Update on etiopathogenesis and treatment of Acne

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Abstract
Acne, the most common skin disease, is a disorder of pilosebaceous units that affects adolescents mainly and adults occasionally. The pathogenesis is multifactorial. Besides genetic predisposition, other major factors include the action of androgens, pro-inflammatory lipids acting as ligands of peroxisome proliferator-activated receptors in the sebocytes, toll-like receptor-2 acting on keratinocytes, recognition of pathogen-associated molecular patterns, cytokines, chemokines, inflammasomes, neuroendocrine regulatory mechanisms, diet and other pro-inflammatory targets implicated in the activation of immune detection and response. Most of these factors converge on mammalian target of rapamycin complex 1 (mTORC1) activation which is further enhanced by the nutrient signaling of Western diet. This multitude of pathogenic factors has led to a new armamentarium of drugs for the treatment of acne. Topical anti-androgens, insulin-like growth factor-1 inhibitors, peroxisome proliferator-activated receptor-modulators, acetylcholine inhibitors, topical retinoic acid metabolism-blocking agents, vitamin D analogues, antimicrobial peptides, interleukin-1α and interleukin-1β blockers and immunotherapy are some of the novel treatment options.

Key words: Acne, peroxisome proliferator-activated receptors, Propionibacterium acnes, toll-like receptors

Introduction
Acne is the most common skin disease with a prevalence of 35%–90% in adolescents. It peaks between the ages of 14 and the beginning of the third decade, but may persist into or develop de novo in adulthood (20% men and 35% women). The disease causes significant physical and psychological morbidity. Acne can be considered as a chronic disease in view of the older and the most recent definitions of chronicity by the World Health Organization.

Etiopathogenesis of Acne
The pathogenesis of acne vulgaris is multifactorial. Cytokines play an important role in the pathogenesis of acne vulgaris, together with other genetic and environmental factors. Tumor necrosis factor-α-308 gene polymorphism might be a predisposing factor for acne susceptibility with no apparent relation to its severity. Acne develops as a result of an interplay between the following four factors [Figure 1]. In addition, research in the areas of diet and nutrition, genetics and oxidative stress have also yielded some interesting insights into the development of acne.

Release of inflammatory mediators into the skin
Inflammation is regarded as a key component in the pathogenesis of acne. An increase in the activity of the pro-inflammatory cytokine, interleukin (IL)-1, is observed before the beginning of hyperproliferation around the uninvolved follicles and is thought to trigger the activation of keratinocyte proliferation. Nuclear factor kappa beta (NF-κβ) regulated mRNA gene levels of the cytokines- tumour necrosis factor (TNF)-α, IL-1β, IL-8 and IL-10 are significantly upregulated in acne-involved skin, compared to the uninvolved normal adjacent skin. In inflammatory acne lesions, these also include many pro-inflammatory cytokine genes including those of matrix metalloproteinases, β-defensin 4, IL-8 and granulysin. Elevated expression of the chemokine IL-8 and the activated protein, activator protein (AP)-1, attracts circulating inflammatory cells into the tissue. Inflammation is further characterized by the action of active lipid mediators such as leukotrienes, prostaglandins and 15-hydroxyicosatetraenoic acids (15-HETE). These molecules are synthesized from arachidonic acid or linolenic acid by the enzyme lipooxygenase (LOX) and cyclooxygenase (COX), respectively.
Both COX isozymes, COX-1 and COX-2, along with 5-LOX are expressed in human sebocytes in vitro. In particular, COX-2 expression is selectively upregulated in acne-involved sebaceous glands in vivo. Phosphodiesterases lower the intracytoplasmic levels of cAMP, leading to the preferential expression of pro-inflammatory cytokines such as TNF-α, IL-1, IL-8, IL-12 and IL-23. Interleukin-1 triggers remodeling of the pilosebaceous unit and promotion of comedogenesis. Interleukin-8 is important in attracting neutrophils to the site of inflammation in the pilosebaceous unit. Interleukin-12 is the major pro-inflammatory cytokine produced by monocytes in response to invading Gram-positive organisms and induces expression of anti-microbial peptides such as defensins, which have been implicated in the evolution of the acne lesion. Psoriasin, a member of the S100 gene family, was shown to be highly expressed in the epidermis and the ductus seboglandularis of acne-involved skin, in contrast to uninvolved controls.

**Toll-like receptors**

Toll-like receptors are a subtype of pattern recognition receptors (PRRs) that can activate innate immune responses through keratinocytes, neutrophils, monocytes/macrophages, natural killer cells and dendritic cells (including Langerhans cells). There are many different toll-like receptors (TLRs); but TLR-2 and TLR-4 appear to be specific for acne pathogenesis. Microbial ligands (such as *Propionibacterium acnes*) can activate several pathways that ultimately set off nuclear factor (NF)-κβ transcription factor which causes the release of inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-12 and TNF-α). Toll-like receptor activation also leads to the release of antimicrobial peptides (human β defensin 1 and human β defensin 2) that play an important role in innate immune responses. Toll-like receptor-mediated cytokines additionally induce matrix metalloproteinases that contribute to acne inflammation, dermal matrix destruction and scar formation.

**Follicular hyperkeratinization with subsequent plugging of the follicle**

Toll-like receptor activation and secretion of IL-1α from keratinocytes may be the initiating steps in comedogenesis and therefore, critical to the pathophysiology of acne. Interleukin-1α is released from the infundibular keratinocyte in response to *P. acnes*-mediated TLR activation and is an important step in the complex natural evolution of the acne lesion. Moreover, IL-1α may contribute to both the creation of a comedogenic cytokine milieu, as well as eventual sebocyte hypercornification, characteristic of acne lesions. Microcomedone, the precursor lesion in acne, results from both follicular keratinization and reduced desquamation of keratinocytes in the infundibulum, thereby forming a keratin plug at the follicular infundibulum. Epithelial hyperproliferation (comedo formation) is driven by increased levels or sensitivity to androgens, changes in sebum lipid composition, *P. acnes* overgrowth and local cytokine milieu [Figure 2]. Biofilm, a complex aggregation of microorganisms encased within an extracellular polysaccharide lining secreted by bacteria, has a role in the formation of a microcomedo by acting as a biological glue; *de novo* formation of inflammatory lesions has also been proven.

**Propionibacterium acnes follicle colonization**

*P. acnes*, a Gram-positive anaerobic bacteria normally found in the sebaceous follicle, plays an important role, both directly and indirectly, in the development of inflammatory acne. Other propionibacteria that may have a role include *Propionibacterium granulosum* and *Propionibacterium avidum*. *P. acnes* releases many enzymes such as proteinases, lipases, hyaluronidases and chemotactic factors that are integral in the inflammatory cascade. It directs immune reactions by modulation of the T helper 1/T helper 2 response and induction of monocyte-derived dendritic cell maturation. *P. acnes* stimulates the host innate immune response by activating toll-like receptors and recognizing pathogen-associated molecular patterns (PAMPs).

*P. acnes* also stimulates inflammasome formation, which are large complexes formed when PAMPs are sensed by DAMP (damage associated molecular patterns) from the host leading to the activation of caspase-1, IL-1β and IL-18 which produce the inflammatory papules of acne [Figure 3].

**Role of sebum in acne**

The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils including triglycerides and fatty acid breakdown products, wax esters, squalene, cholesterol esters and cholesterol. Increased sebum excretion, alteration of lipid composition and changes in the oxidant/antioxidant ratio

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**Figure 1:** Interplay of factors in the etiopathogenesis of acne

**Figure 2:** Inflammation and comedone formation
Acne update

Figure 3: Role of Propionibacterium acnes in the pathogenesis of acne

Figure 4: Role of sebum in acne development

characteristic of the skin surface lipids are the main events in acne pathogenesis. The composition of lipids is of importance. Decreased levels of linoleic acid have been found in skin lipids of acne patients. An important hallmark of sebum in acne patients is the presence of lipoperoxides, mainly due to the peroxidation of squalene and a decrease in the level of vitamin E, the major sebum antioxidant. Both lipoperoxides and monounsaturated fatty acids (MUFA) are capable of inducing alteration in keratinocyte proliferation and differentiation, whereas peroxides are capable of inducing production of pro-inflammatory cytokines and activation of peroxisome proliferator-activated receptors (PPAR) [Figure 4].

The biological function of sebocytes is further regulated by several factors including the ligands of receptors expressed in sebocytes; such as androgens and estrogens, PPAR ligands and neuropeptides (NP), liver-X receptor ligands, histamines, retinoids and vitamin D.

Sebaceous function can also be modified by histamine and conversely, antihistamines, since histamine receptors have been identified in human sebaceous gland cells. Retinoids also affect the biological function of sebocytes. Retinoic acid receptors (isotypes α and γ) and retinoid X receptors (isotypes α, β, γ) are expressed in human sebocytes. All isoforms of all transretinoic acid exhibit antiproliferative effects and inhibit sebocyte differentiation and lipid synthesis. Neuropeptides (with hormonal and nonhormonal actions) can also control the development of clinical inflammation in acne (neurogenic co-control). Substance P can be identified in numerous immune-reactive nerve fibers of acne skin and sebaceous glands respond to it with the synthesis of the neutral endopeptidase.

Vitamin D receptor, vitamin D-25-hydroxyxase, 25-hydroxyvitamin D-1alpha-hydroxylase and 1, 25-dihydroxyvitamin D-24-hydroxylase are expressed in SZ95 sebocytes in vitro. Furthermore, incubation of SZ95 sebocytes with 1,25 (OH)2D3 leads to a dose-dependent modulation of cell proliferation, cell cycle regulation, lipid content and IL-6/IL-8 secretion in vitro.

Acne and hormones

Androgens have long been implicated in acne pathogenesis. Androgens such as testosterone, dehydroepiandrosterone sulfate and dihydrotestosterone, are known to regulate genes responsible for sebaceous gland growth and sebum production. The isozyme 5α-reductase type 1 which catalyzes the conversion of testosterone to 5α-dihydrotestosterone in peripheral tissues by a NADPH-dependent reaction, is expressed predominantly in skin. Higher activity of type 1, 5-α reductase is seen in acne patients whereas higher levels of DHEAS is usually seen in prepubertal acne patients. Dehydroepiandrosterone sulfate has also been shown to regulate sebum production, especially in postmenopausal women, through indirect mechanisms. Estrogen may exert its effects through several mechanisms: Direct opposition effect on androgens, inhibition of androgen secretion or modulation of genes involved in sebaceous gland growth and function. Decreased levels of estrogen in patients with acne have been found in various studies. It is suggested that exogenous estrogens have a beneficial effect on acne. This is also supported by the fact that acne is most common at puberty due to the low level of estrogens during the first few menstrual cycles.

A strong increase in sebum secretion occurs a few hours after birth; this peaks during the 1st week and slowly subsides thereafter. A new rise takes place at about the age of 9 years with adrenarche and continues up to the age of 17 years, when the adult level is reached. Growth hormone is secreted by the pituitary and it stimulates the production of insulin-like growth factors (IGF). Sebocytes express receptors for IGF-1, the interactions resulting in the growth of the sebaceous gland. Proopiomelanocortin, corticotropin-releasing hormone and corticotropin-releasing hormone receptor genes are present in the skin. Corticotropin-releasing hormone (CRH) has been reported to promote lipogenesis and to enhance mRNA expression of Δ5-3-β-hydroxysteroid dehydrogenase, the enzyme that converts dehydroepiandrosterone to testosterone in human sebocytes. Gancviciene et al. hypothesized that CRH may interact with immune factors causing release of inflammatory mediators in acne. Alpha-melanocyte-stimulating hormone has been implicated in increased sebogenesis in rodents via the stimulation of two receptor subtypes; the melanocortin receptor 1 and the melanocortin receptor 5, both of which are expressed in human sebocytes.

Role of diet in acne

Acne in adolescents of developed countries is an epidemic skin disease and has currently been linked to the Western diet. High
glycemic load and dairy protein consumption both increase insulin/insulin-like growth factor-1 (IGF-1) signaling that is superimposed on elevated IGF-1 signaling of puberty. The cell’s nutritional status is primarily sensed by the forkhead box transcription factor O1 (FoxO1) and the serine/threonine kinase mammalian target of rapamycin complex 1 (mTORC1). FoxO1 links nutrient availability to mTORC1-driven processes: Increased protein and lipid synthesis, cell proliferation, cell differentiation including hyperproliferation of acroinfundibular keratinocytes, sebaceous gland hyperplasia, increased sebaceous lipogenesis, insulin resistance and increased body mass index. Enhanced androgen levels and increased TNF-α and IGF-1 signaling due to genetic polymorphisms promoting the risk of acne, all converge in mTORC1 activation which is further enhanced by nutrient signaling of Western diet. Occurrence of acne as part of various syndromes also provides evidence in favor of correlation between IGF-1 and acne. Acne is absent in populations consuming palaeolithic diets with low glycemic load and no consumption of milk or dairy products.

Recent progress in understanding the nutrient-sensitive kinase mTORC1 allows a new view of nutrient signaling in acne by both high glycemic load diet and increased insulin, IGF-1 and leucine signaling due to milk protein consumption. Acne should be regarded as an mTORC1-driven disease of civilization, as obesity, type 2 diabetes and cancer induced by Western diet [Figure 5].

Clinical Features and Assessment
Acne affects the areas of skin with the densest population of sebaceous follicles; the prevalence and severity on the face, chest and back being 92%, 45% and 61%, respectively. In particular, the number of acne patients outside the classic age range, as in acne tarda, is increasing.

Familial predisposition, especially acne in the mother, is significantly associated with a more severe course. Exogenous factors such as androgenic hormones, competitive sports, nicotine and diet with a high hyperglycemic index make the natural course of acne more severe and persistent. In the Glasgow alumni cohort study, students with and without a history of acne were compared; a positive acne history correlated with a clearly reduced risk of coronary artery disease but a higher risk for prostate cancer.

Acne vulgaris is the common type, prevalent in 99% of the acne cases, the lesions being comedones, papules, pustules, nodules, cysts and associated scarring. The other types of acne are acne conglobata, acne excoriee, acne rosacea, acne cosmetica, mallorca acne, pomaede acne, acne fulminans, acne keloidalis nuchae, chloracne, acne mechanica and acne medicamentosa.

Acne assessment
Till now, there are more than 25 different grading systems for the assessment of acne severity that have been published in literature. Lehmann et al. have surveyed at least 25 scales for assessing the global severity of acne. Generally, a grading system aims to achieve simplicity, accuracy and a quick assessment. However, the existence of so many grading systems indicates a lack of consensus on this issue and hence no grading system is considered to be a global standard.

Computational methods for assessment of acne lesions
Researchers have proposed computational imaging methods for aiding in the acne clinical severity grading. Phillips et al. were the first ones to study polarized light photography to assess the comedo counts and inflammatory acne lesion counts. This enhanced the visualization of skin features, color and lighting and were framed in perpendicular polarized photographs.

In 2001, Rizova and Kligman used both parallel and cross polarizing light photography in combination with video microscopy and sebum production measurement. In 2008, Do et al. studied the computer assisted alignment and tracking of acne. Another group of researchers exploited multispectral images, capturing image data at specific wavelengths across the electromagnetic spectrum.

Novel Treatment of Acne
The current effective strategies of management recommended by the global alliance are directed toward one or more of these pathogenic factors and include topical and systemic antibiotics and retinoids, benzoyl peroxide, azelaic acid, salicylic acid and oral antiandrogens, depending on the severity of the disease. However, because of unwanted side effects (irritation, bacterial resistance, systemic side effects) and chronicity, new treatments that target the different pathogenic mechanisms of acne with minimal side effects are desirable. The risk of rhombomylolysis with isotretinoin has been known for 30 years and is small, but every patient should be warned not to engage in over-strenuous activity at work or sports. Clinical observation and laboratory monitoring are recommended. Further research is directed at targeting receptors, adhesion molecules, cytokines, chemokines or other pro-inflammatory targets implicated in the activation of immune detection and response (i.e., TLRs, PPARs) that appear to contribute to the pathophysiology of acne.

Therapeutic options that reduce the need for topical and/or oral antibiotic therapy for acne are welcome as bacterial resistance to antibiotics is a clinically relevant concern.

Agents that primarily target sebum production
Topical antiandrogens
Due to their oral administration and consequent systemic side effects, antiandrogens are only recommended in the treatment of moderate-to-severe acne in female patients who have not responded to conventional therapy alone. Antiiandrogens for topical use are currently undergoing clinical trials and seem to offer a safe approach for controlling sebogenesis.

Figure 5: Role of diet in acne
**Cortenolone 17α-propionate (CB-03-01)**
Cortenolone 17α-propionate, also known as CB-03-01, is a new topical monoester of cortenolone which possesses more potent anti-androgenic actions than other antiandrogens without any systemic side effects. An interaction with the androgen receptor is proposed as the mechanism of action.

**ASC-J9 cream**
ASC-J9 selectively promotes the degradation of the androgen receptor and thus exerts its antiandrogenic effects by inhibiting the interaction of circulating androgens with their receptor. A topical formulation of ASC-J9, ASC-J9 cream has been shown to reduce the sebaceous gland size and decrease sebum production. No systemic or local side effects were reported, thus making ASC-J9, a drug with an adequate safety profile.

**NVN1000**
NVN1000, also called SB204, is a gel that releases nitric oxide when applied topically to the skin. By inhibiting cytochrome 450 and reducing 5α-reductase activity, both of which can be found in sebocytes and are required for independent skin steroidogenesis, nitric oxide is able to decrease skin androgen levels, consequently reducing sebocyte proliferation, and sebum production. Further, as a reactive free radical, nitric oxide exhibits antibacterial effects. In humans, the tolerability, safety and efficacy of different concentrations (1%, 4%, 8%) of NVN1000 have also been evaluated.

**Melanocortin receptor antagonists**
JNJ 10229570, a melanocortin receptor 1 and melanocortin receptor 5 antagonist, decreases the size of sebaceous glands, production of sebaceous lipids and the expression of the sebaceous differentiation marker epithelial-membrane antigen in cultured primary human sebocytes.

**Insulin-like growth factor-1 inhibitors**
Epigallocatechin-3-gallate (EGCG), a major polyphenolic constituent in green tea, significantly reduces size of sebaceous glands, the mean number of sebocytes per gland and the size of comedones, inhibits cell proliferation and lipid synthesis in SZ95 sebocytes in vitro via inhibiting IGF-1 activity, and thus limit dihydrotestosterone-dependent sebum production. Further, EGCG exerts antimicrobial activity against *P. acnes* and has proven to be effective in treatment of acne. Patients treated with EGCG solution showed a 79%–89% reduction in non-inflammatory and inflammatory lesion counts after 8 weeks of treatment. Zinc gluconate has also been shown to reduce the over expression of IGF-1 and IGF-1 receptor caused by *P. acnes*.

**Peroxisome proliferator-activated receptor modulators**
Zileuton, an oral 5-lipoxygenase inhibitor, has been shown to reduce the number of inflammatory lesions in moderate acne by downregulating IL-6 and leukotriene B4 (LTB4), a ligand for PPAR-α, and by temporarily inhibiting the synthesis of sebaceous lipids.

**Acetylcholine inhibitors**
Sebaceous glands express acetylcholine receptors in a highly regulated manner, suggesting a role of acetylcholine in sebum production, probably through promoting sebocyte differentiation. Botulinum toxin inhibits the presynaptic release of acetylcholine and was recently found to noticeably decrease sebum production, oiliness of skin and pore size. Topical anticholinergic agents (poldine methylmethosulfate) have also shown to reduce sebum production.

**Acetyl coenzyme A carboxylase (ACC) inhibitors**
Acetyl coenzyme A carboxylase catalyzes the conversion of acetyl-coenzyme A into malonyl-coenzyme A which in turn has a role in determining whether fatty acids are synthesized or oxidized. Inhibition of ACC has shown to significantly increase fatty acid oxidation and to reduce triglyceride synthesis. DRM01B (an inhibitor of the enzyme ACC) 7.5% gel is under trial.

**Agents that primarily normalize abnormal keratinization within the pilosebaceous unit**

**Retinoic acid metabolism-blocking agents**

**Talarozole**
Is a selective azole derivative that potently inhibits the cytochrome CYP26, an isozyme involved in the metabolism of retinoic acid (RA). The rationale is that talarozole inhibits cytochrome CYP26 and increases the level of retinoic acid, allowing for normalization of desquamation of the follicular epithelium and thus reducing comedo formation. A gel formulation containing 0.35 and 0.7% talarozole provides the effects of retinoic acid formulations with less irritation.

**Monoclonal antibodies anti interleukin-1α**
Interleukin-1α seems to play a role in comedo formation. *P. acnes* activates the release of IL-1α via TLR-2 activation. Retinoic acid RA-18C3, a monoclonal antibody specific for IL-1α, is used to treat patients with moderate-to-severe acne. Subcutaneous injections of 100 or 200 mg of RA-18C3 is given on days 0, 21 and 42 for a total of three injections shows significant improvement.

**Agents that primarily work by modulating Propionibacterium acnes**

**Antimicrobial peptides**
MBI 226, currently known as omiganan pentahydrochloride, is a topical cationic peptide derived from the bovine antimicrobial peptide indolicidin that is shown to have rapid (2–6 h) in vitro microbicidal activity against a variety of Gram-positive and Gram-negative bacteria by disrupting their cytoplasmic membranes and causing depolarization followed by cell death. MBI 226 2.5% and 5.0% solutions when used topically in the treatment of acne vulgaris for 6 weeks, reduced the count of comedones, papules and pustules.

**Antioxidants**
Vitamin C, a potent antioxidant and reactive oxygen species scavenger, has shown to exert antimicrobial effects on *P. acnes*, prevent up to 40% of ultraviolet A-induced sebum oxidation and improve acne lesions in up to 76.9% of patients.

**Agents that primarily work by modulating the inflammatory response**

**Phosphodiesterase inhibitors**
Because phosphodiesterase 4 is the main cAMP-degrading isozyme, its inhibition elevates cyclic adenosine monophosphate levels and thus decreases the activity of pro-inflammatory cytokines. Therefore, drugs such as apremilast, a small-molecule
phosphodiesterase 4 inhibitor, could potentially play a role in acne treatment in the future.106

**Inhibitors of interleukin-1β-mediated inflammatory response**

Gevokizumab, also known as XOMA 052, is a humanized monoclonal immunoglobulin G2 antibody that shows high affinity and specificity to IL-1β which plays a role in inflammatory acne.107,108 The potential use of gevokizumab to treat moderate to severe acne vulgaris is currently being studied.

**Vitamin D analogues**

Treatment of cultured sebocytes with vitamin D decreases the expression of IL-6, IL-8 and matrix metalloproteinase-9.109 Further, vitamin D and its analog calcipotriol are shown to regulate innate immunity by inducing the expression of antimicrobial peptides, such as β-defensin and cathelicidin LL-37, in cultured keratinocytes.110,111 The efficacy of 1 gram calcipotriene cream applied twice daily in the treatment of acne is currently being studied.

**Dapsone 5%**

A topical formulation of dapsone has been approved by the FDA for the treatment of acne vulgaris. Data suggests that dapsone gel (5%) due to its antibacterial and anti-inflammatory effects has the potential to become an established topical drug for the treatment of acne vulgaris.112

**Systemic antiandrogens**

Anti-androgenic effects of oral contraceptives is due to the decreasing levels of circulatory androgens through inhibition of luteinizing hormones and follicle stimulating hormone.113,114 The currently FDA approved agents include norgestomet with ethinyl estradiol and norethindrone acetate with ethinyl estradiol. Cyproterone acetate is an androgen receptor blocking agent which has been well studied and found to be effective in acne in females. Higher doses have been found to be more effective than lower dose. It is also combined (2 mg) with ethinyl estradiol (35 or 50 µg) as an oral contraceptive formulation to treat acne. Other androgen blockers used in acne are spironolactone, flutamide and finasteride.115

**Immunotherapy**

The role of *P. acnes* in acne confers legitimacy on the possible benefits of immunization-based approaches which may represent a solution for limiting the development of antibiotic-resistant *P. acnes*. Various immunization-based approaches have been developed in the last decades, including killed pathogen-based vaccines, vaccination against wall-anchored sialidase, monoclonal antibodies to the Christie, Atkins, Munch-Peterson factor of *P. acnes*, anti-toll-like receptor vaccines and natural antimicrobial peptides.116

**Conclusion**

Various cytokines, chemokines, toll-like receptors and inflammamasomes are involved in the pathogenesis of acne which should be regarded as a mammalian target of rapamycin complex 1-driven disease induced by Western diet. Topical retinoic acid metabolism-blocking agents, topical antiandrogens, vitamin D receptor analogues, antimicrobial peptides, IL-1β blockers and immunotherapy are the recent treatment modalities which will soon be incorporated into newer treatment guidelines so as to target the most pathogenic factors for optimum disease control.

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