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LEADING ARTICLE

Targeting Inflammation in Acne: Current Treatments and Future Prospects

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Abstract

Acne is a common, chronic inflammatory condition affecting millions of people worldwide, with significant negative impact on quality of life and mental health. Acne is characterized by comedones, inflammatory papules, pustules, and nodulocystic lesions, with long-lasting sequelae including scarring and dyspigmentation, the latter of which is more common in skin of color. The four main pillars of acne pathophysiology include alteration of sebum production and concentration, hyperkeratinization of the follicular unit, *Cutibacterium acnes* strains, and an inflammatory immune response. Newer research has provided greater insight into these pathophysiologic categories. This greater understanding of acne pathogenesis has led to numerous new and emerging treatment modalities. These modalities include combinations of existing treatments, repurposing of existing agents historically used for other conditions, new topical treatments, novel antibiotics, topical and oral probiotics, and various procedural devices. This article will provide an overview of emerging treatments of acne and their link to our current and improved understanding of acne pathogenesis.

Key Points

Current treatments for acne include topical and oral antibiotics, retinoids, anti-inflammatory treatments, and hormonal medications, as well as various procedural therapies

Updated knowledge of the interplay between numerous pathophysiologic pathways of acne has allowed for the development of novel therapeutic targets and for the repurposing of existing topical and systemic treatments

Future acne treatments largely focus on reducing inflammation by targeting cytokine pathways known to be upregulated in acne, while novel energy-based devices focus on the target of sebaceous glands

1 Introduction

1.1 Epidemiology

Acne vulgaris is one of the most encountered dermatologic conditions by dermatologists worldwide [1]. Although the true prevalence is difficult to approximate, it is estimated to affect about 9% of the population [1–3]. In the US alone, 5 million physician visits are attributed to acne annually, costing > 2 billion dollars [4]. Cumulative prevalence approaches 100% in adolescence and decreases with age, affecting up to 64% of individuals aged 20–29 years and 43% of individuals aged 30–39 years, respectively [5, 6]. Age, oily skin, family history, and obesity are all risk factors for developing acne [1]. While well-powered studies comparing acne in various racial and ethnic groups are lacking, acne is regarded as very common across global populations [6].

1.2 Clinical Presentation

Acne is classified morphologically, including comedonal, inflammatory, nodulocystic, and mixed phenotypes with varying severity [7]. Acne can affect the face, chest, and back, or a combination of these areas. Scarring and pigmentary changes are frequent, with post-inflammatory dyspigmentation and keloidal scarring being more common in skin of color.

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1.3 Quality of Life

Acne may profoundly impair quality of life by limiting self-esteem and self-confidence, placing individuals at a significantly increased risk for developing psychiatric conditions such as depression and anxiety [8, 9]. Acne is associated with increased risk of self-injury and suicide attempts, highlighting the concerning and significant connection between acne and mental health [9, 10]. The widespread presence of acne along with its effects on quality of life underscore the importance of having a broad spectrum of treatment options targeting its various pathogenetic factors.

2 Acne Pathophysiology

Acne pathophysiology is multifactorial: sebum alteration, aberrant follicular keratinization, and *Cutibacterium acnes* combine to cause microcomedones, ultimately leading to inflammation and acne [11, 12]. Recent advances in the study of acne have identified nuances in these contributing factors, including hormones and neuropeptides, sebum production, the microbiome, and innate and adaptive immunity.

2.1 Hormones and Neuropeptides

Androgens stimulate sebocyte proliferation, augment the formation of intracellular lipid droplets and triglyceride formation, and induce hyperkeratinization of the follicular infrainfundibulum [13]. While androgens certainly influence acne, insulin-like growth factor-1 (IGF-1) is the principal hormonal driver of acne [12]. IGF-1 downregulates nuclear transcription factor Forkhead Box protein O1 (FoxO1), ultimately increasing lipogenesis and androgen receptor transduction as FoxO1 normally suppresses both [12, 14, 15]. IGF-1 additionally promotes a pro-inflammatory sebum higher in monounsaturated fats, induces androgen synthesis, and increases the availability of dihydrotestosterone (DHT) in the skin [16]. Diets comprised of high-glycemic index foods, dairy, and whey protein contribute to acne through stimulation of IGF-1, while omega-3-fatty acids and low-glycemic load diets are protective as they downregulate IGF-1 [17].

Neuropeptides are biologically active molecules found in neurons, and numerous are implicated in acne pathogenesis, including corticotropin-releasing hormone (CRH), substance P (SP) and the proopiomelanocortin (POMC) system [13]. CRH is part of the hypothalamic-pituitary-adrenal axis and is strongly expressed in acne-prone skin, supporting a mechanism for stress-induced acne [18]. CRH also induces lipid synthesis in sebocytes and interacts with androgenetic signaling pathways involved in acne pathogenesis [13]. SP is upregulated by stress and is overexpressed in the nerves surrounding sebaceous glands of individuals with acne [11, 13]. SP leads to expansion of sebaceous glands and promotes upregulation of numerous inflammatory factors [13, 19]. SP also stimulates the expression of peroxisome proliferator-activated γ (PPAR-γ), upregulating lipid production by sebaceous glands [12, 13, 20]. The POMC system, which includes α-melanocyte-stimulating hormone (α-MSH) and β-endorphin, may also be implicated in acne [12, 13]. α-MSH triggers sebocytes to differentiate and produce lipid but also decreases inflammation by IL-8 secretion from sebocytes, so the overall effect on acne pathogenesis requires further study [12, 13]. β-Endorphin's role is unclear, as it both prevents sebocyte proliferation and induces lipid generation [13].

2.2 Sebum and Sebocytes

The pilosebaceous unit is a dynamic cutaneous adnexal structure, interacting with hormones and immune pathways in addition to producing sebum [13]. Androgens stimulate sebocytes to proliferate and induce differentiation and lipid synthesis via mammalian target of rapamycin (mTOR), sterol regulatory element-binding protein-1, and Wnt/β-catenin signaling pathways [12, 13]. Sebocytes also have receptors for IGF-1, SP, CRH, and leptin, suggesting links between these systems; the presence of a leptin receptor supports a link with diet as leptin is secreted from adipocytes to signal satiety [11]. Both sebum overproduction and altered concentration contribute to acne by disturbing follicular barrier function and inducing comedo formation, *C. acnes* overgrowth, and inflammation [12, 13]. Studies suggest that de-saturation of fatty acids in sebum—increasing the ratio of monounsaturated to saturated fatty acids—is proinflammatory and may promote acne [13, 21]. Squalene, a lipid specific to sebum, undergoes peroxidation when exposed to ultraviolet (UV) radiation and leads to comedo formation and inflammation via stimulation of lipoxygenase and IL-6 production [22]. Squalene may also inhibit reactive oxygen species formation in macrophages, decreasing their ability to kill *C. acnes* [23]. Free fatty acids and cholesterol in sebum also activate PPAR pathways to produce pro-inflammatory cytokines [11, 22]. Individuals with acne also have less vitamin E in their sebum, decreasing antioxidant capability [13].

2.3 Hyperkeratinization

Excessive keratinization is one of the most important events that leads to comedo formation [13]. Increased expansion of keratinocytes with less desquamation leads to a keratin plug, putting pressure on the follicle and causing rupture [12, 13]. The drivers of hyperkeratosis have not been fully elucidated but numerous factors are contributory. *Cutibacterium acnes*

activates the release of interleukin (IL) 1α, which induces hyperkeratinization in vitro [15]. Hyperproliferative keratins (keratin 1, 16, and 17) and filaggrin are increasingly expressed in the infundibulum of acne lesions, leading to abnormal keratinization patterns [21]. Change in sebum quality, such as increase in squalene, and monounsaturated fatty acids can induce changes in keratinization as well [13, 15]. Finally, androgens may also bring about hyperkeratosis, supported by the fact that keratinocytes in the infundibulum have an increased ability to metabolize androgens [12].

2.4 *Cutibacterium acnes* and the Microbiome

Cutibacterium acnes, formerly known as *Propionibacterium acnes*, is a commensal bacterium that is the most common bacteria in sebaceous skin [24]. *Cutibacterium acnes* is important for skin homeostasis as it prevents colonization with worrisome pathogens and helps the skin maintain a normal pH [25]. However, in some instances it may act opportunistically [25]. Previously, it was thought that overgrowth of *C. acnes* led to acne, but new data show the amount of *C. acnes* on the skin is similar between acne patients and controls [24]. Newer hypotheses postulate that loss of microbial balance between the *C. acnes* subtypes leads to acne [24]. Certain subtypes, particularly phylotype IA1, are pro-inflammatory, while less acnegenic phylotypes are associated with anti-inflammatory cytokine production [16].

Cutibacterium acnes stimulates inflammation via innate (Toll-like receptors, or TLRs) and adaptive immunity (IL-17A and IFN-γ secretion from CD4+ T cells) and promotes production of matrix metalloproteinases that contribute to scarring [11, 16]. *Cutibacterium acnes* also forms biofilms, which create a pro-inflammatory sebum concentration via increased lipase activity and promote resistance to treatment with antimicrobial agents [16, 25].

Increasing evidence also supports an interplay between the skin and gut microbiomes, although the exact mechanisms have not been fully elucidated [26]. The gut microbiome may directly affect the skin microbiome via transport of gut microbes and metabolic products to the skin via the bloodstream [27]. Studies have demonstrated decreased diversity of the gut microbiome in acne patients, including an increase in *Bacteroidetes*, akin to that seen in those who consume a Western diet [28]. Gut microbiota also influence cell expansion and metabolism via the mTOR signaling pathway, which is implicated in acne, suggesting a further link between gut dysbiosis and acne inflammation [27, 29].

2.5 Innate and Adaptive Immunity

Both the innate and adaptive immune systems are involved in acne pathogenesis. *Cutibacterium acnes* activates TLR-2 and TLR-4 on sebocytes and keratinocytes, leading to the release of pro-inflammatory cytokines IL-6, IL-8, and IL-12 from monocytes [21, 30]. *Cutibacterium acnes* additionally activates the Nod-like receptor 3 (NLRP3) inflammasome in monocytic cells, which leads to increased release of pro-inflammatory IL-1β [31]. TLR-2, TLR-4, and these pro-inflammatory cytokines are all expressed in higher levels in acne lesions [31]. Acne additionally involves adaptive immunity. Early acne lesions contain large amounts of CD4+ T-helper cells; *C. acnes* induces T-cell proliferation and leads to accumulation of T-cells specific for C. acnes [32]. *Cutibacterium acnes* can also cause these specific T-cells to secrete both IFN-γ and IL-17A, leading to a both a Th17 and Th1/Th17 host response [31, 32]. The numerous pathways capable of inducing acne inflammation constitute several potential therapeutic targets.

3 Current Treatments

3.1 Hormonal Medications

As mediators of sebocyte differentiation and sebum production, androgens, including testosterone and DHT, are major targets for acne treatment. Oral contraceptives (OCPs) target ovarian production of androgens and can thus treat hormonal acne in women, particularly those who report perimenstrual flaring of their acne or have associated polycystic ovarian syndrome. The major formulations of OCPs include combined oral contraceptives (COCs), which contain both estrogen and progestins as well as progestin-only pills (POPs). At 6 months of treatment, COCs have been shown to be as effective as systemic antibiotics in reducing acne lesions [33]. POPs have not been studied in acne. Contraindications include a history of thromboembolism, migraine with aura, or smoking in those 35 years or older (due to an increased risk of thromboembolic events) [7, 34].

Spironolactone is a non-selective aldosterone receptor antagonist with moderate activity against androgen receptors, thereby reducing testosterone and DHT levels. It is a longstanding treatment for hormonal acne with proven safety and tolerability that can be used alone or in conjunction with OCPs [35–37]. Adverse effects include menstrual irregularity, breast tenderness, hyperkalemia in those with renal disease, and teratogenicity.

Clascoterone is a recently FDA-approved topical androgen receptor antagonist which competes with DHT to decrease inflammatory cytokine and sebum production. In randomized clinical trials (RCTs), it has demonstrated favorable efficacy with limited side effects including localized irritation [38]. A small percentage of patients may develop reversible adrenal suppression, but the clinical relevance of this finding requires further elucidation [39, 40].

3.2 Sebum Production and Hyperkeratinization

Topical and systemic retinoids are vitamin A derivatives which bind retinoid X and/or retinoic acid (RAR) receptors to suppress sebum production, hyperkeratinization, and pro-inflammatory cytokine production. This ultimately leads to increased keratinocyte turnover, comedolytic properties, normalization of desquamation at the follicular infundibulum, and decreased inflammation. They also help treat post-inflammatory hyperpigmentation (PIH), a common sequela of acne in skin of color [41]. The four FDA-approved topical retinoids are adapalene, tretinoin, tazarotene, and trifarotene (a new selective RAR-γ topical which is useful in treating facial and truncal acne) [42]. Micronized formulations can help reduce cutaneous irritation and erythema resulting from increased transepidermal water loss [43]. Cutaneous irritation and mild photosensitization are common.

Isotretinoin is the only FDA-approved oral retinoid for treating severe, nodulocystic, and/or recalcitrant acne, especially in those with scarring. In addition, isotretinoin is the only acne medication which is thought to target all four major pillars of acne pathogenesis: sebum production, hyperkeratinization, *C. acnes* concentration, and inflammation. Importantly, it may also induce remission of acne after an appropriate cumulative dose is achieved. Common adverse effects include mucocutaneous dryness and irritation, elevated serum triglycerides and liver enzymes (these should be monitored before treatment initiation and at peak dose), and severe teratogenicity requiring monthly pregnancy testing and extensive counseling about contraception [44–46].

3.3 Antibacterial Treatments

Topical antibiotics for the treatment of acne include benzoyl peroxide (BP), clindamycin, erythromycin, dapsone, and minocycline. These agents reduce the concentration of *C. acnes*, have anti-inflammatory properties, and can be combined with topical retinoids for increased efficacy. BP releases free radicals, which break down keratin and cause peroxidation of *C. acnes* without leading to antimicrobial resistance unlike monotherapy with other antibiotics [47]. Common first-line combination therapies include BP with clindamycin or erythromycin. Clindamycin is preferred because of resistance rates of *C. acnes* to erythromycin [48, 49]. Topical dapsone is a newer second-line agent which can also be used as initial therapy in skin of color, women with inflammatory acne, and/or those with sensitive skin, allergies, or other contraindications [50–52]. Another newer agent, topical minocycline, has been shown to have excellent efficacy in treating inflammatory acne [53]. Lastly, sodium sulfacetamide, sulfur, salicylic acid, and azelaic acid are other topical agents with antimicrobial properties which may be useful in treating acne. Salicylic acid and azelaic acid have the added benefit of improving PIH [54]. Adverse effects associated with topical antibiotics include localized irritation.

Oral antibiotics are another cornerstone of acne treatment; tetracyclines are the most utilized, consisting of doxycycline, minocycline, and the newer agent sarecycline. They inhibit the 30S subunit of bacterial ribosomes and have potent anti-inflammatory properties, as evidenced by the sustained efficacy of submicrobial dosing in treating acne [55]. Penicillins, sulfonamides, and macrolides are used less commonly. Adverse effects of oral antibiotics include gastrointestinal upset and, particularly with tetracyclines, photosensitivity and teratogenicity.

3.4 Procedures

Several laser and energy-based light devices have been studied in acne management. Photodynamic therapy (PDT) has been shown to be effective in a limited number of studies in treating inflammatory acne via destruction of pilosebaceous units and decreasing *C. acnes* concentration [56–58]. Light-emitting diode (LED) red and blue light therapies are effective in treating inflammatory acne either alone or in combination with each other [59–62]. Intense pulsed light (IPL) can improve inflammatory acne and reduce the size and number of sebaceous glands [61, 63, 64]. IPL treats inflammatory acne by killing *C. acnes*, downregulating tumor necrosis alpha (TNF-α), and upregulating transforming growth factor beta (TGF-β) [65, 66]. Additionally, pulsed-dye laser (PDL) therapy may also be effective in treating inflammatory acne and has been posited to have a longer-lasting therapeutic effect than IPL [66, 67]. Most lasers require multiple sessions and have similar side effect profiles including localized pain, irritation, bruising, and dyspigmentation. The 1450-nm diode laser, which incorporates a dynamic cooling device, has demonstrated moderate efficacy in the treatment of inflammatory acne and excessive sebum production [68–70]. Various delivery methods have been studied: stacked-pulse delivery may be slightly more efficacious, but caution should be used in Fitzpatrick types IV–VI because of increased risk of hyperpigmentation [68]. Dual regimen treatment (lower fluence directly to inflammatory lesions followed by a micropulsed moving mode administered to the whole face) may be more effective than typical high fluency stamping, is less painful, and may be less likely to cause hyperpigmentation [69].

AviClear™ is a 1726-nm wavelength laser which was recently cleared by the FDA for the treatment of mild-to-severe acne [71]. It selectively targets the sebaceous glands and implements contact cooling, thereby reducing laser-related side effects [72]. Unreleased manufacturer-reported results demonstrate current and future breakout episodes are shorter, less intense, and more infrequent with sustained improvement following three 30-min treatment sessions in

all skin types [71]. The 1726-nm Accure Laser System and a combined vacuum and broadband light device named TheraClear® have also been recently approved by the FDA [73, 74].

Also recently approved by the FDA, topical gold nanoparticle-enhanced selective photothermolysis of sebaceous follicles shows promising results for acne [75–77]. Three weekly facial treatments with topically applied gold microparticles and diode laser pulses led to significant and sustained improvement in inflammatory acne [78]. Similarly, patients who received three treatments with a photopneumatic device preceded by topical gold nanoparticle application found significant improvement in mixed acne [79]. Indeed, topical application of gold salt (auranofin) itself downregulated the NLRP3 inflammasome in a mouse model, suggesting an anti-acne effect [80].

Several superficial to medium depth peels have been studied for acne as well as resultant PIH and scarring, including glycolic acid, salicylic acid, azelaic acid, pyruvic acid, mandelic acid, phytic acid, and Jessner's solution. There is no robust evidence for the superiority of one over the others, as shown in a recent meta-analysis and multiple split-face studies comparing peel regimens. Side effects of chemical peels usually involve post-procedure erythema, dyspigmentation, and risk of infection. Prior to using chemical peels, patient-specific factors should be considered, including the risk of significant irritation and impaired healing depending on the patient's medical status, the risk of dyspigmentation in skin of color, recent treatments and procedures, and the lack of safety data in pregnant women. For skin of color individuals, medium depth peels should be avoided due to risk of dyspigmentation.

Non-ablative fractionated radiofrequency microneedling (FRFM) is useful in treating active acne and scarring [81, 82]. Combining FRFM with isotretinoin is particularly effective in treating inflammatory acne and reducing scarring [83]. In fact, combinations of isotretinoin with other energy-based devices including PDL and ablative fractional lasers are effective treatments for active inflammatory acne as well [84]. Lastly, microneedling devices may be implemented in the transdermal delivery of topical retinoids and salicylic acid and for improving scarring [85].

4 Future Prospects for Targeting Inflammation in Acne

4.1 Topical Treatments

4.1.1 New Formulations and Combinations of Existing Topical Acne Treatments

Several new topical treatments for acne are currently under investigation: this includes new formulations (including microencapsulation of ingredients for improved penetration into the pilosebaceous unit and retinoid lotions), classes, and combinations of longstanding treatments (such as combined BP and retinoids that are more effective and well tolerated than individual components) [86, 87]. The combination of newer topicals and older systemic agents holds promise for increased efficacy, as evidenced by a study on combined topical trifarotene and oral doxycycline [88]. There are numerous novel agents which are currently under investigation for the treatment of acne (Table 1) [87].

4.1.2 Topical Synthetic Cannabinoids

Topical synthetic cannabinoids are reported to treat inflammatory acne by suppressing sebum production, reducing *C. acnes* concentration, and inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) [89–92]. One human trial utilizing a 3% cannabis seed extract cream found reduction in skin sebum production and erythema without significant side effects [93]. A current study is evaluating the efficacy of a topical synthetic cannabinoid in treating acne with promising early results [94].

4.1.3 Topical Tranexamic Acid

Tranexamic acid (TXA) is an anti-fibrinolytic synthetic derivative of the amino acid lysine which inhibits the conversion of plasminogen to plasmin to reduce blood loss [95]. Topical TXA treats melasma by inhibiting UV driven melanocyte activation and reducing plasmin-mediated arachidonic acid and MSH release [96, 97]. Topical TXA has been previously shown to improve acne-induced post-inflammatory erythema, and more recently a split-face RCT of mild-to moderate acne treated with topical TXA 10% serum demonstrated a significant reduction in papulopustular lesions through immunomodulatory mechanisms requiring further study [98, 99].

4.1.4 Topical Meclizine Gel

Meclizine dihydrochloride, an H1 histamine antagonist typically taken orally for motion sickness, has recently showed promising results for acne [100]. Meclizine reduced the in vitro production of IL-8 and IL-1β by *C. acnes*-stimulated human keratinocytes and monocytes and decreased IL-1β, TNF-α, and granulocyte-macrophage colony-stimulating factor production in ex vivo human skin [100]. Meclizine 2% gel reduced acne severity by 20.1% in 60 patients [100].

4.1.5 Topical Antimicrobial Peptides and Bacteriophages

Designed antimicrobial peptides (AMPs) are synthetic analogs of naturally occurring AMPs which comprise part of

Table 1 New treatments targeting inflammation in acne

Treatment	Proposed mechanism of action	Common adverse effects
Topical agents		
Novel combined antibiotic and retinoid formulations: Fixed-dose clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel (IDP-126) Fixed-dose minocycline 3% and adapalene 0.3% foam (FCD105) Fixed-dose tretinoin 0.1% and benzoyl peroxide 3% cream (Twyneo®)	Antimicrobial activity against *Cutibacterium acnes* (*C. acnes*), suppression of sebum production, reduced hyperkeratinization, and decreased production of pro-inflammatory cytokines	Local erythema, irritation, xerosis, and photosensitivity
Topical synthetic cannabinoids	Antimicrobial activity against *C. acnes*, suppression of sebum production, and decreased production of pro-inflammatory cytokines	Not reported
Topical tranexamic acid 10% serum	Not determined	Local erythema, irritation, xerosis, and photosensitivity
Topical meclizine 2% gel	Decreased production of pro-inflammatory cytokines	None reported in limited studies
Topical antimicrobial peptides (AMPs)	Antimicrobial activity against *C. acnes*	Local erythema, irritation, and xerosis
Topical surfactin-oleogel	Antimicrobial activity against *C. acnes* and decreased production of pro-inflammatory cytokines	Not reported
Topical nitric oxide and derivatives	Antimicrobial activity against *C. acnes* and decreased production of pro-inflammatory cytokines	Local erythema, irritation, and xerosis as well as headache, dysmenorrhea, nasopharyngitis, and possible dose-dependent decrease in blood pressure
Topical probiotics	Antimicrobial activity against *C. acnes* and decreased production of pro-inflammatory cytokines	Local erythema, irritation, and xerosis as well as unpleasant odor
Topical ivermectin 1% cream	Antimicrobial activity against *C. acnes* and antiparasitic activity against *Demodex* mites	Local erythema, irritation, and xerosis
Systemic treatments		
Novel antibiotics: Pentobra and Zolav (p-carboethoxy-tristyrylbenzene derivative)	Antimicrobial activity against *C. acnes*	Not reported (have not been studied in humans)
Oral phosphodiesterase inhibitors: apremilast (phosphodiesterase-4 inhibitor)	Decreased production of pro-inflammatory cytokines	Diarrhea, nausea/vomiting, headache, weight loss, musculoskeletal pain, nasopharyngitis
Oral probiotics	Antimicrobial activity against *C. acnes* and decreased production of pro-inflammatory cytokines	Diarrhea or constipation, nausea/vomiting, bloating
Biologic agents: TNF-α inhibitors, IL-17 inhibitors, and IL-23 inhibitors	Inhibition of pro-inflammatory cytokines	Injection site reactions, upper respiratory and urinary tract infections, nausea/vomiting
Procedures		
1726 nm laser devices: AviClear™ and Accure Laser System	Selective photothermolysis of sebaceous glands and thus suppression of sebum production	Local erythema, irritation, xerosis, and edema
Gold nanoparticle-enhanced diode laser and photothermal therapy	Selective photothermolysis of sebaceous glands and thus suppression of sebum production	Local erythema, irritation, xerosis, and edema
Negatively charged air ions: Dermio Care®	Reduction of reactive oxygen species and activation of innate immune system	None reported in limited studies

Table 1 (continued)

Treatment	Proposed mechanism of action	Common adverse effects
Combined systemic and procedural treatments: minocycline and intense pulsed light (IPL) isotretinoin and IPL; isotretinoin and delicate pulsed light (DPL)	Antimicrobial activity against *C. acnes*, suppression of sebum production, reduced hyperkeratinization, and decreased production of pro-inflammatory cytokines	Side effect profiles of included oral agents plus local erythema, irritation, xerosis, and edema from laser therapy

the innate immune response to new pathogens [101]. In vitro and mouse models have demonstrated that specially designed AMPs can neutralize *C. acnes* [94, 95]. An additional future benefit of AMPs is that they could be engineered to address multi-drug-resistant strains of *C. acnes* [101]. A study combining isotretinoin with topical granulysin-derived AMP (GDP-20) for mild-to-moderate mixed acne showed improved results with combination therapy versus isotretinoin alone [102]. A novel topical cationic peptide analog of indolicidin that has bactericidal properties (CLS001/MBI 226, or Omiganan) has finished two RCTs but results are not yet reported [87]. An exogenous, non-synthetically derived AMP produced by *Bacillus brevis* named tyrothricin has also demonstrated potential in inflammatory acne [103]. Lastly, bacteriophages causing lysis of surrounding bacteria have been isolated and formulated into a cream that decreases *C. acnes* concentration in vitro; more human studies are needed [104, 105].

4.1.6 Topical Surfactin-Oleogel

Surfactin is a surfactant with emulsifying and antimicrobial properties that can destroy the cell wall and membrane of *C. acnes* [106, 107]. In a mouse model, surfactin-oleogel (surfactin mixed with grapeseed oil) reduced *C. acnes* concentration and attenuated oxidative stress via inhibition of pro-inflammatory cytokines, nitric oxide, and nuclear factor-κ B-mediated pathways [108]. Moreover, the gel decreased cholesterol and free fatty acids synthesis and increased triglycerides and linoleic acid content [108].

4.1.7 Topical Nitric Oxide and Derivatives

Nitric oxide (NO) is a vasodilator with antimicrobial and immunomodulatory properties [109–111]. NO-releasing nanoparticles have significant bactericidal activity against *C. acnes* and suppress release of TNF-α, IL-1β, IL-6, and IL-8 in human cells [111]. A phase II RCT using NO 4% gel (SB204) found significant reduction in acne lesions without prominent adverse effects [112]. Additionally, a NO-generating serum significantly reduced acne lesions in 30 racially/ethnically diverse patients [113]. Relatedly, a spray containing a strain of the ammonia-oxidizing bacteria *Nitrosomonas eutropha*, a NO-producing bacterial strain designed to repopulate the skin flora with anti-inflammatory bacteria, has been shown to reduce inflammatory acne [87]. Reported side effects included headache, dysmenorrhea, nasopharyngitis, and a dose-dependent decrease in blood pressure.

4.1.8 Topical Probiotics

It is hypothesized that overgrowth of pathogenic *C. acnes* phylotypes can be prevented by bolstering normal skin flora via

topical probiotics [114]. Proposed mechanisms for this effect include increased production of antimicrobial proteins by non-pathogenic bacteria, reduction of pro-inflammatory cytokines, and direct inhibition of *C. acnes* growth [115–119]. One study of a lotion containing enterocins from *Enterococcus faecalis* SL-5 reported significant improvement in inflammatory acne [120]. Another study of a lotion containing a 5% extract of *Lactobacillus plantarum* found it was effective in reducing acne lesion size and erythema [121].

4.1.9 Topical Ivermectin

Approved for the treatment of head lice and rosacea, topical ivermectin 1% cream could also potentially treat acne via inhibition of lipopolysaccharide-mediated inflammation caused by *C. acnes* [122]. Ivermectin may also be beneficial as acne patients may have an increased concentration of *Demodex* organisms on their skin [123]. A small case series showed that topical ivermectin 1% cream improved inflammatory acne, but a study comparing it to combined BP and adapalene gel showed less effectiveness [87, 124].

4.2 Systemic Treatments

4.2.1 New Antibiotics and Related Treatments

A novel peptide-aminoglycoside molecule named Pentobra has been shown in vitro to have more robust bactericidal activity against *C. acnes* than tobramycin [125]. Zolav (p-carboethoxy-tristyrylbenzene derivative) is part of a new class of antibiotics that target the bacterial mechanosensitive ion channels of large conductance [126]. It has been shown to inhibit the growth of *C. acnes* in in vitro and in vivo mouse models of acne [127]. Multiple vaccines against *C. acnes* have been studied in mice; while anti-serum from vaccinated mice decreases human sebocyte cytotoxicity and IL-8 production, vaccines have not been shown to influence the concentration or growth of *C. acnes* [128–130].

4.2.2 Oral Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) inhibitors prevent the breakdown of cyclic adenosine monophosphate, thereby reducing inflammation via modulation of numerous cytokines. Case reports have demonstrated efficacy of apremilast, a PDE-4 inhibitor approved for psoriasis, in treating synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome refractory to biologics as well as recalcitrant isotretinoin-induced acne fulminans [131, 132]. No current studies exist for treating acne.

4.2.3 Oral Probiotics

The literature on the potential role of oral probiotics in treating acne is evolving [114]. Oral probiotics increase levels of anti-inflammatory IL-10 in acne patients [133]. A study comparing an oral probiotic, oral minocycline, and combination therapy reported significant improvement of acne lesions in all three groups after 1 month with combination therapy possessing the greatest efficacy [134]. A recent RCT comparing adapalene and BP with or without concomitant intake of an oral probiotic in mild-to-moderate acne found greater improvement in the probiotic group, albeit not statistically significant [135]. Consumption of lactoferrin-enriched fermented milk can also reduce acne lesions [136]. Lastly, an RCT of 114 patients taking a symbiotic dietary supplement containing multiple probiotic strains and a botanical extract found significant improvement in acne lesions and *C. acnes* concentration [137].

4.2.4 Biologics

In small case reports, biologic agents have been studied in severe manifestations of acne. TNF-α inhibitors like adalimumab and etanercept are considered effective treatments for severe acne conglobata and acne fulminans [138, 139]. Moreover, the IL-17 inhibitor secukinumab and the IL-23 inhibitor risankizumab have been shown to be effective treatments for recalcitrant SAPHO syndrome [140, 141]. Indeed, the IL-17/Th17 pathway has been shown to be active in acne lesions [31]. However, CJM112, a fully human IL-17A inhibitor which targets a different epitope than secukinumab, was not superior to placebo in treating inflammatory acne in a recent RCT [142]. Lastly, anti-IL-1β inhibitor gevokizumab (XOMA 052) has completed an RCT without reported results [87].

4.3 Procedures

4.3.1 Negatively Charged Air Ions

Existing in the atmosphere, negative air ions (NAIs) are electrically charged molecules which enrich the surrounding oxygen, reduce free radicals, and reduce inflammation via unclear mechanisms [143]. A study of twice weekly treatments with a NAI facial device for 3–4 weeks in three patients showed improvement of inflammatory acne without significant adverse effects [143].

4.3.2 Combined Systemic and Procedural Treatments

The combination of systemic and procedural acne treatments has also shown synergy. An RCT showed that oral

minocycline 100 mg daily combined with 3-monthly IPL treatments led to significant and persistent reduction in inflammatory lesions and post-inflammatory erythema as compared to minocycline monotherapy [144]. Similar findings have been reported with the combination of 420 nm IPL and isotretinoin compared to isotretinoin monotherapy [145]. Delicate pulsed light (DPL) is a safer, more specific subtype of IPL with a narrower therapeutic spectrum of 500 to 600 nm [146]. The combination of DPL with low-dose isotretinoin provided greater efficacy in lesion reduction when compared to isotretinoin monotherapy [147].

5 Conclusion

As knowledge of acne pathogenesis expands, novel approaches for targeting inflammation are rapidly emerging in the form of topical, systemic, procedural, and combination therapies. New or modified medications within familiar classes, the repurposing of drugs used to treat other inflammatory conditions, and the development of novel treatment modalities may all be efficacious in treating acne. Some of these treatments have the added benefit of decreasing and treating acne sequelae, including atrophic scarring and dyspigmentation. The diverse mechanisms of action include direct bactericidal activity against *C. acnes*, inhibition of pro-inflammatory factor release, reduction of oxidative stress, activation of the immune system, and modulation of the microbiome. With growing concerns over antimicrobial resistance and with certain individuals unable to tolerate well-established therapies, additional treatment options that are safe and effective in all skin types and colors are needed.

Declarations

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Conflict of Interest Dr. Elbuluk has served as a consultant to Galderma. Dr. Cruz and Dr. Vecerek have no conflicts of interest.

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