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Rosacea as an Inflammatory Disease: An Expert Interview With Brian Berman, MD, PhD CME

Brian Berman, MD, PhD

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Target Audience

This activity is intended for dermatologists and other physicians who treat rosacea.

Goal

The goal of this activity is to discuss recent developments in the management of rosacea.

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Brian Berman, MD, PhD

Editor's Note:

Rosacea is a common condition that is underrecognized and undertreated. Although the disease has a long history - it was described by a French surgeon in the 14th century, and one of Chaucer's Canterbury Tales pilgrims had symptoms of rosacea^[1] -- the cause of the disease has not been well understood, and treatment has been largely empirical.

MedscapeCME Scientific Director Kristin M. Richardson spoke with Brian Berman, MD, PhD, about current advances and trends in the treatment of rosacea. Dr. Berman is Professor of Dermatology and Internal Medicine at the Miller School of Medicine, University of Miami, Miami, Florida.

MedscapeCME: There have been efforts in the past few years to increase awareness about rosacea. Do you think these efforts have been successful? Are more patients seeking treatment?

Dr. Berman: It has been estimated that more than 16 million Americans have rosacea, but probably only 10% actually seek treatment.^[2] This gap may be caused in part by confusion about what the disease process actually is. It's unfortunate that rosacea has historically been called "acne rosacea." It should be called "rosacea" so that it is not confused with acne vulgaris, which clearly occurs in a different age group, has a different pathogenic basis, and is treated with different therapies.

Because rosacea may actually progress over time and increase in severity, it is my belief that the earlier you treat rosacea the better. Clearly, further education directed to those who delay seeking treatment or who do not seek treatment is necessary.

MedscapeCME: What quality-of-life issues do you see in your patients with rosacea?

Dr. Berman: There is, of course, the issue of self-image. These patients are generally not in the adolescent age group -- they are in the workforce, and it's an unfortunate truth that people perceive individuals in the workplace based on their appearance. That's a major concern, at least among my patients. On a more personal level, intuitively one wants to maximize and optimize attractiveness and cosmesis, and rosacea is a chronic inflammatory process that can't be ignored indefinitely.

MedscapeCME: Could you briefly discuss some of the recent advances in our understanding of the pathophysiology of rosacea?

Dr. Berman: It has become clear that rosacea is primarily an inflammatory and not an infectious process, and research has focused on identifying the "bad actors" in rosacea. One of the more recent insights has to do with an entity called "cathelicidins," which have also been designated alarmins because they alarm the body that it is being attacked. Cathelicidins have some antibacterial and even some antiviral activity, but their main job is to cause an alarm manifested by inflammation.

Cathelicidins induce a cytokine called interleukin 8, which recruits and activates polymorphonuclear leukocytes. In fact, these leukocytes are the predominant cells in the pustules that characterize the papulopustular form of rosacea. That cathelicidins are elevated in rosacea was a hypothesis that has since been validated.^[3] They also enhance angiogenesis, another problem in rosacea.

The good news is that everyone has cathelicidins but not everyone has rosacea. Activation of cathelicidins requires an enzyme to cleave a portion of the cathelicidin, which then becomes an active, proinflammatory agent. In fact, both the base cathelicidin and the enzyme that activates the cathelicidins are elevated in rosacea.

This is relevant because, as I mentioned, rosacea is indeed an inflammatory process rather than a bacterial infection. One of the mainstays of rosacea therapy are the tetracyclines, which historically have been used as antibiotics. But it turns out that the tetracyclines have anti-inflammatory activities, and one of the anti-inflammatory activities of the tetracyclines is inhibition of the enzyme, a serum protease, that activates the cathelicidins.

MedscapeCME: Could you discuss some of the other anti-inflammatory mechanisms of tetracyclines that are relevant to the treatment of rosacea?

Dr. Berman: I mentioned that the tetracyclines inhibit serum proteases, but there are 3 other proinflammatory bad actors that are overexpressed in rosacea: interleukin 1-beta, interleukin 6, and tumor necrosis factor-alpha. Tetracyclines are able to reduce the expression of all 3 of these proinflammatory cytokines that promote leukocyte chemotaxis and thus pustular rosacea. Tetracyclines also inhibit the activity of matrix metalloproteinases, reactive oxygen species, and nitric oxide. It has been suggested by recent data in the rat cornea model that the tetracyclines may actually block angiogenesis -- new blood vessel formation.^[4]

One last bit of new information in research: There are 2 classic major enzymes that break down and metabolize the reactive oxygen species so that they are no longer inflammatory and damaging. It turns out that patients with rosacea have a greater proclivity to have a deletion of the gene for both of those enzymes.^[5] So not only are people with rosacea elaborating reactive oxygen species, they also can't get rid of them as well as people who don't have rosacea.

MedscapeCME: It's so interesting that after years of essentially empirical therapy, new research is elucidating the mechanisms of action of rosacea treatments.

Dr. Berman: It has also led to fine-tuning some of the classic ways we have treated rosacea. We have used tetracyclines to treat rosacea, but historically we used antibiotic levels of these drugs because that's how tetracyclines were used. Indeed, antibiotic levels of the tetracyclines do express anti-inflammatory activities, but unfortunately they also express antibiotic activities and all of the associated adverse events. As I mentioned, it's a very rare patient who has an active bacterial infection in rosacea.

The insight that rosacea is an inflammatory process and that the tetracyclines have anti-inflammatory properties allowed the development of the only US Food and Drug Administration-approved oral medication for the treatment of the inflammatory lesions of rosacea: doxycycline in a delayed-release, 40-mg capsule that never achieves antibiotic activity.

Take the example of aspirin. At 81 mg it has cardioprotective activity but no activity as a pain reliever -- you have to use much higher doses to achieve pain relief. So the question is, "Why don't you use the higher doses of the tetracyclines that also have antibiotic activity, since you are already covering the anti-inflammatory activity?" It turns out that higher doses of tetracyclines cause greater adverse events, such as gastrointestinal distress. There are also data that show that we induce bacterial resistance when we use doxycycline in antibacterial dosing. This is not simply a theoretical concern, because *Staphylococcus aureus* skin infections are a major concern, and doxycycline is one of the oral medications that is effective in the treatment of methicillin-resistant *S aureus* skin infections. It would be inappropriate for us to use antibiotic dosing for a disease that is not bacteria-based, especially if the antibiotic dosing doesn't bring anything to the table in terms of rapidity of response or efficacy.

MedscapeCME: Has it been demonstrated that sub-antimicrobial doses of tetracyclines are as effective as antimicrobial doses of tetracyclines in rosacea?

Dr. Berman: Very much so. Maximum anti-inflammatory activity can be achieved at a dose that is not antibiotic. A head-to-head study of an antibiotic dose of doxycycline against the delayed-release, anti-inflammatory form of doxycycline demonstrated that the anti-inflammatory dose was just as fast and just as profound in its efficacy in rosacea as the antibiotic dose.^[6]

MedscapeCME: Could you briefly discuss the role of combination therapy in rosacea?

Dr. Berman: We often use a topically applied agent as well as an oral agent in papulopustular rosacea. Metronidazole gel is one of the classic topical treatments in rosacea, and it is effective, but using the combination of metronidazole plus the anti-inflammatory dosing of doxycycline has been shown to be more effective. In one study, the topical medication was discontinued and the oral medication was able to maintain the same level of efficacy.^[7]

MedscapeCME: What are the challenges for the future?

Dr. Berman: We have been focusing on the papulopustular form of rosacea, but treatment of the flushing, blushing, and background erythema associated with the erythematotelangiectatic form is a challenge. There are some topical antiangiogenic agents in development. Historically, agents like clonidine, aspirin, and propranolol have been used with limited effectiveness to treat the background erythema associated with rosacea. Intense pulsed light can be effective in reducing erythema and visibility of dilated blood vessels.

The other challenge is where we began this conversation: education. Patients need to be educated that rosacea is a disease that can be treated, and they should be encouraged to seek medical care. Even dermatologists, who treat

most patients with rosacea, need education so they are updated on the new insights into rosacea as an inflammatory disease and how these findings affect treatment.

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