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New and emerging treatments in dermatology: acne

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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).

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Systemic treatments

Antibiotics

Antibiotics such as tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline), trimethoprim, and macrolide antibiotics

Table 1. Standard and new antiacne treatments

Standard treatments	New and emerging treatments
Systemic antibiotics	*Systemic antibiotics*
Tetracyclines	Lymecycline
Macrolides	Azithromycin
Trimethoprim	New tetracycline formulations
clindamycin	
Topical treatments	*Topical combination formulations*
Benzyl peroxide	
Retinoids	
Azelaic acid	
Antibiotics	
Oral isotretinoin	*Oral isotretinoin*
	Low-dose
	Intermittent regimens
	New formulations
Hormonal treatments	*Insulin-sensitizing agents*
Anti-androgens: cyproterone acetate, flutamide, spironolactone	Metformin
Combined oral contraceptives	Thiazolidinediones
Low-dose oral glucocorticoids	
Gonadotrophin-releasing hormone (GnRH) agonists	
	Zinc
	Dietary intervention
	Photodynamic therapy
	Blocking the activation of toll-like receptors (TLRs)
	PPAR antagonists

(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

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

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 effcicacy 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*, isofavonoids, 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 dehycrogenase 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-4-ene steroids in steroidogenic tissues. The gestagens cyproterone acetate, norgestrel, and norethisterone, which are antiandrogens, also inhibit 3β-HSD (84). In addition, isofalvonoids 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 PPARã 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

1. Graham GM, Farrar MD, Cruse-Sawyer JE, et al. Proinflammatory cytokine production by human keratinocytes stimulated with *Propionibacterium acnes* and *P. acnes* GroEL. Br J Dermatol 2004: **150**: 421–428.
2. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne management. J Am Acad Dermatol 2007: **56**: 651–663.
3. Katsambas A, Papakonstantinou A. Acne: systemic treatment. Clin Dermatol 2004: **22**: 412–418.
4. Orfanos CE, Adler YD, Zouboulis CC. The SAHA sydnrome. Horm Res 2000: **54**: 251–258.
5. Trivedi NR, Cong Z, Nelson AM, et al. Peroxisome proliferator-activated receptors increase human sebum production. J Invest Dermatol 2006: **126**: 2002–2009.
6. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. Dermatol Clin 2007: **25**: 133–135.
7. Sapadin AN, Fleischmajer R. Tetracyclines: Nonantibiotic properties and their implications. J Am Acad Dermatol 2006: **54**: 258–265.
8. Del Rosso JQ. Recently approved systemic therapies for acne vulgaris and rosacea. Cutis 2007: **80**: 113–120.
9. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003: **148**: 467–478.
10. Eady EA, Jones CE, Tipper JL, et al. Antibiotic-resistant propionibacteria in acne: need for policies to modify antibiotic usage. BMJ 1993: **306**: 555–556.
11. Eady EA, Cove JH, Holland KD, Cunliffe WJ. Erythromycin-resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br J Dermatol 1989: **121**: 51–57.
12. Cunliffe WJ, Grosshans E, Belaich S, Meynadier J, Alirezai M, Thomas L. A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. Eur J Dermatol 1998: **8**: 161–166.
13. Bossuyt L, Bosschaert J, Richert B, et al. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. Eur J Dermatol 2003: **13**: 130–135.
14. Cunliffe WJ, Meynadier J, Alirezai M, et al. Is combined oral and topical therapy better that oral therapy alone in patients with moderate to moderately severe acne vulgaris? A comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1% versus lymecycline plus gel vehicle. J Am Acad Dermatol 2003: **49** (3 Suppl.): S218–S226.
15. Peters DH, Friedel HA, McTavish D. Azithromycin. A review of its antimicrobial, pharmacokinetic properties, and clinical efficacy. Drugs 1992: **44**: 750–799.
16. Fernandez-Obregon AC. Azithromycin for the treatment of acne. Int J Dermatol 2000: **39**: 45–50.
17. Kapadia N, Talib A. Acne treated successfully with azithromycin. Int J Dermatol 2004: **43**: 766–767.
18. Rafiei R, Yaghoobi R. Azithromycin versus tetracycline in the treatment of acne vulgaris. J Dermatol Treat 2006: **17**: 217–221.
19. Gruber F, Grubisic-Greblo H, Kastelan M. Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. J Chemother 1998: **10**: 469–473.
20. Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs doxycycline in the treatment of acne vulgaris. Clin Exp Dermatol 2005: **30**: 215–220.
21. Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol 2003: **139**: 459–464.
22. Zouboulis ChC, Orfanos CE. Retinoids. In: Millikan LE, ed. Drug therapy in dermatology. New York Based: Marcel Dekker, 2000: 171–233.
23. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-*cis* retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. J Invest Dermatol 2006: **126**: 2178–2189.
24. Amichai B, Shemer A, Grunwald MH, et al. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol 2006: **54**: 644–646.
25. Zouboulis CC, Piquero-Martin J. Update and future of systemic acne treatment. Dermatology 2003: **206**: 37–53.
26. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multi-centered dose-response study. J Am Acad Dermatol 1984: **111**: 83–92.
27. Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol 1997: **137**: 106–108.
28. Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild to moderate acne vulgaris. J Eur Acad Dermatol Venereol 2006: **20**: 1526–1260.

29. Plewig G, Dressel H, Pfleger M, Michelsen S, Kligman A. Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. JDDG 2004: **2**: 31–45.
30. Lowenstein EJ. Diagnosis and management of the dermatologic manifestations of the polycystic ovary syndrome. Dermatol Ther 2006: **19**: 210–223.
31. Rosenfield RL. Polycystic ovary syndrome and insulin-resistant hyperinsulinemia. J Am Acad Dermatol 2001: **45**: s95–s104.
32. Sattar N, Hopkinson ZE, Greer IA. Insulin-sensitising agents in polycystic ovary syndrome. Lancet 1998: **351**: 305–307.
33. Essah PA, Wickham EP III, Nunley JR, Nestler JE. Dermatology of androgen-related disorders. Clin Dermatol 2006: **24**: 289–298.
34. Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril 2000: **73**: 1149–1154.
35. Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 2003: **88**: 4116–4123.
36. Kelly CJ, Gordon D. The effect of metformin on hirsutism in polycystic ovary syndrome. Eur J Endocrinol 2002: **147**: 217–221.
37. Boyd AS. Thiazolidinediones in dermatology. Int J Dermatol 2007: **46**: 557–563.
38. Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab 2001: **86**: 1626–1632.
39. Dereli D, Dereli T, Bayraktar F, et al. Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. Endocr J 2005: **52**: 299–308.
40. Michaëlsson G, Juhlin L, Ljunghall K. A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris. Br J Dermatol 1977: **97**: 561–566.
41. Cunliffe WJ, Burke B, Dodman B, Gould DJ. A double-blind trial of a zinc sulphate/citrate complex and tetracycline in the treatment of acne vulgaris. Br J Dermatol 1979: **101**: 321–325.
42. Dreno B, Amblard P, Agache P, Sirot S, Litoux P. Low doses of zinc gluconate for inflammatory acne. Acta Derm Venereol (Stockh) 1989: **69**: 541–543.
43. Dreno B, Moyse D, Alirezai M, et al. Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. Dermatology 2001: **203**: 135–140.
44. Dreno B, Trossaert M, Boiteau HL, Litoux P. Zinc salt effects on granulocyte zinc concentration and chemotaxis in acne patients. Acta Derm Venereol (Stockh) 1992: **72**: 250–252.
45. Guenihe A, Viac J, Lizard G. Protective effect of zinc on keratinocyte activation markers induced by interferon or nickel. Acta Derm Venereol (Stockh) 1995: **75**: 19–23.
46. Sainte-Marie I, Jumbou O, Tenaud I, Dreno B. Comparative study of the in vitro inflammatory activity of three nickel salts on keratinocytes. Acta Derm Venereol (Stockh) 1998: **78**: 169–172.
47. Jarrousse V, Castex-Rizzi N, Khammari A, Charveron M, Dreno B. Zinc salts inhibit in vitro Toll-like receptor 2 surface expression by keratinocytes. Eur J Dermatol 2007: **13**: 492–496.
48. Holland KT, Bojar RA, Cunliffe WJ, et al. The effect of zinc and erythromycin on the growth of erythromycin-resistant and erythromycin-sensitive isolates of *Propionibacterium acnes*: an in vitro study. Br J Dermatol 1992: **126**: 505–509.
49. Habbema L, Koopmans B, Menke HE, et al. A 4% erythromycin and zinc combination (Zinerty) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. Br J Dermatol 1989: **4**: 497–502.
50. Gollnick H, Cunliffe W, Berson D, et al. Combination therapy. J Am Acad Dermatol 2003: **49**: S12–S15.
51. Cunliffe WJ, Fernandez C, Bojar R, Kanis R, West F, Zindaclin Clinical Study Group. An observer-blind parallel-group, randomized, multicentre clinical and microbiological study of a topical clindamycin/zinc gel and a topical clindamycin lotion in patients with mild/moderate acne. J Dermatol Treat 2005: **16**: 213–218.
52. Langner A, Sheehan-Dare R, Layton A. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris. J Eur Acad Dermatol Venereol 2007: **21**: 311–319.
53. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazard F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol 2000: **143**: 498–505.
54. Heffernan MP, Nelson MM, Anadkat MJ. A pilot study of the safety and efficacy of picolinic acid gel in the treatment of acne vulgaris. Br J Dermatol 2007: **156**: 548–552.
55. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol 2007: **56**: 439.e1–e10.
56. Pollock B, Turner D, Stringer MR, et al. Topical aminolaevulinic acid – photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. Br J Dermatol 2004: 616–622.
57. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. Br J Dermatol 2006: **154**: 969–976.
58. Nestor MS. The use of photodynamic therapy for treatment of acne vulgaris. Dermatol Clin 2007: **25**: 47–57.
59. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. J Am Acad Dermatol 2006: **54**: 647–651.
60. Hongcharu W, Taylor CR, Chang Y, et al. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol 2000: **115**: 183–192.
61. Itoh Y, Ninomiya Y, Tajima S, et al. Photodynamic therapy for acne vulgaris with topical 5-aminolevulinic acid. Arch Dermatol 2000: **136**: 1093–1095.
62. Itoh Y, Ninomiya Y, Tajima S, et al. Photodynamic therapy of acnevulgaris with topical animolaevulinic acid and incoherent light in Japanese patients. Br J Dermatol 2001: **144**: 575–579.
63. Hörfelt C, Funk J, Frohm-Nilsson M, et al. Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. Br J Dermatol 2006: **155**: 608–613.
64. Bett DG, Morland J, Yudkin J. Sugar consumption in acne vulgaris and seborrheic dermatitis. Br Med J 1967: **3**: 153–155.
65. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. JAMA 1969: **210**: 2071–2074.
66. Anderson PC. Foods as the cause of acne. Am Fam Physician 1971: **3**: 102–103.

67. Wolf R, Matz H, Orion E. Acne and diet. Clin Dermatol 2004: **22**: 387–393.
68. Schaefer O. When the Eskimo comes to town. Nutr Today 1971: **6**: 8–16.
69. Bendiner E. Disastrous trade-off: Eskimo health for white "civilization." Hosp Pract 1974: **101**: 449–453.
70. Thiboutot D, Strauss J. Diet and acne revisited. Arch Dermatol 2002: **138**: 1591–1592.
71. Cordain L, Lindeberg S, Hurtado M, et al. Acne vulgaris. A diseas of western civilization. Arch Dermatol 2002: **138**: 1584–1590.
72. Adebamowo CA, Spiegelman D, Danby EW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. J Am Acad Dermatol 2005: **52**: 207–214.
73. Ostman EM, Liljeberg Elmstahl HG, Bjorck IM. Inconsistency between glycemie and insulinemic responses to regular and fermented milk products. Am J Clin Nutr 2001: **74**: 96–100.
74. Lovejoy J. The influence of dietary fat on insulin resistance. Curr Diab Rep 2002: 435–440.
75. Lovejoy J, Smith S, Champagne C, et al. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. Diabetes Care 2002: **25**: 1283–1288.
76. Meyer K, Kushi L, Jacobe D, et al. Carbohydrates, dietary fiber, and incidence of type 2 diabetes in older women. Am J Clin Nutr 2000: **71**: 921–930.
77. Smith RN, Mann NJ, Braue A, Mäceläinen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol 2007: **57**: 247–256.
78. Chen W, Thiboutot D, Zouboulis ChC. Cutaneous androgen metabolism: basic research and clinical perspectives. J Invest Dermatol 2002: **119**: 992–1007.
79. Kaufman KD. Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol Clin 1996: **14**: 697–711.
80. Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5 alpha-reductase exhibits regional differences in isolated sebaceous glands and whole skin. J Invest Dermatol 1995: **105**: 209–214.
81. Thiboutot D, Bayne E, Thorne J, et al. Immunolocalization of 5 alpha-reductase isoenzymes in acne lesions and normal skin. Arch Dermatol 2000: **136**: 1125–1129.
82. Imperato-McGinley J, Gautier T, Cai LQ, Yee B, Epstein J, Pochi P. The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. J Clin Endocrinol Metab 1993: **76**: 524–528.
83. Chen W, Zouboulis CC, Orfanos CE. The 5 alpha-reductase system and its inhibitors. Recent development and its perspective in treating androgen-dependent skin disorders. Dermatology 1996: **193**: 177–184.
84. Dumont M, Luu-The V, Dupont E, Pelletier G, Labrie F. Characterization, expression and immunohistochemical localization of 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4 isomerase in human skin. J Invest Dermatol 1992: **99**: 415–421.
85. Le Bail JC, Champavier Y, Chulia AJ, Habrioux G. Effects of phytoestrogens on aromatase, 3beta and 17-beta-hydroxysteroid dehydrogenase activities and human breast cancer cells. Life Sci 2000: **66**: 1281–1291.
86. Arlt W, Auchus RJ, Miller WL. Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450cl7 and 3 beta-hydroxysteroid dehydrognease. J Biol Chem 2001: **276**: 16767–16771.
87. Jugeau S, Tenaud I, Knol AC, et al. Induction of toll-like receptors by *Propionibacterium acnes*. Br J Dermatol 2005: **153**: 1105–1113.
88. Zouboulis CC, Eady A, Philpott M, et al. What is the pathogenesis of acne? Exp Dermatol 2005: **14**: 143–152.
89. Kuenzli S, Saurat JH. Peroxisome proliferator-activated receptors in cutaneous biology. Br J Dermatol 2003: **149**: 229–236.
90. Rosenfield RL, Kentsis A, Deplewski D, Ciletti N. Rat preputial sebocyte differentiation involves peroxisome proliferators-activated receptors. J Invest Dermatol 1999: **112**: 226–232.
91. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis ChC. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. J Invest Dermatol 2006: **126**: 2430–2437.
92. Zouboulis ChC, Nestoris S, Adler YD, et al. A new concept for acne therapy. A pilot study with zileuton, an oral 5-lipoxygenase inhibitor. Arch Dermatol 2003: **139**: 668–670.