In one study that looked at combination versus antibiotic alone, the efficacy was only about 8 percent. With the doxycycline, 100 mg once a day, you look at this, you're like, "Oh, my goodness." So when we look at the efficacy here as monotherapy, and again we don't tend to use the oral antibiotics as monotherapy, but for clinical trials we have to look at it by itself, and actually the efficacy was pretty good, about 22 percent of patients got to clear or almost clear.—

--As you mentioned, they come in with moderate to severe disease. And there was a nice delta or difference between the active drug and the placebo. So it does work fairly well.

JACQUELYN DOSAL, MD, FAAD: Are you typically reaching for this first now, before others?

LINDA F. STEIN GOLD, MD, FAAD: A lot of it comes down to access. But if you think about it, ideally we want a drug that has good efficacy. We want an antibiotic that has a narrow spectrum. We want an antibiotic that has a good safety profile. So I think when you look at all of our choices, this drug is superior in each one of those aspects. In addition, we have data on the chest and back, which makes sense if you're taking a pill. We see that the efficacy was actually quite good, up to 30 percent or so on the chest and the back.—

--So it comes down to access. It comes down to are we able to get it for our patients. But I do think that it makes sense.

JACQUELYN DOSAL, MD, FAAD: This is something that we need to consider more often. Any special considerations for our patients with skin of color? Does that affect your choice of therapy when you see somebody with bad inflammatory acne and they're a patient of skin of color?

LINDA F. STEIN GOLD, MD, FAAD: It does. And it's really important, because often when we look at our acne patients, we're looking at them and we're looking to see, "How is your active acne? How many bumps do you have?" And when we look at the dyspigmentation, which we understand is a sequelae of the acne, we often pooh-pooh it and say, "Well, as long as the bumps are going down, we're doing great." We have to remember though in skin of color, the dyspigmentation, the postinflammatory hyperpigmentation, often cause more devastation for the patient than even the active acne lesions.—

--So with these patients, I feel like we have to get the acne under control as rapidly as possible. We know that often, those dyspigmented areas, often when you biopsy them there's still inflammation there. So I'll continue to treat, even through those lesions, and try to have a game plan in place. We have to remember that when we're looking at our patients that have maybe those pink spots or those brown spots, we know with the development of atrophic scars that these erythematous and hyperpigmented lesions in some cases can go on to cause atrophic scars.—

--So I like to use the most potent antiinflammatory medications that I can.

JACQUELYN DOSAL, MD, FAAD: That's such a great tip and I didn't know that, so that's going to change the way I practice, thank you. That was fantastic, thank you so much. I really learned a lot. It's so exciting to have something new in our toolbox, because we see acne so much. So thank you for your expertise and those great tidbits that we got. And thanks for your time.

LINDA F. STEIN GOLD, MD, FAAD: A pleasure chatting with you and a really nice conversation, so thanks for having me.

JACQUELYN DOSAL, MD, FAAD: Thank you.