New and emerging treatments in dermatology: acne

A. KATSAMBS & C. DESSINIOTI
Department of Dermatology, A. Sygros Hospital, University of Athens, Greece

ABSTRACT: Topical retinoids, benzoyl peroxide, azelaic acid, and topical and oral antibiotics remain the milestone of treatment for mild to moderate acne vulgaris. Oral isotretinoin is useful for the treatment of severe nodular acne, treatment-resistant acne, and acne with a risk of physical or psychological scarring. Hormonal treatment in female acne is useful in resistant or late-onset acne. With increasing concerns regarding teratogenicity of isotretinoin and increasing antibiotic resistance, there is a clear need for therapeutic alternatives to these long-used treatments. Research in the pathogenesis of acne has allowed for new therapies and future perspectives regarding acne to evolve. They include low-dose long-term isotretinoin regimens, insulin-sensitizing agents, 5α-reductase type 1 inhibitors, topical photodynamic therapy, new combination formulations, dietary interventions, and antiinflammatory agents such as lipoxygenase inhibitors.

KEYWORDS: acne, new treatments, review

Introduction

Acne vulgaris is the most common skin disorder affecting mainly adolescents, although it may present at any age (1). It has been defined as a chronic inflammatory dermatosis that is characterized by comedones and inflammatory lesions including papules, pustules, and nodules. It may be associated with a severe psychological and social impairment, as it may result in dysmorphia and permanent scarring, with a risk of low self-esteem and depression (2).

The four major pathophysiologic factors that influence acne pathogenesis include sebaceous gland hyperplasia with hyperseborrhea, abnormal follicular differentiation, hypercolonization of the follicle with Propionibacterium acnes, inflammation and immune reaction (2). Although each of these factors may represent a potential therapeutic target, the sequence of events has not been elucidated yet.

Standard acne treatments include topical retinoids, benzoyl peroxide, azelaic acid, antibiotics, and oral isotretinoin. Also, hormonal therapy for women with acne is indicated when repeated courses of isotretinoin are needed to control acne, when there are clinical or biochemical evidence of ovarian or adrenal hyperandrogenism, and for late-onset acne (2,3,4). However, current acne treatment is limited by the lack of effective and safe agents that reduce sebum apart from oral isotretinoin and hormonal treatments (5). With increasing concerns regarding teratogenicity of isotretinoin and increasing antibiotic resistance, there is a clear need for therapeutic alternatives to these long-used treatments.

In recent years, research has led to a greater understanding of the pathogenesis of acne, thus opening the way for the design of new therapeutic modalities. In this review new and emerging treatments for acne vulgaris will be presented (Table 1).

Systemic treatments

Antibiotics

Antibiotics such as tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline), trimethoprim, and macrolide antibiotics
Table 1. Standard and new antiacne treatments

<table>
<thead>
<tr>
<th>Standard treatments</th>
<th>New and emerging treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic antibiotics</strong></td>
<td><strong>Systemic antibiotics</strong></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Lymecycline</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>New tetracycline formulations</td>
</tr>
<tr>
<td>clindamycin</td>
<td><strong>Topical combination formulations</strong></td>
</tr>
<tr>
<td><strong>Topical treatments</strong></td>
<td></td>
</tr>
<tr>
<td>Benzyl peroxide</td>
<td></td>
</tr>
<tr>
<td>Retinoids</td>
<td></td>
</tr>
<tr>
<td>Azelaic acid</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Oral isotretinoin</td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal treatments</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-androgens: cyproterone acetate,</td>
<td></td>
</tr>
<tr>
<td>flutamide, spironolactone</td>
<td></td>
</tr>
<tr>
<td>Combined oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Low-dose oral glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Gonadotrophin-releasing hormone (GnRH) agonists</td>
<td></td>
</tr>
</tbody>
</table>

(erythromycin) have been a mainstay of treatment for moderate and severe acne and treatment resistant forms of inflammatory acne, for more than 30 years (2). The efficacy of tetracycline derivatives in acne vulgaris is believed to be related, besides to their antibiotic effects, also to their antiinflammatory effects. Antiinflammatory action may be exerted via reduction in neutrophil chemotaxis, as well as via inhibition of proinflammatory cytokines and matrix metalloproteinase-9 (MMP-9) (6,7).

Nevertheless, data concerning antibiotic use in acne have been based on anecdotal reports, clinical experience, and small clinical trials (8).

Resistance of *P. acnes* to antibiotics is an emerging problem. Resistance is more common with erythromycin, less common with tetracycline, doxycycline, and trimethoprim and rare with minocycline (9,10). Although acne itself is not infectious, antibiotic-resistant propionibacteria should be considered transmissible between susceptible individuals (9). Also, resistance may reduce the clinical efficacy of antibiotic treatments (11). Whether the development of new antibiotic formulations and the use of low-dosage regimens may reduce resistance, remains to be seen.

New and emerging systemic antibiotics that may be proposed for acne represent lymecycline, azithromycin, antiinflammatory dose doxycycline, and a new minocycline formulation.

**Lymecycline.** Lymecycline is a second-generation, semisynthetic tetracycline, with improved oral absorption, enhanced tissue penetration, and slower elimination than tetracycline (12). It has been shown to have a comparable efficacy and safety profile to minocycline for the treatment of acne, while being four times more cost effective (13). Also, combination treatment with lymecycline plus adapalene gel 0.1%, offers the potential for improved efficacy and a shorter duration of treatment when compared with either drug alone, which may reduce the chance of antibiotic resistance (14). Lymecycline is proposed at a dosage of 300 mg/day for 12 weeks (13,14).

**Azithromycin.** Azithromycin is a methyl derivative of erythromycin that effectively inhibits significant intracellular pathogens, as well as Gram-positive and Gram-negative aerobic and anaerobic bacteria, including *P. acnes* (15). It has been found to be effective in treating noninflammatory and
inflammatory acne lesions (16,17), and when compared, at least as effective as tetracycline (18), minocycline (19), and doxycycline (20). Whether its efficacy is mediated primarily through antimicrobial or antiinflammatory action remains unclear (16).

It has a favorable safety profile, and it can be used safely during pregnancy. Reported adverse events include gastrointestinal disturbances in the form of diarrhea and nausea (16,17).

Because of its improved tissue pharmacokinetics, including its longer half-life, azithromycin has been proposed at a dosage of 500 mg thrice weekly for 12 weeks (17). Further randomized, controlled trials are needed for an optimal dosage regimen to be recommended.

There are no data on azithromycin resistance developing in *P. acnes*; however, because of high bacterial resistance to azithromycin in the population (20–27.4%), its use as a first-line therapy for acne is not advised. However, it may be considered as an alternative to conventional anti-acne treatment (20).

**New tetracycline formulations.** Released in 2006, antiinflammatory dose doxycycline (40 mg capsule containing 30 mg immediate-release and 10 mg delayed-release beads) administered once daily was approved by the US Food and Drug Administration (FDA) for the treatment of rosacea. This new formulation presents antiinflammatory activity devoid of antibiotic effects, so that there is no evidence of antimicrobial selection pressure associated with its use (8).

In patients with moderate acne, doxycycline at a subantimicrobial dosage (20 mg twice daily) has been shown to reduce both inflammatory and noninflammatory lesions, whereas no resistant strains of *P. acnes* were evident (21).

Moreover, an extended-release (ER) minocycline tablet, administered at a dosage of 1 mg/kg daily for 12 weeks, was FDA-approved for moderate to severe inflammatory acne vulgaris in patients over 12 years old. This formulation produces a slower release of active drug, which is believed to reduce the risk of side effects such as acute vestibular adverse reactions, and overall drug exposure with time (8).

**Isotretinoin**

Systemic isotretinoin (13-cis retinoic acid) has revolutionized the treatment of severe acne. It is the only drug that targets all four pathogenic factors of the disease, and is the most potent inhibitor of sebum production. Isotretinoin has been shown to exert its sebosuppressive effect, at least in part, via induction of cell cycle arrest and apoptosis in human SEB-1 sebocytes, by a retinoid acid receptor (RAR)-independent mechanism (22,23). Isotretinoin is approved for the treatment of severe nodular acne; however, it is also useful for acne that is either treatment-resistant or producing physical or psychological scarring (2).

Isotretinoin is recommended at a dosage at 0.5–2.0 mg/kg/day, although it may cause initial flaring. This, however, can be minimized with a beginning dosage of less than 0.5 mg/kg/day, for longer time periods, for a total cumulative dosage of 120–150 mg/kg (24).

New developments and future trends are low-dose long-term isotretinoin regimens and new isotretinoin formulations (micronized isotretinoin) (25). Moderate-dose isotretinoin has the advantage of reducing side effects, which are known to be dose related (26). Intermittent moderate-dose isotretinoin has been proposed for adult patients with mild acne unresponsive, or rapidly relapsing after treatment with oral antibiotics. In a study of 80 patients, isotretinoin was used at a dosage of 0.5 mg/kg per day for 1 week every 4 weeks for a total period of 6 months. The acne resolved in 88% of the patients, but 12 months after treatment, 39% of the patients had relapsed (27).

Another intermittent isotretinoin regimen that was found to be a safe and effective option for the treatment of mild to moderate acne, consisted of isotretinoin 0.5–0.75 mg/kg/day for 1 week, every 4 weeks for a total period of 6 months (cumulative dose 35 mg/kg) (28). The application of 0.05% tretinoin cream has been proposed together with isotretinoin 0.5 mg/kg/day for 5 months for papulopustular acne (29).

**Insulin sensitizing agents**

Polycystic ovary syndrome (PCOS) may present with acne as a marker of hyperandrogenism. Although uncommon, acne may be the sole clinical cutaneous manifestation of PCOS (30).

Hyperinsulinemia seems to be an important factor in many cases of PCOS. It results from resistance to the effects of insulin on glucose metabolism, which has been found to occur independently of obesity, and to be related to hyperandrogenism. Insulin may directly stimulate androgen-responsive pilosebaceous units (31).

Hyperinsulinemia appears to be a major factor in the ovarian dysfunction of PCOS. Any treatment that lowers insulin levels such as weight loss, will decrease androgen levels. Also, antidiabetic agents that improve insulin sensitivity, including metformin
and thiazolidinediones, lower insulin levels, and consequently improve ovarian function and plasma androgens (32). Insulin-sensitizing agents not only improve the menstrual and metabolic abnormalities associated with PCOS, but have also been reported to be effective in treating hirsutism and acne (33). Further research is warranted in order to clarify the mechanism of action of insulin sensitizing agents in acne.

**Metformin.** Metformin, a biguanide, is the most commonly used insulin sensitizer for the treatment of PCOS. It inhibits hepatic glucose production and increases peripheral insulin sensitivity, but does not cause hypoglycemia (34). Treatment with metformin 1500 mg daily for 14 months has been shown to reduce hirsutism in women with PCOS, and improve mild acne, with no changes in sebum excretion rates (35,36).

Thirty-nine women with PCOS and fasting hyperinsulinemia received 1500 mg metformin for 12 weeks. Metformin treatment resulted in a decline of insulin, as well as total and free testosterone, thus leading to improvement of clinical signs of hyperandrogenism, such as acne (34).

**Thiazolidinediones.** Thiazolidinediones, also known as glitazones, include pioglitazone and rosiglitazone, represent a relatively new class of medication used for glycemic control in patients with type II diabetes mellitus (37). They are used for treatment of hirsutism in women with PCOS, as they improve hyperinsulinemia via interaction with peroxisome proliferator-activated receptor γ (PPARγ) independently of weight loss (37). Three types of PPARs have been elucidated – PPARα, PPARβ, and PPARγ. All forms have been found in human keratinocytes (37). PPARγ heterodimerizes with retinoid X receptors to stimulate gene transcription. Paradoxically, activation of PPARγ may result in stimulation of sebum formation.

Thiazolidinediones are potent and highly selective agonists for PPARγ. They require the presence of insulin to produce normoglycemia and do not function as secretagogues, that may explain the absence of hypoglycemia in patients treated with this medication. Side effects include weight gain, paradoxical dyslipidemia, anemia, and hepatotoxicity (37).

It has been reported that troglitazone 600 mg daily for 44 weeks (38) and rosiglitazone at a dosage of 2–4 mg daily for 8 months (39) may improve hirsutism in women with PCOS.

Potential use of thiazolidinediones in acne has not been investigated.

**Zinc**

Zinc sulfate (40,41) and zinc gluconate (42,43) have been used for the treatment of inflammatory acne vulgaris with conflicting results. Zinc salts have been used at a dose of 30–150 mg of elemental zinc daily for 3 months. Adverse events during zinc treatment involve the gastrointestinal tract.

The mechanism of action of zinc salts is only partially known. Zinc acts via inhibition of polymorphonuclear cell chemotaxis and inhibition of growth of *P. acnes* (44). Also, its anti-inflammatory activity could be related to a decrease in TNF-α production (45) and the modulation of the expression of integrins (46), and the inhibition of Toll-like receptor 2 (TLR2) surface expression by keratinocytes (47).

Zinc gluconate has been proposed as an alternative therapy for inflammatory acne; it may be a useful treatment for pregnant women because of its favorable safety profile, and it may be proposed during summer as it causes no photosensitivity (43). In addition, zinc gluconate does not induce bacterial resistance and when combined in a topical formulation with erythromycin, it has been shown to prevent the growth of erythromycin-resistant *P. acnes* strains (48), and to be more effective in inflammatory acne than erythromycin alone (49).

**Topical treatments**

Use of antibiotics may result in an increase of resistance of *P. acnes* and an increase in the pool of resistant organisms, including *Staphylococcus aureus* (50). In order to avoid this, one strategy is the use of therapeutic agents with complementary but different mechanisms of action.

**Combination treatments**

Topical retinoids in combination with topical antimicrobials have been shown to reduce inflammatory and noninflammatory acne lesions faster and to a greater degree than antimicrobial therapy alone. This may be explained by the fact that combination treatments target several areas of acne pathophysiology simultaneously. In addition, topical retinoids may affect skin permeability and facilitate the penetration of the topical antibiotic (50).

Clindamycin/zinc gel contains zinc acetate dehydrate applied once or twice daily in a formulation that reduces the extent of absorption of clindamycin through the skin, whereas showing equivalent efficacy
and safety to clindamycin lotion (51). Combinations of zinc with erythromycin result in reduction in the development of microbial resistance (48).

Once-daily applied topical clindamycin/benzoyl peroxide and twice-daily erythromycin + zinc acetate are both effective treatments for acne, but clindamycin/benzoyl peroxide has an earlier onset of action (52). Also, a fixed clindamycin phosphate/tretinoin gel formulation applied once daily was more effective and faster acting in reducing acne lesions than clindamycin lotion formulation applied twice daily (53).

**Picolinic acid gel 10%**

Picolinic acid is an intermediate metabolite of the amino acid tryptophan. It has antiviral, antibacterial, and immunomodulatory properties. It seems to play a key role in zinc transport, as it acts by perturbing zinc binding in zinc finger proteins (ZFPs). It chelates transition metal ions (Zn\(^{2+}\)) and is also involved in their absorption and transport. Picolinic acid gel 10% applied twice daily for 12 weeks has been shown to be a safe and effective treatment for inflammatory and noninflammatory lesions in 20 patients with mild to moderate acne vulgaris (54). Further randomized, controlled trials are warranted to confirm these findings.

**Dapsone gel 5%**

Dapsone is a sulfone with both antiinflammatory and antimicrobial properties. Advances in cutaneous pharmacology have produced a new topical formulation of 5% dapsone gel, which was shown to be an effective and safe treatment when applied twice daily for 12 weeks. Glucose-6-phosphate dehydrogenase-deficient patients presented no laboratory abnormalities. It has been proposed that its action may be the result of a direct inhibition of leukocyte trafficking and the generation of chemical mediators of inflammation by leukocytes. Alternatively, topical dapsone might act indirectly in acne, by altering the levels and/or activity of propionibacteria (55).

**Photodynamic therapy**

It is known that *P. acnes* produces porphyrins, particularly coproporphyrin III. Visible light is able to activate these porphyrins to produce a photodynamic reaction that has the potential to destroy bacteria (56).

Aminolaevulinic acid (ALA) is known to be preferentially taken up by the pilosebacous units. ALA will convert in situ, via the haem cycle, into protoporphyrin IX (PpIX). PpIX is an extremely active photosensitizer that is activated by blue and red light (57). ALA-PDT is proposed as an alternative to traditional acne treatment for patients with recalcitrant acne or who are intolerant to side effects (56). The most effective treatment regimen for ALA-PDT in acne has not yet been established, and different approaches have been used (Table 2). It has been suggested that the

---

**Table 2. Proposed regimens of PDT for acne vulgaris**

<table>
<thead>
<tr>
<th>Study</th>
<th>Topical cream</th>
<th>Light source</th>
<th>Time of illumination</th>
<th>Parameters of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollock B et al. (56)</td>
<td>ALA</td>
<td>Diode laser</td>
<td>10 minutes, once a week for 3 weeks</td>
<td>635 nm, 25 mW/cm(^2), 15 J/cm(^2)</td>
</tr>
<tr>
<td>Hongcharu et al. (60)</td>
<td>ALA</td>
<td>Broad band light</td>
<td>Once</td>
<td>550–700 nm, 17 mW/cm(^2), 13 J/cm(^2)</td>
</tr>
<tr>
<td>Itoh et al. (61)</td>
<td>ALA</td>
<td>Laser</td>
<td>Once</td>
<td>635 nm, 5 J/cm(^2)</td>
</tr>
<tr>
<td>Itoh et al. (62)</td>
<td>ALA</td>
<td>Halogen lamp</td>
<td>Once</td>
<td>600–700 nm, fluence rate 17 mW/cm(^2), 13 J/cm(^2)</td>
</tr>
<tr>
<td>Hörfelt et al. (63)</td>
<td>MAL</td>
<td>Noncoherent red light (Aktilite CL 128 Photocure ASA)</td>
<td>Two treatments, 2 weeks apart</td>
<td>Average 635 nm, 37 J/cm(^2)</td>
</tr>
<tr>
<td>Wiegell et al. (57)</td>
<td>MAL</td>
<td>Red light (Aktilite CL 128 Photocure ASA)</td>
<td>Two treatments, 2 weeks apart</td>
<td>9 min, total dose 37 J/cm(^2)</td>
</tr>
<tr>
<td>Wiegell et al. (59)</td>
<td>MAL</td>
<td>Red light (Aktilite CL 128 Photocure ASA)</td>
<td>Once</td>
<td>9 min, 34 mW/cm(^2), total dose 37 J/cm(^2)</td>
</tr>
</tbody>
</table>
What’s new in acne treatments

Mechanism of PDT action in acne includes photodestruction of *P. acnes*, reduction of the sebaceous gland size, and of sebum production, and a reduction of the follicle hypercornification (58).

Methyl aminolaevulinate (MAL) is a lipophilic derivative of ALA. MAL is de-esterified into ALA by intracellular enzymes. Recent studies have shown the efficacy of MAL-PDT for moderate to severe inflammatory acne vulgaris (57). Furthermore, a comparison study of ALA-PDT and MAL-PDT in facial acne in 15 patients revealed no differences in the response rate between these two treatments, although ALA-PDT resulted in more prolonged and severe adverse events after treatment (59).

Adverse events of PDT include edematous erythema in the treatment area, mild to moderate pain, crusting a few days after treatment, a sterile pustular eruption in the treated area, and superinfection (57,59). Approaches that have been used to reduce PDT-associated pain include treating smaller areas and using ice water, although it has been observed that the pain is less during the second treatment. No residual hyperpigmentation or scarring formation has been reported with PDT (57).

ALA- and MAL-PDT seem to be an efficient treatment for inflammatory acne; however, further work is warranted in order to optimize their use.

Is there a role for diet in acne?

Despite conflicting arguments on the controversial association between diet and acne, the majority of papers published conclude that not enough valid scientific data are available to support such a link (2). However, these suggestions are largely based on archaic studies (64–66) whose methodology has been criticized. A review of the literature reveals that there are no meta-analyses, randomized controlled clinical studies, or well-designed scientific trials that may provide consistent and good-quality patient oriented evidence on this controversial issue (67).

It has been shown that the prevalence of acne is lower in rural, nonindustrialized societies than in modernized Western populations, although the role of confounding factors, such as genetic factors cannot be ruled out (68–71). It has been suggested that the absence of acne reported in non-Westernized societies is attributable to local diets, which have a lower glycemic index than a Western diet. It is possible that adolescents in Westernized societies are hyperinsulinemic as a result of a high-glycemic diet (71). Another feature of non-Westernized diets is the absence of milk, which exhibits a low glycemic index but paradoxically is highly insulinotropic and has been associated with acne (72,73). Interestingly, it has been reported that the prevalence of acne in these non-Westernized isolated populations became similar with that in Western societies after their acculturation (68).

Hyperinsulinemia may promote acne through stimulation of ovarian and adrenal androgen production, decrease of sex hormone–binding globulin (SHBG) synthesis by the liver, and up-regulation of IGF-1 production by the liver (31,67).

Previous studies investigating whether certain foods may cause hyperinsulinemia in humans failed to provide a link between dietary fat intake (especially saturated fats) (74,75) or carbohydrate content (glycemic index) (76) and insulin resistance. The influence of dietary composition on acne vulgaris has been recently investigated. The intervention diet consisted of 25% energy from protein and 45% from low-glycemic index carbohydrates for 12 weeks. Dietary intervention resulted in a significantly greater reduction of acne lesion counts, as well as a significant reduction in testosterone bioavailability, dehydroepiandrosterone sulfate, and a significant increase in insulin-like growth factor binding protein-1 (IGFBP-1) (77).

However, the present authors feel that more systematic controlled studies are warranted so that a final conclusion may be drawn. Until then, it is premature to either reject or accept the diet–acne hypothesis.

Future research

Steroidogenic enzyme inhibitors

The skin has been shown to be a steroidogenic organ and to possess all major enzyme systems that are necessary for synthesizing androgens de novo from cholesterol and for locally converting circulating weaker androgens to more potent ones. The enzymes that are involved in cutaneous androgen metabolism include steroid sulfatase, 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase, steroid 5α-reductase, 3α-hydroxysteroid dehydrogenase, and aromatase (78). Research on the exact role of steroidogenic enzymes in cutaneous androgen metabolism may shed new light on the pathophysiology of androgen-dependent disorders such as acne, and open the way for selective isoenzymes inhibitors for optimal acne treatment.
5α-Reductase inhibitors. In the skin, the potent androgen testosterone can be further activated to the most potent tissue androgen 5α-dihydrotestosterone via the action of 5α-reductase (79). Two isoenzymes of 5α-reductase have been identified, namely type 1 and type 2. Type 1 5α-reductase exists predominantly in the skin, and its activity is concentrated in sebaceous glands from the face and scalp (80). On the other hand, the type 2 isoenzyme has been localized within the companion layer of the follicle, but not in the sebaceous glands (81). The exclusive predominance of type 1 5α-reductase in sebaceous glands and its role on sebum production via modulation of local androgen metabolism is further confirmed by the observation that adult men with type 2 5α-reductase deficiency had identical sebum production scores to controls. Also, treatment of male patients suffering from benign prostate hyperplasia with finasteride (a specific competitive inhibitor of type 2 5α-reductase), resulted in lower serum 5α-DHT levels, but no change in sebum score (82).

Inhibitors of 5α-reductase can be classified based on their chemical structures as steroidal versus nonsteroidal inhibitors or according to the isoenzyme specificity as type 1, type 2, and type-1/2 dual inhibitors (83). Type 1 inhibitors include plant extracts such as green tea extract catechins, zinc, and azelaic acid. Dual inhibitors include steroidal antagonists such as dutasterid, and nonsteroidal antagonists such as benzoquinolinone, plant extracts such as *Serenoa repens* extract permixon, *Artocarpus incisus*, isoflavonoids, curcumin, and γ-linolenic acid (78,83).

Steroid sulfatase inhibitors. Steroid sulfatase is a microsomal enzyme that catalyzes the conversion of circulating dehydroepiandrosterone sulfate to dehydroepiandrosterone. Inhibition of steroid sulfatase may be beneficial in the treatment of androgen-sensitive diseases and merits further investigation (78).

3β-hydroxysteroid dehydrogenase (3β-HSD). 3-β hydroxysteroid dehydrogenase catalyzes an obligatory step in the biosynthesis of all classes of hormonal steroids, namely, the oxidation/isomerization of 3β-hydroxy-5ene steroids into 3-keto-4ene steroids in steroidogenic tissues. The gestagens cyproterone acetate, norgestrel, and norethisterone, which are antiandrogens, also inhibit 3β-HSD (84). In addition, isoflavonoids such as genistein and daidzein (85), as well as thiazolidinediones (86), have been shown to act as 3β-HSD inhibitors.

Blocking the activation of TLRs

*Propionibacterium acnes* has been shown to induce an increased expression of TLR-2, TLR-4 and MMP-9 by human keratinocytes and to stimulate keratinocyte proliferation. This mechanism could play an important role in the initiation and spread of inflammation reaction in acne and could therefore represent a potential therapeutic target in the future (87).

PPAR antagonists

It has been postulated that PPARs may be important in the regulation of human sebum production and the development of acne (88). PPARs are ligand-activated transcription factors that form heterodimers with retinoid X receptors and regulate the expression of target genes involved in many cellular functions including cell proliferation, differentiation, and immune/inflammation response (89). It has been shown that PPARs are expressed in human skin where they localize to epidermis, sebaceous glands, and hair follicles (5).

PPAR-α ligands include hypolipemic drugs such as fibrates, long-chain polyunsaturated acids such as linoleic acid and arachidonic acid, and lipoxygenase metabolites such as leukotriene B4 (89). Activation of PPARα and PPARβ by their respective specific ligands, thiazolidinedione, rosiglitazone and the fibrate, WY-14643, were found to stimulate lipid droplet accumulation in cultured immature sebocytes (90). In patients treated with fibrates (PPARα agonists) for hyperlipidemia and in patients treated with thiazolidinediones for type II diabetes, sebum production was found to be significantly greater compared to controls. Interestingly, although sebum production was increased, no increase in the incidence of acne has been reported in patients who have been treated with fibrates or thiazolidinediones. This may be explained by the advanced age of these patients (5).

Because increased sebum production is an important element in the pathogenesis of acne vulgaris, development of PPAR antagonists that can interfere selectively with sebum formation may have implications for the treatment of acne (89).

5-Lipoxygenase inhibitor

Squalene is a characteristic human sebaceous lipid. Changes in secretion rates and composition of sebum seem to be associated with hypercornification of the sebaceous duct during comedogenesis and with the initiation of inflammatory processes (88). Recent data indicate the involvement
of peroxidated squalene in the development of comedone formation and early stages of inflammation in acne. Peroxidated squalene treatment of the human keratinocyte cell line, HaCaT, resulted in increased cell proliferation, increased lipoxygenase activity, and increased secretion of proinflammatory cytokine IL-6 and PPARα mRNA and protein levels (91).

Moreover, 5-lipoxygenase and leukotriene A4 hydrolase catalyze synthesis of LTB4. Leukotriene B4 is a proinflammatory mediator synthesized from arachidonic acid. It is a potent chemoattractant agent that recruits neutrophils and macrophages, which could account for the neutrophil infiltration in acne lesions (25,92).

Zileuton, an oral 5-lipoxygenase inhibitor, has been found to reduce inflammatory lesions in acne, and also to inhibit sebaceous lipids, especially pro-inflammatory sebum peroxides. It has been suggested that this may be due to an effect of zileuton on PPAR-α (92).

Conclusion

Future trends in acne therapy represent low-dose, long-term isotretinoin regimens, insulin-sensitizing agents, 5α-reductase type 1 inhibitors, topical photodynamic therapy, new combination formulations, dietary interventions, and antiinflammatory agents such as lipoxygenase inhibitors. Further research regarding the pathophysiology of acne may contribute to the present authors’ understanding of this condition and enable the design of new anti-acne treatments.

References


What's new in acne treatments