ORIGINAL ARTICLES
SPECIAL TOPIC
Journal of Drugs in Dermatology

Why Is Rosacea Considered to Be an Inflammatory Disorder? The Primary Role, Clinical Relevance, and Therapeutic Correlations of Abnormal Innate Immune Response in Rosacea-Prone Skin

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ABSTRACT

The pathophysiology of rosacea has undergone renewed interest over the past decade, with a large body of evidence supporting the role of an abnormal innate immune response in rosacea. Many mechanisms interact with the cutaneous innate immune system that may be operative. A variety of potential triggers stimulate this immune detection system which is upregulated and hyper-responsive in facial skin of patients with rosacea as compared to normal skin. Based on the most current data, two conclusions have been reached. First, the major presentations of rosacea appear to be inflammatory dermatoses. Second, the presence of a microbial organism is not a primary or mandatory component of the pathogenesis of rosacea. Available therapies for rosacea exhibit reported modes of action that appear to correlate with the inhibition of inflammatory processes involved in the pathophysiology of at least some presentations of rosacea.

J Drugs Dermatol. 2012;11(6):694-700.

INTRODUCTION

Rosacea is well recognized globally as a common dermatologic disorder encountered in clinical practice. Although prevalence estimates vary depending on the population evaluated and the methodology used to capture the diagnosis for demographic or epidemiologic purposes, there is little disagreement that at least the major presentations that have been classified as rosacea are commonly encountered in clinical practice.[1-4] For the purposes of having a reasonably accepted "diagnostic language" for discussion, the common presentations of rosacea were first designated as subtypes in 2002, and subsequently in other references.[2] Among the four major subtypes, the two most common are erythematotelangiectatic rosacea (ETR) and papulopustular rosacea (PPR). Although rosacea has long been recognized as being most common in patients with very fair skin with a reported prevalence of up to 10% in individuals of Northern European or Celtic heritage (Fitzpatrick Skin Type I-II), it has also been reported to affect approximately 4% of individuals with darker skin types.[5-7] To add, there is some evidence that African Americans are more likely to be affected by rosacea if one of the parents is of Northern European ancestry.[8] Nevertheless, a thorough evaluation of the prevalence of rosacea, including a breakdown of individual subtypes or specific presentations, has not been completed in patients with skin of color (Fitzpatrick Skin Types IV-VI) or among different ethnicities where darker skin types than Fitzpatrick I-II are predominant.

Clinical Differentiation of Common Presentations of Rosacea

Clinical features that characteristically manifest in ETR that are also observed in many patients with PPR include diffuse central facial erythema, telangiectasias, and associated symptoms (ie, stinging, burning) and signs (ie, scaling, flaking, redness) of "skin sensitivity" and stratum corneum (SC) permeability barrier impairment.[1-5,8] PPR differs clinically from ETR by the presence of inflammatory lesions in PPR. The inflammatory lesions of PPR are commonly papules and pustules that are most pronounced on the central face with associated perilesional erythema, although some patients with PPR may have few or many inflammatory lesions with little to no diffuse central facial erythema that is not perilesional in nature.[1-3,8-11]

Overall, the threshold for inducing symptoms of skin sensitivity tends to be lower in patients with ETR as compared to those with PPR.[1-3,8-11] However, both clinical experience and controlled clinical studies have shown that many patients with PPR exhibit the same symptoms and signs that are characteristic of sensitive skin and are commonly associated with rosacea-prone skin.[12-16]

Inflammatory Mechanisms and the Pathophysiology of Rosacea

Much has been studied and written about the pathophysiological mechanisms of rosacea. However, it has been difficult to uncover all the relevant pieces of the puzzle or to accurately connect the comment elements of cogent evidence.[1-3,8-11,17-22]

Although more research is needed to further define the pathogenesis of rosacea, the most recent body of scientific data provides strong support that patients with the common presenting manifestations of rosacea innately exhibit rosacea-prone skin. Based on a collection of studies and analyses, a predominant and fundamental property of rosacea-prone skin is an abnormal innate immune detection and response system. A hyper-responsive innate immune system has been reported to be operative early in the pathogenesis of rosacea, and in the three common cutaneous subtypes of rosacea (ie, ETR, PPR, phymatous).[8,18,19,22-24] As a result, certain triggers can incite an exaggerated immune response that is facilitated by the inherent properties of facial skin in the rosacea-prone individual. In such patients, this facilitated triggering of the innate immune response system induces the signaling of cascades of inflammation that influence patterns of inflammation and alter vascular biology.[8,18,19,22,24,25-28] The clinical consequences of this inflammatory process includes acute changes associated with rosacea flares (ie, vasodilation with increased blood flow, central facial erythema, and possibly inflammatory lesions) as well as some responses that correlate with chronic changes of rosacea (chronic vascular and perivascular inflammation, enlarged cutaneous vasculature, persistent diffuse erythema, telangiectasias).[1-3,5,8-11,14,17-20,25-28] Importantly, vasodilation is recognized as a central pathophysiologic finding in rosacea, with enlarged caliber and dilation of cutaneous vasculature noted as compared to normal facial skin and in the facial skin of patients with seborrheic dermatitis, another very common inflammatory dermatosis associated with erythema.[1,2,8,18,20,25]

Other published research findings support neurovascular dysregulation and other neural-related physiochemical and structural changes noted within rosacea-prone skin. These include colocalization patterns of some sensory nerves and vessels; increased density of certain neuroregulatory/vasoregulatory receptors in ETR as compared to normal skin; increased expression of specific vasoregulatory receptor-positive nerve fibers in skin from biopsies of patients with rosacea; potential for activation by protease enzymes of transient receptor potential (TRP) channels involved in pain-temperature sensation and inflammation; and upregulation of some neuropeptides that are likely to be operative in neurovascular response and neurogenic inflammation in rosacea.[1,8,9,11,20,29] Current evidence supports neurovascular dysregulation and altered immune response as integral components of vasodilatory reactivity and "neurogenic" symptoms such as stinging and burning.[8,9,11,18,29] Upregulation of several matrix metalloproteinase enzymes (MMPs), such as collagenases, gelatinase, and elastase, has also been noted in facial skin of rosacea patients and has been correlated with dermal matrix degradation, vascular effects, and activation of SC serine protease enzymes involved in innate immune and inflammatory pathways in rosacea.[1,8,30]

Physiochemical characteristics have been identified in facial skin of patients affected by PPR as compared to normal skin. It is important to note that the recognition receptor system (ie, Toll-like receptors [TLRs]), antimicrobial peptides (AMPs), and SC serine protease enzymes function in normal skin primarily as the first line of defense (innate immune response) against invasion by pathogens, however, this innate immune response system has been shown to be abnormal in facial skin affected by rosacea.[18,19,22-24]

Innate Immune Response in Normal Skin

How does innate immune response function in normal skin? In normal skin, TLRs (such as TLR-2) serve to detect the proliferation of microbes (ie, bacterial, fungal, viral), which are perceived as a threat to invade and cause infection.[18,19,31] The triggering of specific TLRs activates an immediate host response to combat microbial proliferation and invasion. Antimicrobial peptides (AMPs) such as cathelicidin are a major component of this innate defense. Cathelicidin exists as an inactive precursor form within the SC of the epidermis.[18,19,22] Upon activation by a triggering agent (ie, bacteria, virus), conversion and degradation of cathelicidin by a SC serine protease enzyme called kallikrein-5 (KLK-5) results in the formation of pro-inflammatory peptides.[18,22,32-35] The major cathelicidin-derived peptide in skin is LL-37 which exhibits antimicrobial properties and promotes vasodilation, angiogenesis, and inflammation locally at the affected cutaneous site.[18,22-24,26-28] Without the innate immune system, microbial organisms that find the opportunity to proliferate and invade compromised skin would remain unchecked as the acquired immunity system takes days to elicit and mount a directed antimicrobial immunologic response. Importantly, the innate immune response system is capable of being activated by certain ligands that have the capacity to bind to specific TLRs, although these ligands are not microbial in origin.[31] Examples include ligands produced by physical injury or damage from ultraviolet light, and exogenously applied imiquimod, which binds to TLR-7.[31]

Innate Immune Response in Rosacea-Prone Facial Skin

In patients with cutaneous rosacea, the innate immunity system is abnormal leading to dysregulation of immune detection and response. A large body of research has demonstrated that the overall innate immune system in rosacea-prone facial

skin is hyper-responsive leading to the signaling of inflammatory pathways that correlate with commonly observed clinical manifestations of rosacea.[8,18,22-24] Findings noted in cutaneous rosacea that correlate pathophysiologically with clinical manifestations of rosacea include an increased expression of TLR-2 (a recognition receptor), an increase in the precursor of cathelicidin (hCap18), and an increase in the SC serine protease enzyme KLK-5.[8,18,22-24] In rosacea-prone skin, keratinocytes with higher levels of TLR-2 promote an increase in KLK-5 activity.[18,22,24] As a result, the larger quantity of cathelicidin coupled with the enhanced enzymatic activity of KLK-5 activates the conversion of cathelicidin to multiple variant peptides. These peptides promote the signaling of inflammatory cascades and vascular responses that can lead to chemoattraction of inflammatory cells, vasodilation with perivascular edema, and downstream signaling which can promote alterations in vasculature (ie, increase in vascular endothelial growth factor [VGEF]).[18,22,24,26,27] The marked inflammatory infiltrate shown to be present in all three major subtypes of rosacea (ie, ETR, PPR, phymatous) is diffuse, predominantly perivascular, and heavily composed of Th1 cells and macrophages, even in the absence of inflammatory lesions, further suggesting that an augmented innate immune response plays a very active and early role in rosacea.[8] In cases where inflammatory lesions (ie, papules, pustules) are present, both LL-37 and interleukin-8 (IL-8) are believed to be operative in the chemoattraction of neutrophils.[8,26]

Importantly, unique to rosacea-prone skin as compared to normal skin (based on studies of subjects with PPR) is the production of varient cathelicidin-derived peptides in addition to LL-37. These variant forms exhibit greater ability to precipitate inflammation and induce changes in cutaneous vasculature as compared to the shorter forms of LL-37 produced in normal skin.[18,22]

Ultimately, the collective biologic effects of the abnormal innate immune response associated with rosacea correlate with both specific pathophysiological responses and visible changes noted on clinical examination. The pathophysiological responses include diffuse dermal inflammatory cell infiltration, chemoattraction of neutrophils in some cases, vasodilation with perivascular inflammation and increased cutaneous blood flow, and structural changes in vasculature including promotion of neovascularization.[8,18-20,22-28] The visible cutaneous manifestations include erythema, variable amounts of edema, telangiectasias, and in some cases inflammatory lesions.

Potential Triggers and Innate Immune Response in Rosacea

Current evidence supports that a microbial source (ie, bacterium, *Demodex* mites) is not a mandatory component of the pathogenesis of rosacea, including both ETR and PPR.[1,3,8,10,18,19,22,30] Thorough review of several published references coupled with the most recent basic science and clinic research supports the predominant pathogenic roles of abnormal innate immune response and neurovascular dysregulation/neurogenic inflammation, both early and later in the emergence and development of cutaneous rosacea.[8,18,19,23,24,36,37]

With regard to the role of microbial organisms in the pathogenesis of rosacea, especially patients presenting clinically as PPR, it is currently believed that proliferation of organisms such as *Demodex folliculorum* may serve as *a pro-inflammatory trigg*er that in selected cases interacts with the heightened innate immune response of rosacea-prone skin.[1,36] In other cases, the trigger that incites the immunologic response in rosacea-prone skin may prove to be exposure to ultraviolet light or increased ambient heat, without any involvement of a microbial trigger.[8,37,38] However, as noted above, a microbe such as a bacterium or mite is not believed to be a mandatory component of the pathogenesis of rosacea but may in some cases be involved with inciting a flare by triggering innate immunologic response which is both dysregulated and augmented in cutaneous rosacea.

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Correlation of Other Potential Pathophysiologic Factors and Innate Immune Response in Rosacea

With regard to the pathophysiologal mechanisms involved in rosacea, several potential pathways have been reported that can "cross talk" with and modulate innate immune response. These include increases in several matrix metalloproteinase enzymes (MMPs), which are most pronounced in PPR and phymatous rosacea; upregulated epidermal and dermal expression of several MMPs by reactive oxygen species (ROS); signaling of activation of SC serine proteases (ie, KLK-5) by some MMPs; participation of MMPs and cathelicidin-derived peptide (ie, LL-37) in modulating dermal matrix degradation; increased magnitude of depletion of cutaneous antioxidant reserve in rosacea as compared to normal skin; and the direct correlation of cutaneous antioxidant depletion with rosacea severity.[8,9,18,21,22,29,37,39]

Another pathophysiological connection with innate immune response relates to status and function of the SC permeability barrier in rosacea. An increase in transepidermal water loss (TEWL) has been documented in central facial skin of patients

with rosacea (ETR > PPR) reflecting impairment of the SC permeability barrier, a factor that appears to correlate with sensitive skin in many rosacea patients.[1,3,40-42] As such, an important connection between the SC permeability barrier and innate immunity is the increased expression and secretion of AMPs (ie, cathelicidin) in response to impairment of the SC permeability barrier, the role of cathelicidin-derived LL-37 in SC permeability barrier homeostasis, and the direct correlation of activity of some serine proteases (including kallikreins) with impairment of SC permeability barrier function even when visible signs of skin irritation are not present.[43,44] In the presence of SC permeability barrier impairment and increased TEWL, AMPs are packaged within lamellar bodies that deposit precursor lipids into the SC at the juncture of the granular layer as a homeostatic response to replenish and repair the SC intercellular lipid bilayer.[45] Also, elevation of serine proteases can influence SC permeability barrier dysfunction and neurogenic inflammation through signaling of protease-activated receptors.[44] Hence, the SC permeability barrier and the innate immune response system are intertwined both structurally and functionally.[43-45]

Medical Therapies Used in the Management of Rosacea

A variety of medical therapies have been used for the treatment of cutaneous rosacea, predominantly for PPR.[4,12-14,46,47] Topical agents approved by the United States Food and Drug Administration (FDA) for use in patients with PPR are metronidazole (0.75% gel, cream, and lotion twice daily; 1% gel and cream once daily) and azelaic acid (15% gel twice daily). Both of these topical agents are backed by large-scale studies designed and submitted for FDA approval (in PPR) as well as several other studies demonstrating efficacy and safety for treatment of PPR.[4,12-14,46-51] Topical sulfacetamide 10% sulfur 5%, available in several "leave on" and wash formulations, has an FDA approved monograph that includes rosacea as an indication, however, none of the formulations were submitted through the formal FDA drug approval process that would include phase II and phase III controlled studies.[46,57,50] Other topical agents have been reported for the "off label" treatment of rosacea, primarily PPR, including antimicrobials (ie, benzoyl peroxide, erythromycin, clindamycin), calcineurin inhibitors (pimecrolimus, tacrolimus), and retinoids (adapalene, tretinoin), however, overall data is relatively limited with these topical agents.[4,46,47,51]

Among the oral agents used to treat rosacea, only anti-inflammatory dose doxycycline (doxycycline 40 mg modified-release capsule once daily) is FDA-approved.[4,46,47,50] As with topical metronidazole (0.75%, 1%) and topical azelaic acid (15%), anti-inflammatory dose doxycycline is FDA approved for use in patients with PPR, and has been shown to be effective and safe in this study population with absence of antibiotic activity and antibiotic selection pressure (subantimicrobial dosing of doxycycline).[4,30,46,50-54] Although not FDA approved for rosacea, antibiotic doses of tetracycline agents (tetracycline, doxycycline, minocycline) are effective in PPR, as are other oral agents used "off-label" to treat PPR, such as metronidaziole, azithromycin, and isotretinoin.[46,50,51,55,56]

Modulation of Inflammation by Medical Therapy in Rosacea

As discussed above related to treatment of rosacea, FDA approved medical therapies and the majority of data on other medical therapies used "off label" evaluated therapeutic outcomes in patients with PPR. Although a review of the potentially relevant modes of action of all the topical and oral agents used for the treatment of rosacea is beyond the scope of this article, an evaluation of the FDA approved agents suggests certain modes of action that may relate to the efficacy of these agents in rosacea.[30,39,46,47,51] Importantly, the FDA approved agents and the majority of off-label medical therapies primarily exhibit therapeutic benefit for reduction of inflammatory lesions (ie, papules, pustules) and associated perilesional erythema. These agents exhibit lesser or negligible ability to decrease diffuse central facial erythema that is not directly related to the presence of inflammatory lesions and tends to persist to some degree after they resolve.[4,12-14,30,46-54] The clinical manifestation of persistent diffuse central facial erythema is believed to correlate with fixed vascular changes of rosacea that are poorly responsive to most currently used medical therapies for rosacea.[4,12-14,25,46-54,57,58] In order to address this recognized "unmet need" in medical therapy for rosacea, topical alpha-adrenergic receptor agonists (brimonidine, oxymetazoline) are being researched for the treatment of diffuse facial erythema of rosacea, with preliminary results from phase II studies (brominidine tartrate) and a few case reports (oxymetazoline) showing favorable outcomes thus far.[50,59,60] Further studies are in progress with these alpha-adrenergic receptor agonists. At present, there is no medical therapy that is FDA approved for use solely for the facial erythema of rosacea.[46,50,57-60]

The following reviews the FDA approved agents used to treat rosacea with focus on modes of action that may be operative in modulating inflammatory processes that appear to be involved in the pathogenesis of rosacea (Table 1).

Metronidazole

Topical metronidazole is FDA approved for treatment of PPR in several formulations. Metronidazole has been shown in vitro to inhibit neutrophil functions and the effects of ROS, findings that may correlate with efficacy in treating PPR and associated perilesional erythema.[60-63] As ROS stimulate the upregulation of some MMPs that have also been shown to be increased in rosacea-affected facial skin (ie, MMP-1, MMP-3, MMP-9), and KLK-5 activation and dermal matrix degradation have been correlated with the presence of some MMPs, inhibition of ROS and neutrophil function by metronidazole may possibly explain at least some of its mode of action in patients with PPR.[8,39,57,58,64] Further research is warranted, including human facial skin studies, to more fully understand the modes of action of topical metronidazole in rosacea.

TABLE 1.

Potential Modes of Action of FDA-approved Medical Therapies for Rosacea

Agent	Potential Modes of Action in Rosacea
Topical	
Metronidazole#	• Approved for use in papulopustular rosacea • Inhibition of neutrophil function and reactive oxygen species (ROS)
Azelaic acid+	• Approved for treatment of papulopustular rosacea • Inhibition of neutrophil function and ROS • Decrease in Toll-like receptor-2, cathelicidin, and kallikrein-5
Oral	
Doxycycline^	• Approved for use in papulopustular rosacea • Inhibition of matrix metalloproteinases • Indirect inhibition of kallikrein-5 activity • Inhibition of neutrophil chemotaxis • Decrease in activity of reactive oxygen species • Inhibition of several pro-inflammatory cytokines • Inhibition of granuloma formation • Decrease in activity of nitric oxide

#Metronidazole is FDA approved for use in papulopustular rosacea in the following formulations: 0.75% gel, cream, or lotion BID; 1% gel, cream QD; +Azelaic acid 15% gel BID is FDA approved for use in papulopustular rosacea in the following formulations: 15% gel BID; ^Doxycycline is FDA approved for use in PPR as a 40 mg modified-release capsule administered QD (subantimicrobial and anti-inflammatory dose).

Azelaic Acid

Topical azelaic acid 15% gel is FDA approved for the treatment of PPR. As with metronidazole, azelaic acid also inhibits neutrophil function and generation of ROS.[65] As described above, ROS inhibition appears to be beneficial in the treatment of rosacea, possibly due to reduction in ROS-induced MMP upregulation, a decrease in MMP-induced activation of KLK-5, and/or reduction in MMP-related dermal matrix degradation.[39,57,58] In addition, azelaic acid in vitro in a murine skin model has been shown to decrease several components of innate immune response including expression of TLR-2, cathelicidin, and KLK-5, although the magnitude of these effects relevant to rosacea-affected human skin warrants additional study.[66]

Doxycycline

Tetracyclines have been shown to exhibit a wide variety of biologic and anti-inflammatory effects unrelated to their antibiotic activity, which has led to their use in a variety of non-infectious disorders, such as bullous diseases, sarcoidosis, and some rheumatologic diseases.[30,67-70] Inhibition of MMP activity by tetracyclines, has been shown in research models, including inhibition of MMP-1 (collagenase 1), MMP-2 (gelatinase A), MMP-8 (collagenase 2, neutrophil collagenase), MMP-9 (gelatinase B), MMP-12 (macrophage elastase), and MMP-13 (collagenase 3).[8,30,68-70] To date, a dose-response separation between anti-inflammatory and antibiotic activities has been demonstrated only with doxycycline based on both the pharmacokinetic profile after repeated dosing (steady-state) and placebo-controlled microbiologic assays obtained from gingiva, the gastrointestinal tract, skin, and the vaginal tract, completed over 6 to 18 months.[18,30,52,53,69,70] A recent study completed with doxycycline using human skin keratinocytes demonstrated that doxycycline does not directly inhibit KLK-5 activity.[39] Rather, activation of KLK-5 from its precursor protein is dependent on MMPs. Therefore, MMP inhibition by doxycycline resulted in downstream inhibition of KLK-5 activity and subsequently reduced activation of cathelicidin . The end result of this cascade is decreased production of cathelicidin-derived proinflammatory and vasoactive peptides (ie, LL-37).[39]

Multiple in vitro, ex vivo, and in vivo studies have demonstrated a variety of other biologic and anti-inflammatory mechanisms related to one or more of the tetracyclines that may correlate with therapeutic activity in rosacea (ie, PPR). These include inhibition of neutrophil chemotaxis, downregulation of several proinflammatory cytokines (ie, TNF-alpha, IL-1beta, IL-8, IL-10, TGF-beta1), inhibition of granuloma formation, inhibition of ROS, and decreased expression of nitric oxide (NO) synthases and activity of NO, the latter serving as an endogenous chemical inducer of vasodilation.[30,67-70] Although it is difficult to determine which of these effects are clinically relevant, and if so, to establish their relative therapeutic contribution in the treatment of rosacea, each of these biologic and/or anti-inflammatory properties shown with tetracycline agents using various research models may potentially contribute to improvement based on our current understanding of the pathogenesis of rosacea.[30,57,58,67-70] As noted above, improvement of patients with PPR has been demonstrated with use of oral doxycycline using either anti-inflammatory dose therapy that is devoid of antibiotic activity or with daily doses that produce antibiotic activity (> 50 mg daily).[4,46,50-54,57,58,68-70] In addition, anti-inflammatory dose doxycycline has been shown to demonstrate speed of onset and extent of efficacy equivalent to doxycycline 100 mg daily based on inflammatory lesion reductions and investigator global assessments (IGA) in a comparative, blinded, randomized study of patients who were also treated with topical metronidazole for PPR. Ultimately, the collective data evaluating the potential modes of action and clinical use of tetracyclines, including the FDA approved approach of anti-inflammatory dose doxycycline, further supports that it is the anti-inflammatory and other biologic properties of doxycycline and other tetracyclines that correlate with therapeutic benefit in rosacea, and not antibiotic activity.[4,30,46,50,58,68]

CONCLUSION

The pathophysiology of rosacea has undergone renewed interest over the past decade and has been the focus of several advances in basic science and clinical research. There is a large body of evidence supporting the role of an abnormal innate immune response in rosacea as well as other mechanisms that interact with the innate immune system. As a result, a variety of potential triggers stimulate this immune detection system

which is upregulated and hyper-responsive in facial skin of patients with rosacea as compared to normal skin. Studies in rosacea have demonstrated enhanced receptor recognition through increased expression of TLR-2, and increases in both the AMP cathelicidin and SC serine protease activity (KLK-5), which leads to greater production of pro-inflammatory and vasoactive peptides (ie, LL-37). Clinical manifestations of rosacea correlate with the augmented immune response including erythema associated with diffuse dermal infiltration with lymphocytes (Th1) and macrophages, vascular inflammation with vasodilation and perivascular edema, and in some cases inflammatory lesions related to the chemoattraction of neutrophils with perifollicular inflammation. Other mechanisms associated with rosacea interface with the innate immune response such as MMPs, ROS, and SC permeability barrier function. Ultimately, the major presentations of rosacea appear to be inflammatory dermatoses with a variety of mechanisms contributing to the underlying pathophysiology. Current evidence supports that the presence of a microbial organism is not a primary or mandatory component of the pathogenesis of rosacea. Currently, available therapies for rosacea exhibit modes of action that appear to correlate with the inhibition of inflammatory cascades involved in the pathophysiology of at least some presentations of rosacea. Additional studies are needed to further clarify the pathogenesis of rosacea and modes of action of therapeutic agents used in treatment, including new therapies.

DISCLOSURES

This article is based on an academic rountable discussion completed in New York City in August 2011 chaired by the lead author with participation by all the authors listed on this article. Much of the discussion was based on research presented by Dr. Richard Gallo as well as information from literature review. The paper was mostly written by the lead author with input from the other authors, with administrative support from Educational Awareness Solutions (Norwalk, Connecticut) and without input from any other sources. The participants at the roundtable did receive an honorarium for their attendance and involvement at the roundtable, and in the case of the chairperson, for assisting in review and preparation of a large body of references provided to the participants. None of the authors received honoraria related to writing of the article. The project was supported by an educational grant from Galderma Laboratories provided to Educational Awareness Solutions (Norwalk, Connecticut).

Dr. Del Rosso has served as a consultant, speaker, and/or researcher for Allergan, Bayer (Intendis), Galderma, LeoPharma, Medicis, NitroBio, Obagi Medical Products, Onset Dermatologics, Pharmaderm, Primus, Promius, Ranbaxy, TriaBeauty, Triax, Unilever, Valeant, and Warner-Chilcott.

Dr. Gallo completed research that was funded by the National Institutes of Health and US Veterans Affairs and in the past by the National Rosacea Foundation. He has served as a consultant, and/or researcher for Allergan, Bayer (Intendis), Galderma, Novartis, Johnson and Johnson, Colgate-Palmolive, Sente, and Skin Epibiotics.

Dr. Kircik has served as a speaker, consultant, and/or researcher for Abbott, Acambis, Allergan, Amgen, Assos Pharma, Astellas Pharma, Asubio, Bayer (Intendis), Biogen-Idec, Biolife, Biopelle, Breckinridge Pharma, Colbar, Centocor, Combinatrix, Dusa, Embil, EOS, Ferndale, Galderma, Genentech, GlaxoSmithKline, Innovail, Johnson & Johnson, Laboratory Skin Care, LeoPharma, Medical International Technologies, Medicis, Merz, NanoBio, Novartis, Nucryst Pharmaceutical, Obagi Medical Products, Onset Dermatologics, Promius, PharmaDerm, Quatrix, Serono, SkinMedica, ToleRx, Triax, UCB, Valeant, Warner-Chilcott, and ZAGE.

Dr. Thiboutot has served as a consultant for Galderma and Bayer (Intendis) and as a researcher for Galderma.

Dr. Baldwin has served as a speaker, consultant and/or researcher for Allergan, Galderma, GlaxoSmithKline, Medicis, Onset Dermatologics, Ranbaxy, and Valeant.

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