

Rosacea as an Inflammatory Disorder

James Del Rosso, DO: Hello. I am Jim Del Rosso, a dermatologist in private practice in Las Vegas and research director at JDR Dermatology Research, and am joined by Linda Stein Gold, the director of dermatology clinical research at Henry Ford Health System in Detroit. We are discussing rosacea as an inflammatory disorder.

Rosacea has been the subject of basic science and clinical research. It is now considered a chronic inflammatory dermatosis involving the face. Dr. Stein Gold, can you give me some thoughts based on this research?

Linda Stein Gold, MD: Rosacea has gone through an explosion in terms of understanding it. It is not acne, in which an organism is central to pathogenesis, but again, an inflammatory disorder. I think of it as the innate immune system overreacting to certain stimuli. At the center is the cathelicidin pathway, the antimicrobial peptides, which should be our first line of defense. Instead of protecting us, though, it starts to spark a chronic inflammatory condition. Do you think the cathelicidins are important?

Dr. Del Rosso: There are different circuits: neurovascular dysregulation, with different neurotransmitters and chemical mediators that trigger flushing and some stinging and burning, and the cathelicidin pathway. The cathelicidin pathway is involved in the development of background erythema and inflammation, but it does not explain the entire story. Immune dysfunction and neurovascular dysregulation lead to signs and symptoms that can vary over time and among patients as to what is dominant.

This is what makes it complicated. We used to mix everything together regarding clinical presentation, but now we look at individual features because we have different therapies to target them. It has helped me in evaluating patients. Let's say a new patient comes in who has not used therapy in a long time, their face is red with diffuse erythema, papules and pustules, and they are in a flared state. How you evaluate and explain it to the patient is important.

Dr. Stein Gold: Yes, the whole process is complex. We have different factors that go into pathogenesis, the neurovascular pathway, cathelicidin pathway, and triggers. All come into play when we see a patient. In the past, it didn't matter what signs or symptoms they had, we wrote for topical metronidazole.

We know now that's not the best approach. When I see a patient, I say, "Okay, what exactly am I treating?" If someone presents with papules and pustules, they need a topical or oral anti-inflammatory drug. If they also have background erythema, they'll probably need a topical alpha-adrenergic agonist. If they have scattered broken blood vessels, the patient isn't going to be happy because I made their bumps and redness go away, as those blood vessels remain.

Dr. Del Rosso: When they're flared, it may take several steps to address. If they have a lot of background erythema, I might integrate the alpha agonist early or wait to calm it down. I explain we might need to use things at different times, but first I calm down the flare with the papules and pustules to see everything better.

I use topical ivermectin, which data show is an excellent drug. I also use azelaic acid and

metronidazole along with oral doxycycline. I like to use subantibiotic-dose doxycycline to avoid the resistance factor, but I may not use both long term, depending on how the patient does and how I integrate the alpha agonist. I use more oxymetazoline, because I have less issue with worsening erythema, although brimonidine works on many patients. When they're really flared, I get that perilesional erythema under control as quickly as possible.

Dr. Stein Gold: Often with patients who are really inflamed, a lot of papules come in. They have not only perilesional erythema but also background erythema. Once you calm everything down, they are not as red as you might have thought.

But I agree, we tell them this is a staged approach. Once we get the initial condition under control, I explain that the blood vessels will be treated separately. I ask about eye symptoms with these patients. Many have ocular rosacea that goes undiagnosed.

Dr. Del Rosso: It is important to ask about ocular symptomatology. They could have allergies or itchy eyes and not equate it with rosacea. They'll often improve, especially on an oral drug.

Dr. Stein Gold: As to using lower- or submicrobial-dose doxycycline, this goes back to rosacea being an inflammatory disease. We don't need higher-dose antibiotics because these are not being used as antibiotics but for their anti-inflammatory properties.

Dr. Del Rosso: Let's take the patient without papules and pustules who comes in with diffuse central facial erythema and tells you when it intensifies, but their cheeks stay red. But you are seeing them in a nonflared state. They have persistent facial erythema and may or may not have ocular symptoms. How do you approach that?

Dr. Stein Gold: If I see just background erythema, I go with a topical alpha-adrenergic agonist.



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If I'm going with oxymetazoline, I wait to use it in patients, especially if they have papules, in combination with the topical ivermectin.

Dr. Del Rosso: Another agent, brimonidine, initially came in multiple pea sizes and was being overused. Skin care was not recommended. I use it in a very thin amount, and with some moisturizer, many patients do well. But it's very potent, the highest concentration of that drug. Oxymetazoline has a middle concentration that doesn't blanch out the skin as intensely. Having both options lets you judge how much erythema you're going after.

Dr. Stein Gold: And it's individualized for each patient. Brimonidine has a more significant effect, while that with oxymetazoline is gentler.

Dr. Del Rosso: With oxymetazoline, there is less chance of paradoxical erythema, but both are very helpful in patients if used consistently and they know the erythema will come back in about 12 hours. I tell the patient the first time you use one, we don't know how it's going to kick in. We need to learn how it's going to work for you so you'll know how to apply it and how long it will last.

Sometimes I have trouble explaining rosacea to patients. What are key things you say to patients to get them to understand rosacea?

Dr. Stein Gold: First, it's not your fault. People want to know what they are doing wrong or if they are not eating right. Rosacea is a complicated condition. For many patients it's inherited. It commonly occurs, more in women and in Caucasians, but we can see it in anyone. I explain there's nothing you're necessarily doing wrong, but many people have triggers that can make it worse. So although it's not spicy or hot foods causing you to flare up, maybe you don't want to go out on a first date and order hot chicken soup and turn red. And you need to have sunscreen on.

I explain this is a process, an inflammatory condition many have throughout their adult life. You learn how to control it and deal with it.

Dr. Dell Rosso: What you said is important, to let them know it's not their fault. We have treatments to help control it even long term if they're compliant and work with us. You develop that partnership when they're not looking for a quick cure because it's not curable. Although they can

have prolonged periods during which they don't flare, it varies. Data show we can decrease flushing episodes by using anti-inflammatory agents like ivermectin and doxycycline.

Dr. Stein Gold: This is a holistic approach to skin care. It's not just that I can give you a pill to take and it will make you better. You have to be an equal partner in getting your skin under control, not buying toners and scrubs, and using gentle cleansers.

Dr. Del Rosso: What about management of phymas? In early phymas that are inflammatory, the topical agents effective against papular pustular disease like doxycycline can improve that inflammation. Do you use isotretinoin in early phymas or in more difficult cases of rosacea?

Dr. Stein Gold: I have. Sometimes though, a patient will come in with severe rosacea, and I'm thinking we have to use oral isotretinoin. I start them on oral doxycycline and a potent topical. Some respond nicely without having to go to isotretinoin.

Dr. Del Rosso: I am more aggressive with isotretinoin when seeing sebaceous hyperplasia with inflammation developing that will lead to a phyma before it becomes fibrotic or mucinous. I may prevent that if I catch it early enough with isotretinoin. Then patients can be on intermittent low doses to control it.

Do you have any other suggestions in managing rosacea?

Dr. Stein Gold: Very commonly, I use monotherapy. Now that we have topical ivermectin, monotherapy works in many cases. But when do you start with combinations?

Dr. Del Rosso: It's based on severity of disease. There are patients for whom I'll try topical alone, ivermectin or azelaic acid. In clinical studies, topical ivermectin went after a higher severity based on lesion counts. So it works well as monotherapy. But some patients have too much inflammation to depend on one treatment. I get them on subantibiotic-dose doxycycline with the topical. After a couple of months, we'll look at monotherapy. If any persistent facial erythema is minimal, they may not need the alpha agonist or a device.

Dr. Stein Gold: Sometimes, I'll use a combination to make sure it kicks in faster to get the patient more rapidly and completely under control.

Dr. Del Rosso: Data support it's quicker to use doxycycline and topical ivermectin or metronidazole or azelaic acid, but not every patient needs that depending on severity.

Dr. Stein Gold: It's important to have all these drugs. We need them because for every patient, we can't predict who's going to do well with which drug.

Dr. Del Rosso: Each patient is different and requires assessment of their manifestations. We select treatment based on what's bothering them most, but some therapies are not used all at once. We might have to stagger in different treatments depending on the manifestation being targeted.

What about the time course of response? When starting a treatment, we need to let a patient know how long it's going to take before a change is visible.

Dr. Stein Gold: People see drugs advertised as getting them better overnight, so setting realistic expectations is huge. Also, when we do clinical trials, we study drugs for 3 or 4 months, but some patients do not hit their peak by then. I'll say they may be on this medication for a long time because I didn't cure you, just controlled it.

Dr. Del Rosso: Data from long-term studies show more endpoint success with patients continuing to use treatment. More patients do better if they're consistent over a longer time.

Dr. Stein Gold: Absolutely. For most patients, we're going to have to use it for longer periods. What about maintenance therapy after the patient gets clear?

Dr. Del Rosso: If patients continue to apply medication or stay on a regimen like subantibiotic-dose doxycycline, they will reduce flares. It doesn't mean they're never going to get a flare or need more medication. I encourage them to stay on long-term treatment, but it costs. Refill data show that when better, they forego it. We may want that nirvana of having patients on therapy long term, but often that's wishful thinking.

Dr. Stein Gold: Right, but it is important to reinforce that I didn't cure you. I feel better if a patient is not on an antibiotic for long periods. If the patient's on submicrobial-dose doxycycline, I am okay saying this is a long-term control. I'm not concerned we're doing anything to negatively affect overall health. ■