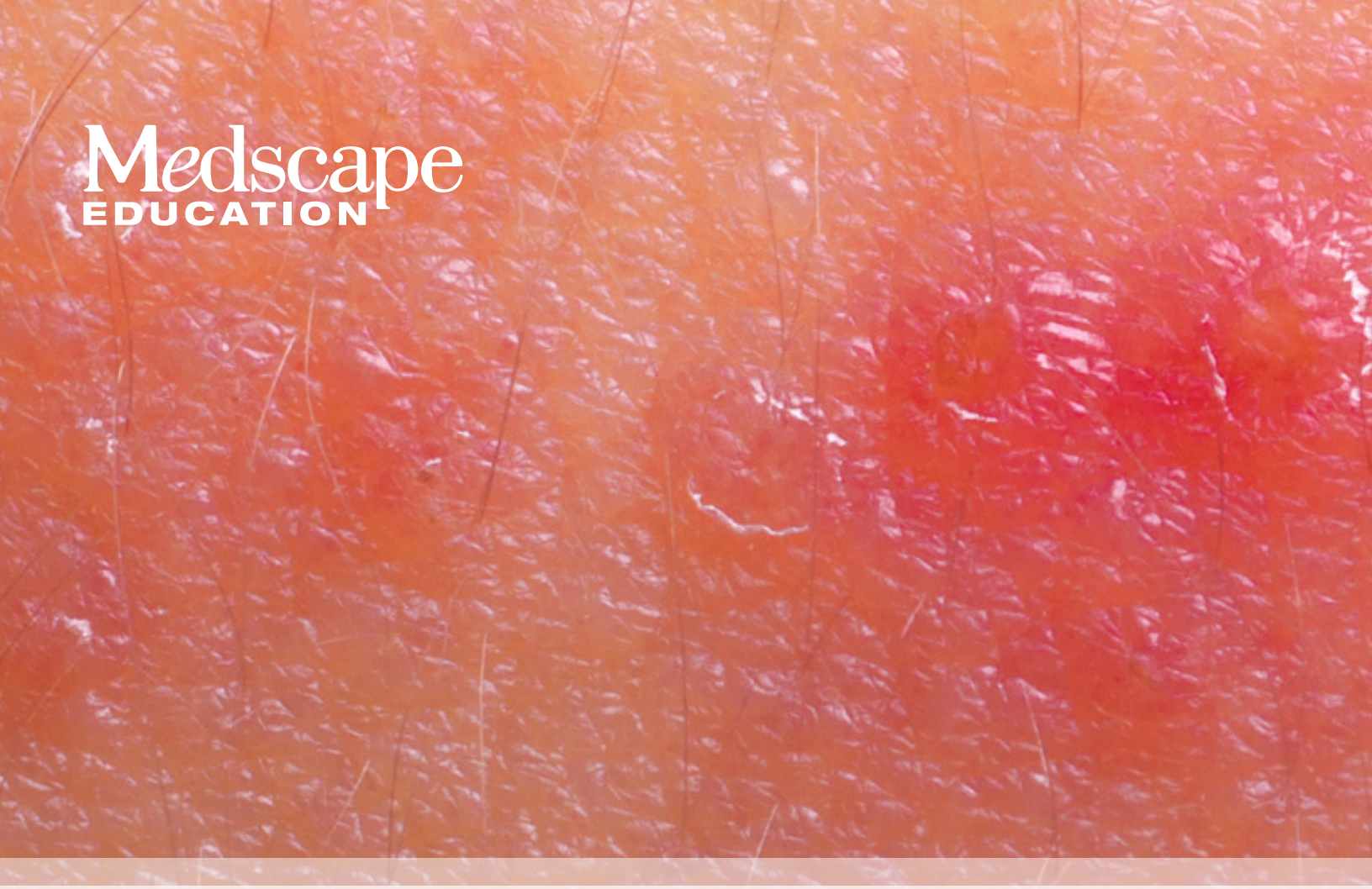

Medscape EDUCATION

# Targeting the Multifactorial Pathophysiology of Rosacea: MOA of Therapeutic Options CME/CE

*Julie C. Harper, MD*

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**CME released: 11/29/2012; valid for credit through 11/29/2013**
**Pharmacist CE released: 04/25/2013; valid for credit through 04/25/2014**

## Target Audience
This activity is intended for dermatologists, pharmacists, and primary care providers who care for patients with rosacea.

## Goal
The goal of this activity is to educate clinicians on the multifactorial pathophysiology of rosacea and to understand treatment options in the context of disease pathophysiology.

## Learning Objectives
Upon completion of this activity, participants will be able to:

1. Describe the current understanding of multifactorial pathophysiology of rosacea
2. Evaluate the mode of action and therapeutic rationale of treatment options for rosacea in the context of the pathophysiology of the disease

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## Targeting the Multifactorial Pathophysiology of Rosacea: MOA of Therapeutic Options CME/CE

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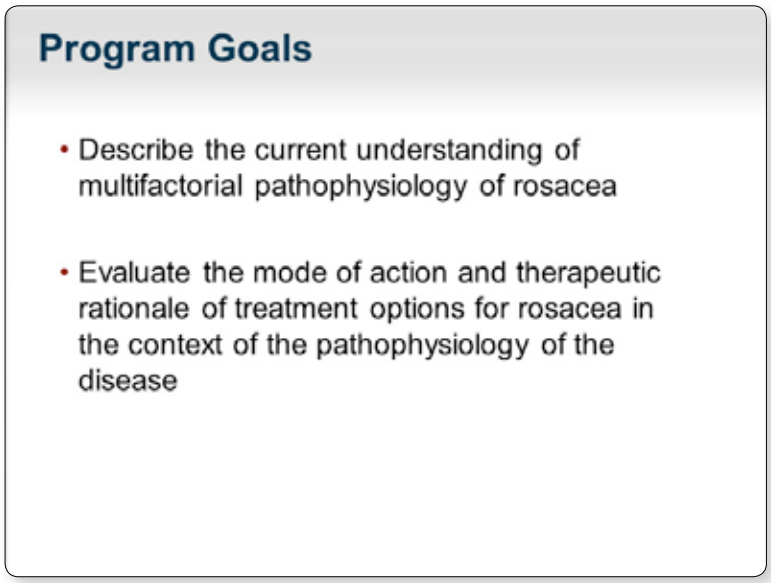
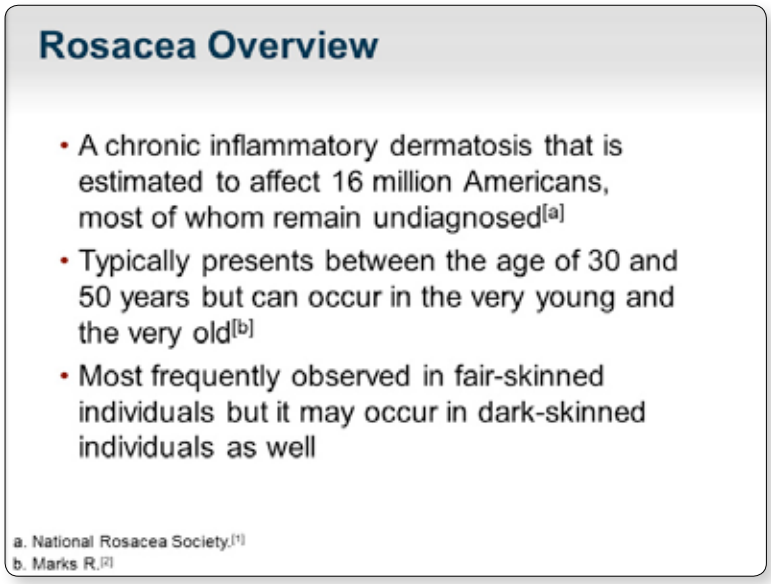
**Julie C. Harper, MD:** Hello. I am Dr Julie C. Harper, clinical associate professor of dermatology at the University of Alabama-Birmingham School of Medicine in Birmingham, Alabama. I would like to welcome you to this program titled "Targeting the Multifactorial Pathophysiology of Rosacea: Mechanisms of Action of Therapeutic Options." Before we begin, I would like to note that this program will include off-label discussion of treatment options.

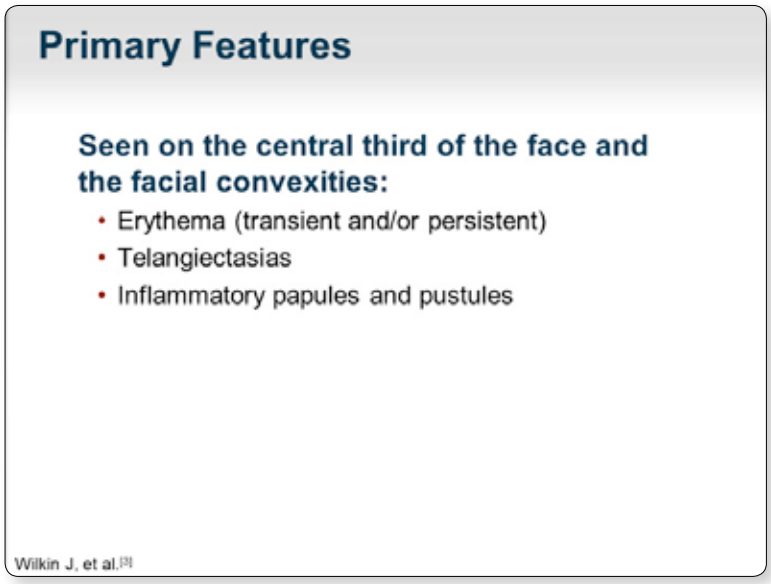



The goals of this program are to describe the current understanding of the multifactorial pathophysiology of rosacea and to evaluate the mode of action and therapeutic rationale of treatment options for rosacea in the context of the pathophysiology of the disease.

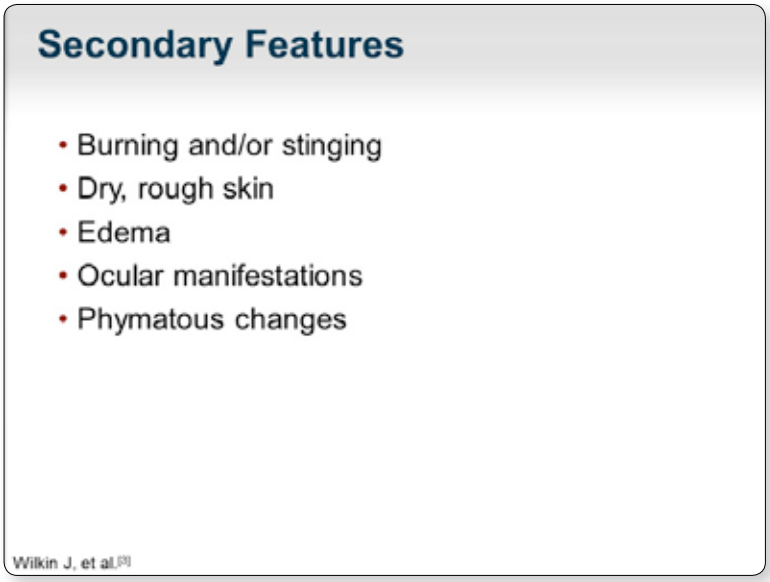



Let us start by talking about what rosacea is and who rosacea really affects. Rosacea is a chronic inflammatory dermatosis. It is estimated to affect probably 16 million Americans,[1] and I say probably because most of these people go undiagnosed. I do not think we know specifically why they go undiagnosed, but in many cases, the disease is simply not recognized by those who suffer with it. Perhaps they diagnose themselves with sun damage or sunburn or an adult form of acne. We do know that rosacea typically manifests between the ages of 30 and 50 years.[2] Rosacea does not play by the rules, however. It can affect the very young and can be seen in the pediatric population. It can also present after the age of 50 years and be seen in more elderly individuals.

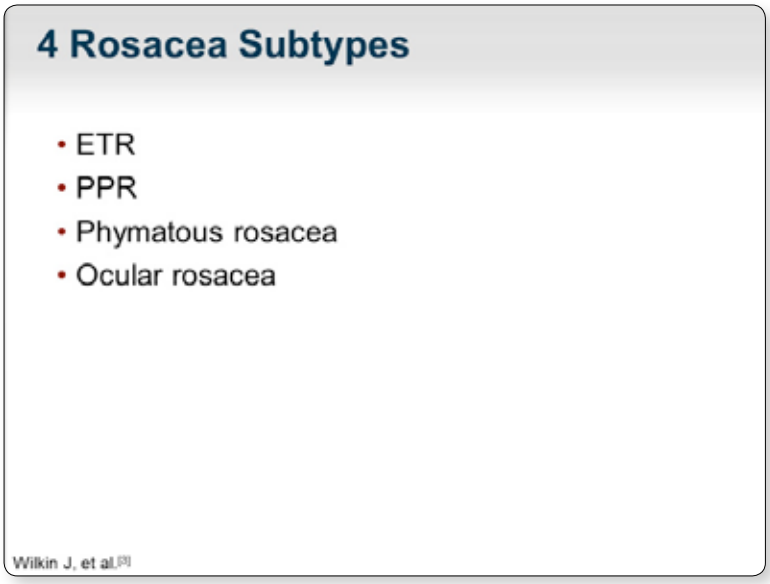
We think of rosacea as classically being seen in a Celtic skin type, ie, fair-skinned individuals, but we see rosacea in any skin type and any ethnicity. It is more difficult to see clinically in darker-skinned individuals, so it may go untreated.



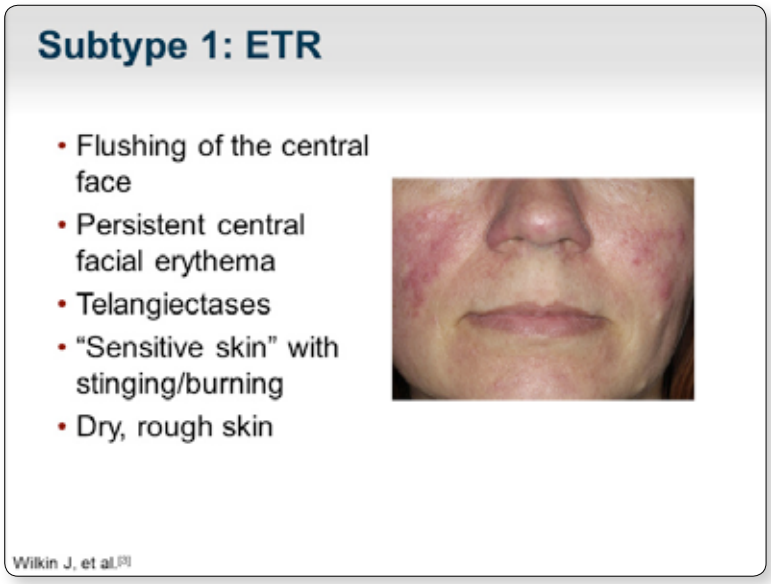

I remember in my training, I learned early on that there were 3 primary features in rosacea: redness of the face, or erythema; telangiectasias; and, at least in some subtypes, inflammatory papules and pustules. These features are almost always on the central third of the face, involving the convexities of the face -- the forehead, the medial cheeks, the nose, and the chin. It is interesting that those areas that we think of as being recessed or more sun-protected, like the area right under the nose or the area around the eyes and certainly the area right under the submental part of the chin, are usually not affected by rosacea.



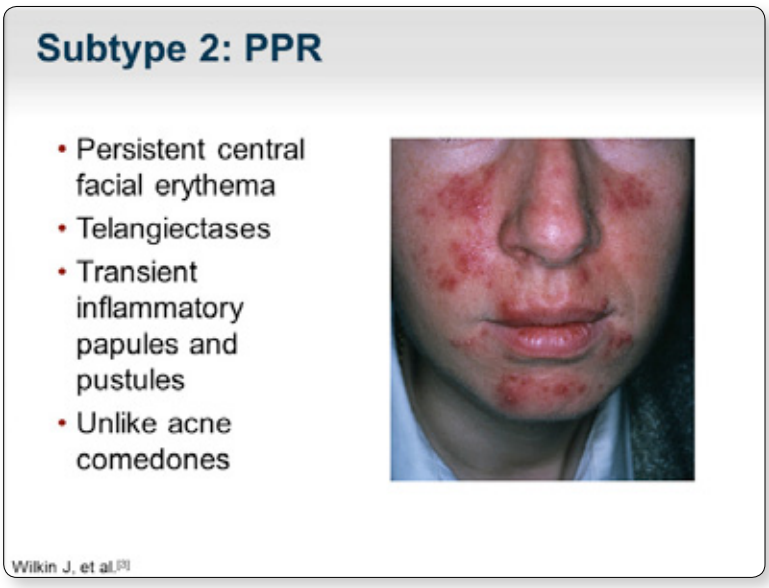

Secondary features have been documented as well. Those of us who practice dermatology and see and treat rosacea are used to seeing and hearing about these. The first is burning and/or stinging of the skin. Many of our patients with rosacea have very sensitive skin, and this bothers them in their life and in their daily routine. They also frequently have dry, rough skin, which may be a sign that the skin barrier is not working appropriately. Additional secondary features include swelling and eye manifestations, which is something that they do not put together with rosacea. We must really make the effort to specifically ask about eye manifestations. There can also be phymatous changes of the skin.



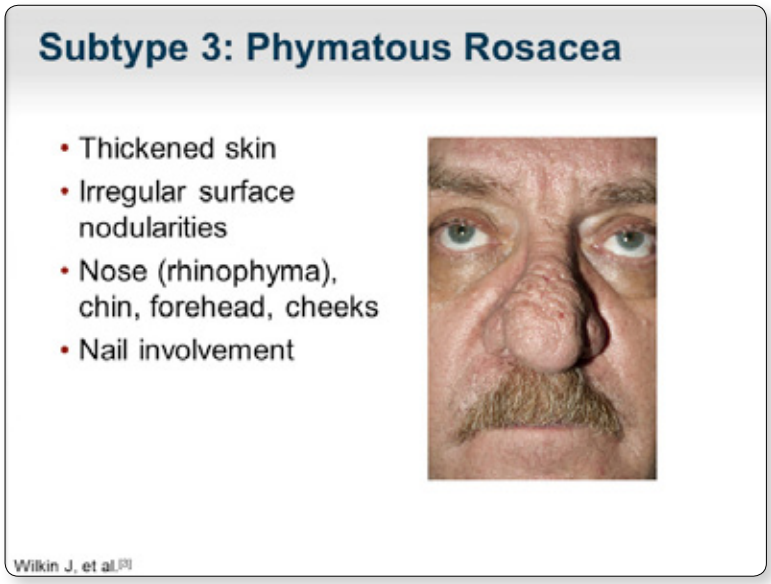

There are 4 subtypes of rosacea. Erythematotelangiectatic rosacea (ETR) is the first subtype. Papulopustular rosacea (PPR) is the second type. Phymatous rosacea is the third subtype. The fourth subtype is ocular rosacea.



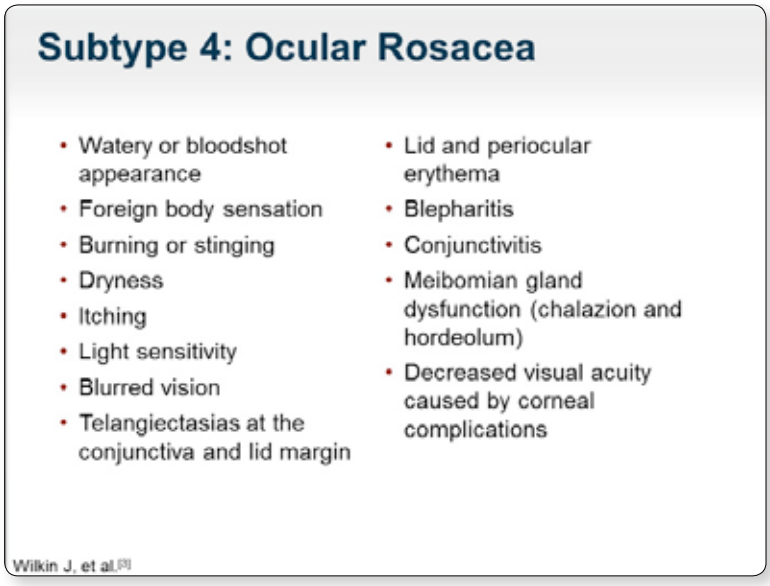

Let us start with ETR. It is characterized by flushing of the central face. This is not simple blushing, although often people with rosacea can give a history even in their adolescence of being flushers and blushers. The type of flushing that we are talking about here hangs around a little bit longer and is usually present for at least 10 minutes and can be present all the time. Trigger factors can make that worse or create persistent facial erythema. Telangiectasias and -- as I mentioned earlier -- sensitive skin are also present. In particular, ETR patients frequently suffer with sensitive skin. They complain of stinging and burning with any skin care product that they are using. Their skin, again, may be dry or rough, which is a signal that there is some disruption of the skin barrier.



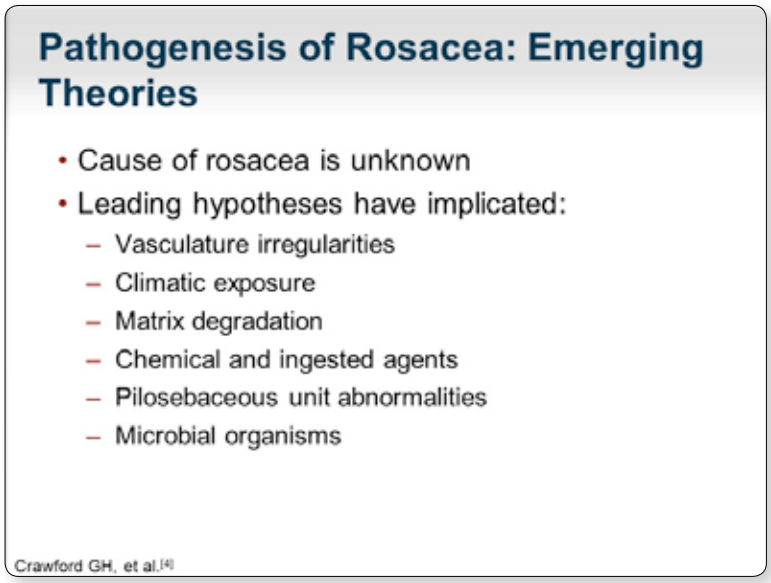

PPR looks a lot like ETR, and patients may have some of the same presenting features in the clinic. In PPR, however, we also see transient bumps -- inflammatory papules and pustules. These can look to the layperson a lot like acne. To the dermatologist, they look a little bit different. We do not see comedones present at the same time, at least not usually, or blackheads, but we do see these inflammatory papules and pustules. Controversy surrounds these lesions -- are the papules and pustules centered around the follicle like an acne lesion is? Or is all of this inflammation around the vasculature? I think to date, the data lean toward them being inflamed around the vasculature.




Phymatous rosacea is the most classic appearance. I think when people in the lay population probably think about rosacea, they might think of these pictures of thickened skin and irregular surface nodularities. We think of it as affecting the nose (rhinophyma), but this can also affect the chin, the forehead, or the cheeks. This is one subtype that seems to have a little bit of a male preponderance. The other types seem to be a little more common in women.




The list of symptoms that can be part of ocular rosacea is long. I think the take-home message here is just, do not forget the eyes if you have a patient who has any of the subtypes of rosacea. Be sure you ask about eye findings. Some of the eye symptoms can be watery or bloodshot appearance of the eye; a foreign body sensation; burning or stinging of the eye; dryness; itching; light sensitivity; blurred vision; telangiectasias at the conjunctiva and the lid margin; lid and periocular erythema; blepharitis; conjunctivitis; meibomian gland dysfunction with chalazion and hordeolum formation; and even decreased visual acuity caused by corneal complications. I think that is a very long list, and some of these seem very nonspecific, but it is important that we ask about them, because eye symptoms in rosacea are certainly not uncommon.




We will focus for the majority of our talk on the pathogenesis of rosacea. Unfortunately, I have to start this part of the conversation off by saying that we do not really know what the underlying cause of rosacea is. There have been many hypotheses over the last several years. I would like to talk about some of these for a minute because I do not think we are at a point where we can completely eliminate any of them. We have learned so much more about inflammation. We will talk about that in just a moment.

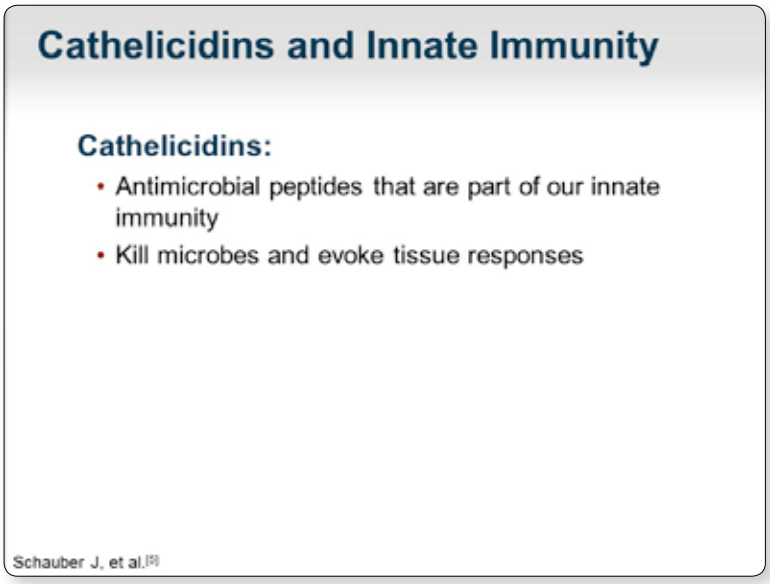
The leading hypothesis up to this point has been the vascular hypothesis -- that there is some problem with the vasculature that causes rosacea, but other hypotheses exist: Maybe it has something to do with climatic exposure. Maybe it is just degradation of the dermal matrix. Maybe it is something ingested or a chemical that is applied to the skin. Maybe there is something going on in the pilosebaceous units, somewhat like acne. Maybe there is a microbial organism that triggers the development of rosacea.

The vascular hypothesis is probably most familiar. I think we have come to that naturally because people who have rosacea often start out as flushers and blushers, and erythema is such a prominent feature of rosacea. Maybe there is something with the vasculature, an instability Maybe there is something circulating in the body that makes the vasculature unstable. Over time, these blood vessels dilate. They dilate enough that they become leaky. They leak proinflammatory mediators out into the dermis. This can lead to ongoing inflammation.

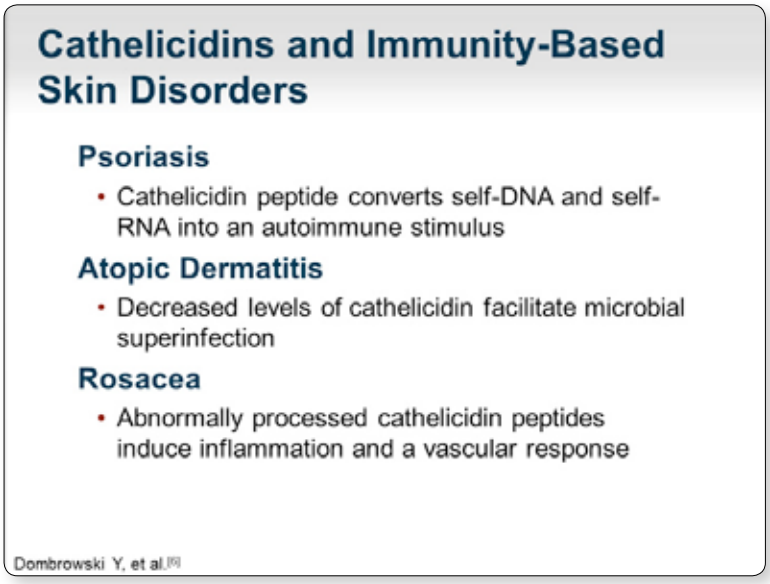
When we consider the climatic exposure hypothesis, I think largely what we are talking about is sun damage. We think about rosacea as being a condition affecting fair-complexioned individuals -- people who might be more at risk for sun damage. We know that sun damage can damage both the vessels and the dermis. Those are 2 of the key areas that we biopsy to see whether inflammation is present. Not everybody who has rosacea has evidence of sun damage, however. A recent study showed that sun-damaged skin looks a bit different than rosacea in biopsy. It is not a perfect hypothesis, but it is food for thought.

Matrix degradation hypothesis stems from chemical and ingested agents. One of the first agents that comes to mind is topical corticosteroids. We are all very familiar with steroid-induced rosacea. We know that there are triggers that can be applied to the skin that can cause something that looks much like rosacea.

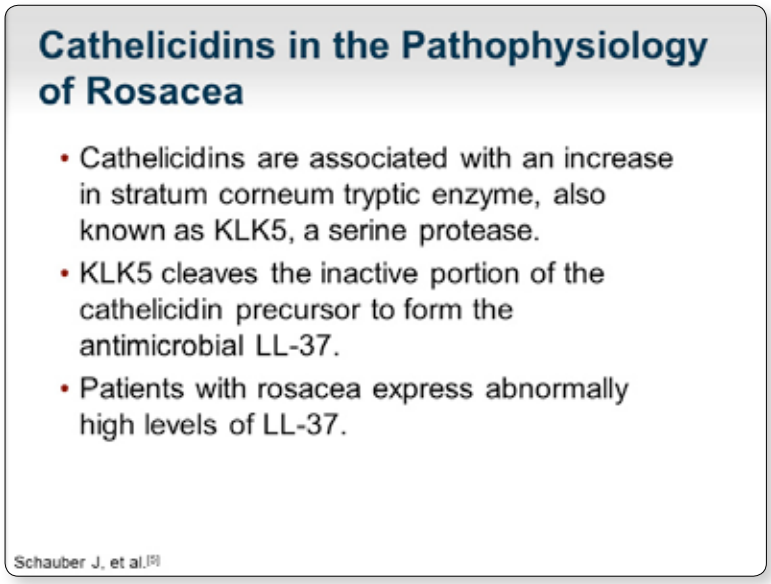
I mentioned earlier, more evidence supports that this is a perivascular condition and not a condition of the pilosebaceous unit such as acne. Lastly, when we consider microbial organisms, the one that comes to mind for all of us is *Demodex*. Is *Demodex* an innocent bystander? Or is *Demodex* really an important part of the pathophysiology of rosacea?[4]



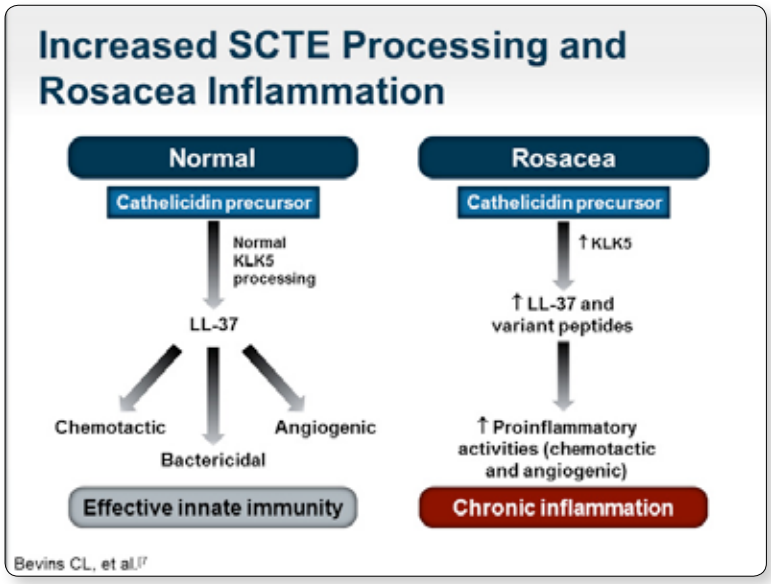

Let us now talk about what we have learned most recently -- the innate immune system in rosacea, in particular, cathelicidins. Think about the innate immune system as being the body's first line of defense against microbes that are trying to penetrate the skin, or even against environmental damage. Once those cathelicidins are turned on, they appropriately respond with inflammation. They respond to kill microbes, and they respond by evoking inflammatory tissue responses.[5]




We can see cathelicidins at work in several common dermatologic conditions, psoriasis, for example. In psoriasis, we think cathelicidin peptides convert self-deoxyribonucleic acid (DNA) and self-ribonucleic acid (RNA) into an autoimmune stimulus.[6] If you go back and think about what we just said, cathelicidins help to protect against infection. Think about a condition where we have superinfection over and over again, as in atopic dermatitis. Some evidence supports that there are decreased levels of cathelicidin present in atopic dermatitis. It stands to reason that this would facilitate microbial superinfection. The flip side of that is, too much of a good thing is not good anymore. In rosacea, we know that abnormally processed cathelicidin peptides induce inflammation and a vascular response. They might do too much of that, and they might do it too well.

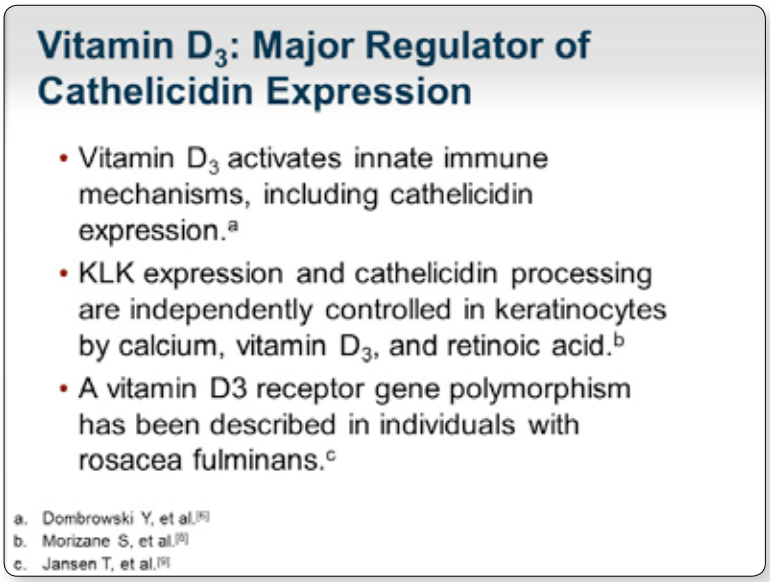



When we talk about cathelicidin specifically in rosacea, we know that cathelicidins are associated with an increase in stratum corneum tryptic enzyme. That is also known as kallikrein 5 (KLK5). Kallikrein 5 is a serine protease. Kallikrein 5 cleaves the inactive portion of the cathelicidin, or the pro-cathelicidin, and turns it into the active cathelicidin, LL-37. LL-37 is not specific to rosacea, but it has been found to be expressed at abnormally high levels in rosacea. LL-37 is an interesting cathelicidin. Not all cathelicidins cause both inflammation and angiogenesis, but LL-37 does. Those are certainly things that we would anticipate seeing in a condition like rosacea that is associated with clinically observed inflammation and also telangiectasias.[7]

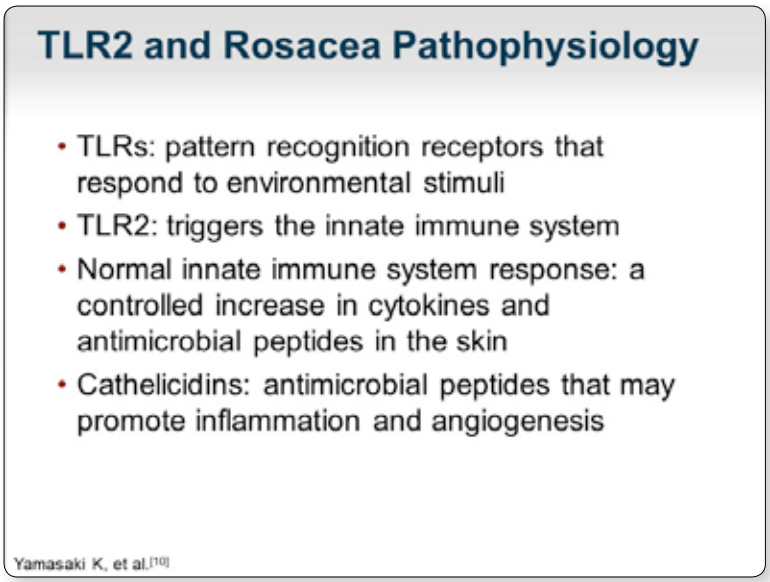



This schematic goes over what we were talking about. Here is normal cathelicidin processing: we have cathelicidin precursor and normal KLK5 processing. At the normal level, we need these cathelicidins. They are not bad. We get normal LL-37. This is good. It is chemotactic. It calls in more inflammation to try to rid the body of any potential problem. It is bactericidal in and of itself. It is angiogenic.

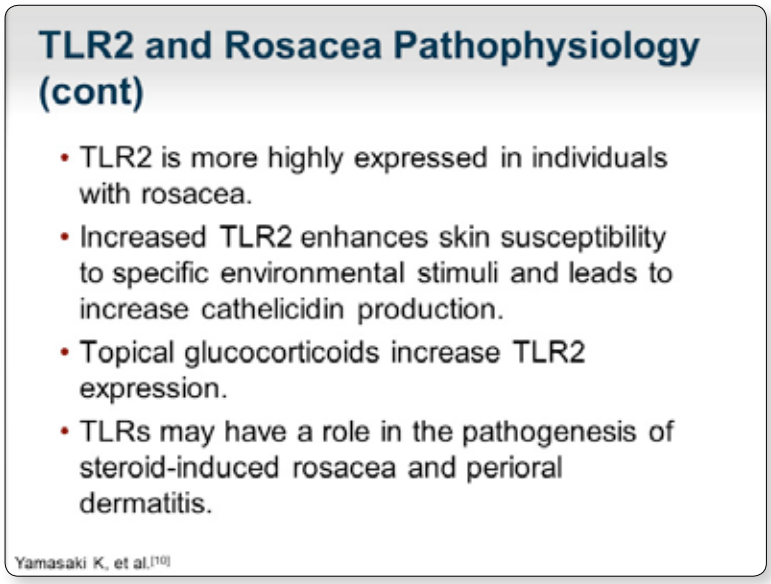
In rosacea, too much of a good thing is not good anymore. Here we have the cathelicidin precursor. We have too much KLK5. We have too much LL-37 and other peptides. Now, we have too much inflammation. We have chemotaxis that is pouring all kinds of inflammation into the dermal milieu, and it is angiogenic. This sets up a picture of chronic inflammation that just gets turned on and keeps going and very likely permits these things that we see on the skin of individuals with rosacea, meaning telangiectasias and erythema.



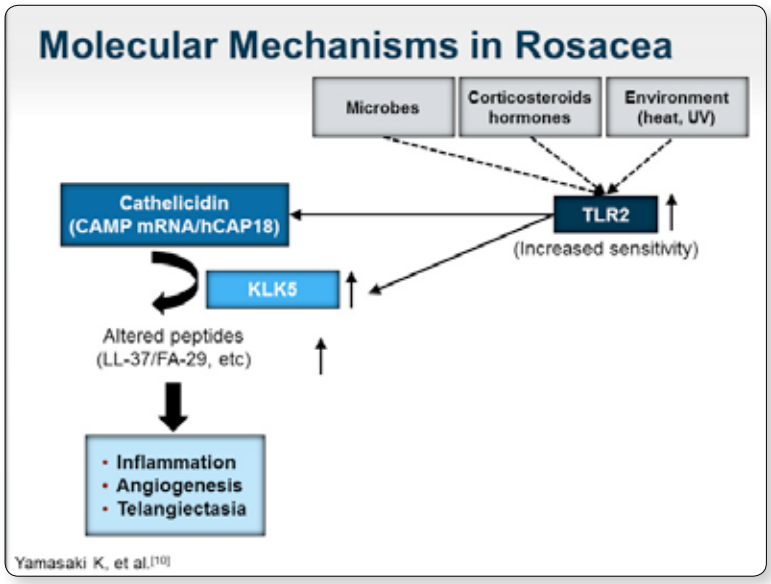

Several things help to regulate this innate immune system. One is vitamin $D_3$, which activates innate immune mechanisms including cathelicidin expression. Vitamin $D_3$ often suppresses acquired immunity. This is backwards of what you might remember from immunology, where vitamin $D_3$ activates the innate immune mechanisms. Kallikrein expression and cathelicidin processing are independently controlled in keratinocytes by calcium, vitamin $D_3$, and retinoic acid.[8] I think it was very interesting. This was published several years ago. A vitamin $D_3$ receptor gene polymorphism has been described in individuals with rosacea fulminans.[9] Remember, individuals with rosacea fulminans have explosive, severe rosacea. It is interesting that maybe dysregulation of the cathelicidin pathway may play a role in the pathophysiology of the most severe types of rosacea.




Let us talk a bit about Toll-like receptors (TLRs). We have heard about TLRs in other dermatology conditions, including acne. We are talking about Toll-like receptor 2 (TLR2) now in rosacea. I think a good way to think about TLR is that it acts as a satellite on the skin. It is a radar, so to speak, and it gets turned on by a number of different stimuli including ultraviolet light, microbes, and physical and chemical trauma, including disruption of the skin barrier. If you think about that, our patients with rosacea will frequently say, "What flares my rosacea?" Sunlight and skin care products that are drying or irritating that impair the skin barrier. These are things that trigger TLR. Toll-like receptor 2 then triggers the innate immune system. It can trigger cathelicidin. As we said, normal innate immune system response is good. It is a very controlled release of this inflammation. When it is dysregulated, it is out of control inflammation.

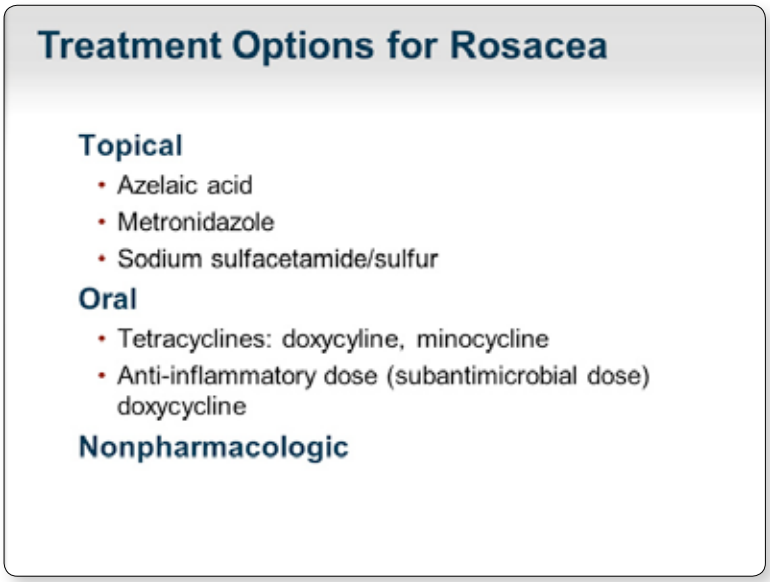



We know TLR2 is more highly expressed in individuals with rosacea.[10] Increased TLR2 enhances skin susceptibility to these environmental stimuli that we just mentioned and increases cathelicidin production. It's interesting for those of us who are used to seeing things like perioral dermatitis and steroid-induced rosacea that topical glucocorticoids increase TLR2 expression. This gives us at least 1 potential pathway of how the steroids may induce rosacea and perioral dermatitis through the TLR and through cathelicidin.

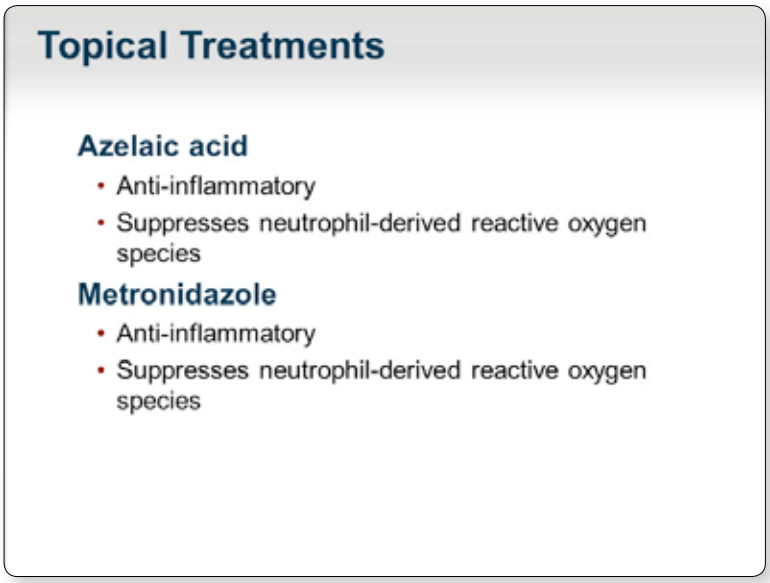



This schematic sums up what we are trying to get across here. This is still hypothesis, however; we need more studies that will confirm what we are learning about this. We have this TLR2 sitting on the skin surface and acting as a radar system being turned on and up-regulated in the presence of things like heat and ultraviolet light, maybe a portion of *Demodex*, maybe a topical steroid that is applied to the skin. TLR2, in turn, increases cathelicidin and the serine protease, KLK5, which we said is necessary to cleave that pro-cathelicidin to active cathelicidin. We get inflammation, angiogenesis, and telangiectasias.

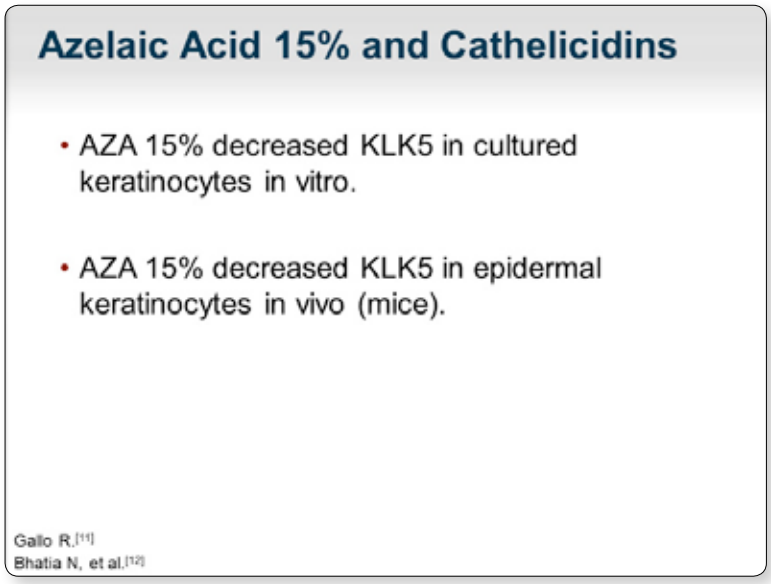
When we talk about the primary features of rosacea, the redness is one of the signs of inflammation. We talked about telangiectasias and inflammatory papules. You can see how we get this unifying theory from these common triggers that our patients tell us through this complicated TLR2 and cathelicidin pathway to what we see clinically. I think this is a unifying hypothesis that helps to pull the whole story together.



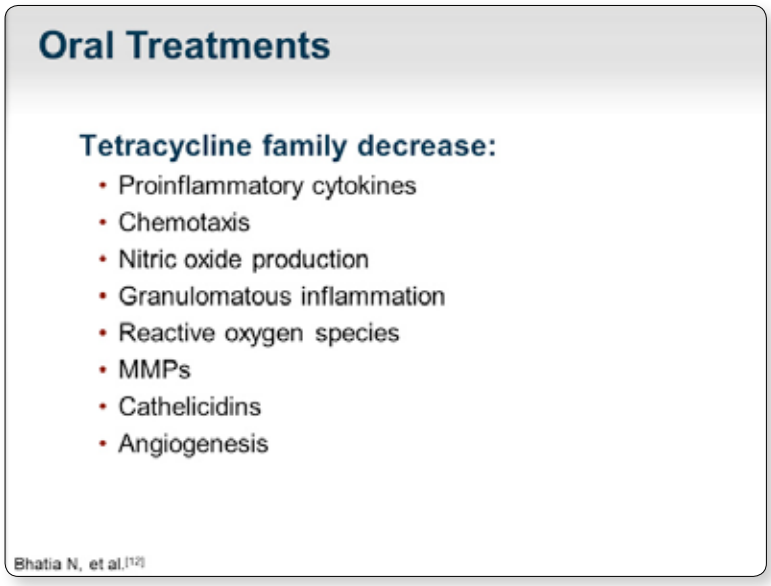

How does what we are learning about the pathophysiology of rosacea affect the treatment of rosacea? The common treatment options for rosacea are topical products and oral products. The 3 topical products that we use most commonly are azelaic acid, metronidazole, and sodium sulfacetamide and sulfur. The oral products are antibiotics -- doxycycline and minocycline -- and an anti-inflammatory dose, a subantimicrobial-dose, doxycycline.



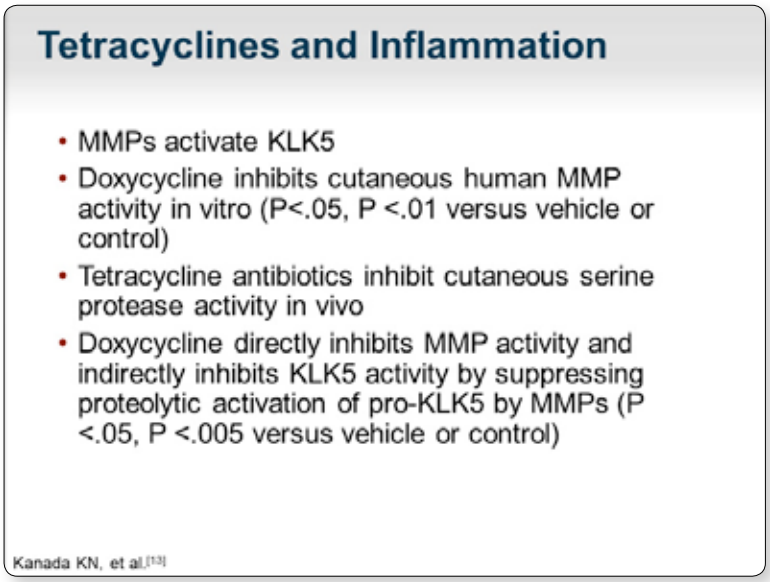

Azelaic acid is a topical product that is anti-inflammatory. We do not know exactly how it is anti-inflammatory. We do know that there is evidence that it suppresses the neutrophil, and in particular suppresses neutrophil-derived reactive oxygen species. Metronidazole probably works through a similar mechanism. Although again, we have to say we do not know specifically how the product works, but it is also anti-inflammatory, and it suppresses those neutrophil-derived reactive oxygen species. I think we will undoubtedly learn more about how these 2 products work as we learn more about the potential pathophysiology of the disease.



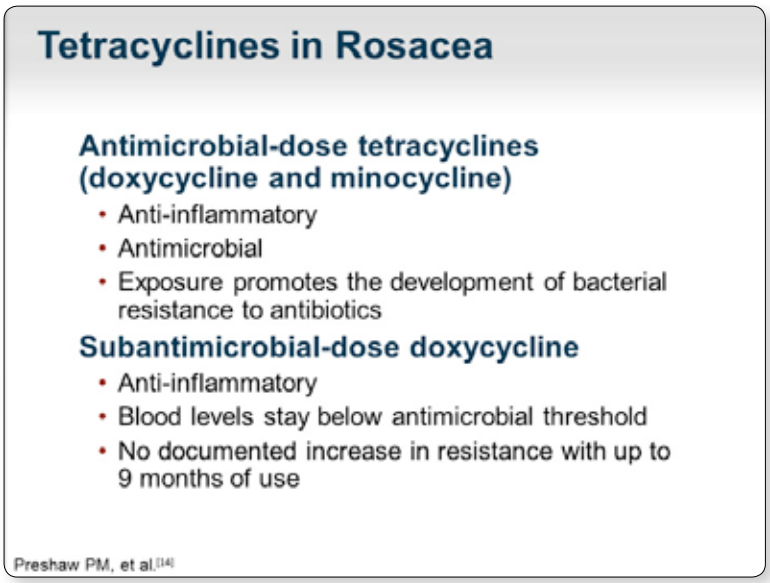

We have already learned a little bit more about azelaic acid. Azelaic acid 15% has been shown to impact the cathelicidin pathway. There has been an in vitro study. There have been in vivo studies. First of all, azelaic acid 15% has been shown to decrease KLK5 in cultured keratinocytes in vitro.[9] We always want to be very cautious when we are trying to translate an in vitro study over to the clinical setting. In addition, azelaic acid 15% has been shown to decrease KLK5 in epidermal keratinocytes in vivo.[10] Although this is an in vivo study, it is a mouse study. I can tell you that some human studies have been ongoing. We can to expect to see those in publication very soon. There is some early evidence that even in humans in vivo, the azelaic acid may impact these cathelicidin peptides as well.




We in dermatology are very comfortable with the tetracycline group of drugs. We have used them in our clinics for infections and many inflammatory skin conditions because they have a host of different anti-inflammatory properties. The tetracycline group of drugs as a family can decrease proinflammatory cytokines, chemotaxis, nitric oxide production, granulomatous inflammation, reactive oxygen species, MMPs, cathelicidins, and angiogenesis. Taken all together, many of these effects are through the tetracyclines' impact on the neutrophil, in particular, chemotaxis and nitric oxide production, MMPs, and reactive oxygen species. Impacting the neutrophil affects inflammation in several ways.

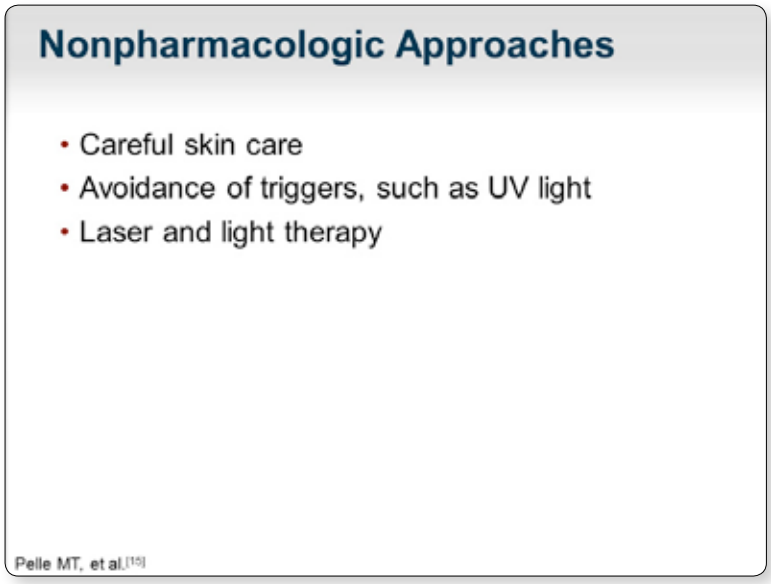



As we have learned more about the pathophysiology, it has made us go back and question whether the products that we have used and we have had success with could potentially be working in this pathway that we are starting to see and to work out. A study was done that tried to see if doxycycline had any impact on this cathelicidin pathway.[13] The ideas going into it are that MMPs activate KLK5. Remember, KLK5 is what takes pro-cathelicidin to cathelicidin. We also know that doxycycline can inhibit cutaneous human MMP activity in vitro. If we can inhibit the MMP, maybe we can inhibit the KLK5. We also know that tetracycline antibiotics inhibit cutaneous serine protease activity in vivo. That is something that we have known for quite some time. Maybe they even impact KLK5 directly. This particular study did show that doxycycline could directly inhibit MMPs and therefore could indirectly inhibit KLK5. We could go even further and say that doxycycline indirectly inhibits cathelicidin. It does all of these by suppressing proteolytic activation of pro-KLK5. That is by inhibiting MMPs.




We can use antimicrobial tetracyclines, which are what were used in for many years to treat rosacea.[14] These are in fact not approved specifically by the US Food and Drug Administration (FDA) for the treatment for of rosacea. They are used because they are anti-inflammatory agents. They are also antimicrobial and if you recall, even when we were going through the long list of potential hypotheses for the disease of rosacea, we never talked about bacterial pathogens as real players. There is some concern that if we are using an antimicrobial product, maybe there is unnecessary exposure that can promote the development of bacterial resistance to antibiotics. Still, these products are anti-inflammatory. They may play a very important role in the treatment of rosacea.

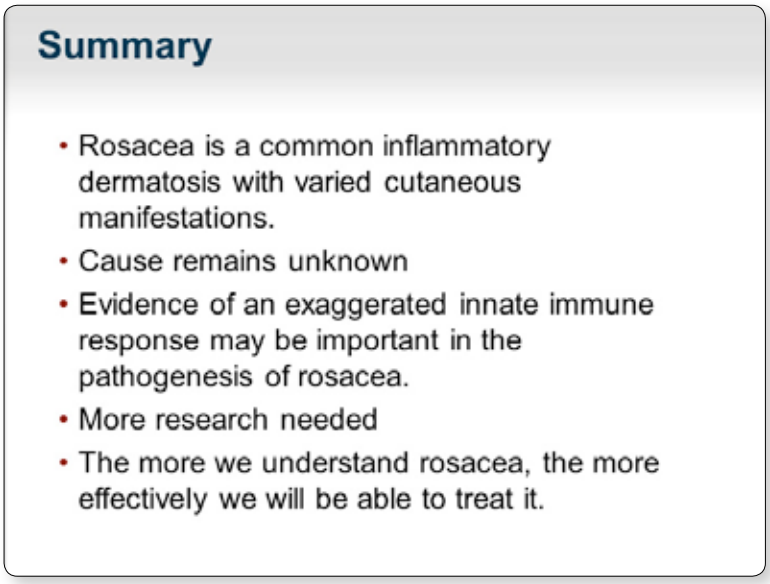
The subantimicrobial-dose doxycycline maintains the anti-inflammatory properties of the doxycycline product. The blood levels stay below the antimicrobial threshold, so this is no longer an antimicrobial, and studies show that there is no documented increase in resistance with the use of this product for up to 9 months of use.[14]




We can also talk about nonprescription treatments. We doctors in dermatology are so keen to use our topical and oral prescription products, but it is very important that we do not underestimate the value of skin care. We talked earlier that TLR2 and the cathelicidin pathway can be triggered by the skin barrier being disrupted. Many of our patients come to clinic having self-treated and self-diagnosed. Many of them have not done a very good job of that. They have used skin care products that they have bought over-the-counter at the drug store. Many of these products can be irritating to the skin, particularly to skin that is sensitive and prone to inflammation. They have caused a real problem there. It is important that we take control of the skin care and make sure that our patients are using very mild skin care products and things that will promote healing of the skin barrier and not disruption of the skin barrier.[15]

We also talked a little bit about triggers. Some of the factors that can trigger a rosacea flare may do that through the TLR. One of these is ultraviolet light. It is imperative that we teach all of our patients, regardless of skin type or skin color, that they must use sun protection on a daily basis. This is not just the dermatologists' mantra; this is really looking at the pathophysiology of rosacea. If we can block some of that ultraviolet damage and we can block the ultraviolet stimulus that may be turning on TLR, we may be able to impact the inflammation of rosacea that way too.

We can also rely on lasers and lights. Laser and lights are a very important part of treating, particularly, erythematotelangiectatic rosacea. Those individuals come in frequently with redness that is, to them, disfiguring in many ways. They may have numerous dilated blood vessels on the face. We can rely on lasers that target erythema as their chromophore and improve rosacea for patients that way. It is more difficult to assess how those lasers and lights may work through the cathelicidin pathway. I would not rule that out as a potential mechanism of action. We need to learn more about that. We need to learn more about the potential role of lasers and lights as we are learning more about the pathophysiology of rosacea.




Rosacea is a common inflammatory dermatosis with varied cutaneous manifestations. We have explored ETR, PPR, ocular rosacea, and phymatous rosacea. All of these things look very distinct. Some of them are seen together in 1 individual, but sometimes they are completely separate. In fact, they are so separate at times that it leads some people to wonder if maybe we are talking about more than 1 disease. The cause of rosacea remains unknown. We do have some early evidence that there is an exaggerated innate immune response that may be important in the pathogenesis of rosacea.

We really need to know more. We need several more confirmatory studies that look at this cathelicidin pathway. We need to know more about how the drugs that we have relied on for so long impact this cathelicidin pathway. We need to know about new drugs that may impact this cathelicidin pathway. We still need to look past the cathelicidins. The story is not complete yet, and more remains to be learned about rosacea. We also need to get the word out about rosacea. We need people to seek treatment for this condition. We do know in the end that the more we understand about this condition, the more effectively we will be able to treat it.

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## Abbreviations

AZA = azelaic acid
CAMP = cathelicidin antimicrobial peptide
DNA = deoxyribonucleic acid
ETR = erythematotelangiectatic rosacea
FDA = US Food and Drug Administration
MMP = matrix metalloproteinase
MOA = mechanism of action
mRNA = messenger RNA
PPR = papulopustular rosacea
KLK5 = kallikrein 5
RNA = ribonucleic acid
SCTE = stratum corneum tryptic enzyme
TLR = Toll-like receptor
TLR2 = Toll-like receptor 2
UV = ultraviolet

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