New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group

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The Global Alliance to Improve Outcomes in Acne published recommendations for the management of acne as a supplement to the *Journal of the American Academy of Dermatology* in 2003. The recommendations incorporated evidence-based strategies when possible and the collective clinical experience of the group when evidence was lacking. This update reviews new information about acne pathophysiology and treatment—such as lasers and light therapy—and relevant topics where published data were sparse in 2003 but are now available including combination therapy, revision of acne scarring, and maintenance therapy. The update also includes a new way of looking at acne as a chronic disease, a discussion of the changing role of antibiotics in acne management as a result of concerns about microbial resistance, and factors that affect adherence to acne treatments. Summary statements and recommendations are provided throughout the update along with an indication of the level of evidence that currently supports each finding. As in the original supplement, the authors have based recommendations on published evidence as much as possible. (J Am Acad Dermatol 2009;60:S1-50.)

Key words: acne; acne scarring; adherence; antibiotic resistance; lasers; maintenance; pathophysiology; retinoids.

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INTRODUCTION

In 2003, a group of physicians and researchers in the field of acne, known as the Global Alliance to Improve Outcomes in Acne, published recommendations for the management of acne.[1] The goal was to make recommendations that were evidence based when possible and that included input from numerous countries. Since the initial meeting of the Global Alliance in 2001, the group has continued to meet regularly to discuss various aspects of acne management and create educational initiatives for dermatologists around the world. Regional groups in Europe, Asia, and Latin America have been established. Global Alliance members have actively worked with national dermatology societies to formulate guidelines for management of acne that take into account the individual characteristics of the country while harmonizing with the international recommendations. In addition, the Global Alliance presented a written consensus opinion to the US Food and Drug Administration (FDA) Guidance for

Abbreviations used:

ALA:	aminolevulinic acid
AP-1:	activator protein
BPO:	benzoyl peroxide
CO_2:	carbon dioxide
ECCA:	échelle d'évaluation Clinique des cicatrices d'acné
ECOB:	Elaboration d'un outil d'evaluation de l'observance des traitements medicamenteux
Er:YAG:	erbium-doped yttrium-aluminum-garnet
FDA:	Food and Drug Administration
HLA-DR:	Human leukocyte antigen-DR
ICAM:	intercellular adhesion molecule
ICG:	indocyanine green
IL:	interleukin
IPL:	intense pulsed light
MAL:	methyl aminolevulinate
MMP:	matrix metalloproteinase
PDL:	pulsed dye laser
PDT:	photodynamic therapy
RF:	radiofrequency
TCA:	trichloroacetic acid
TLR:	toll-like receptor
VCAM:	vascular cell adhesion molecule

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Preparation of the manuscript was a joint effort as follows. The manuscript outline, content development and selection of references, review of the data, and generation of the first draft were done in sections, with responsibilities as follows. "Recognizing the chronicity of acne" section: Drs Shear, Finlay, and Gollnick, and Ms Sanders. "Update: Pathogenesis of acne" section: Drs Thiboutot, Kang, and Gollnick, and Ms Sanders. "Update: Treatment of acne" was further subdivided into the following sections. "The changing role of antibiotics in managing acne" section: Drs Layton, Bettoli, Miyachi, Dréno, Perez, and Leyden, and Ms Sanders. "Retinoid-based combination therapy for acne" section: Drs Thiboutot, Kaminsky, Gollnick, Miyachi, Wolf, Herane, and Piquero Martin, and Ms Sanders. "Does enough evidence now exist for using lasers and lights to treat inflammatory acne?" section: Drs Leyden, Berson, Kang, See, Shalita, Torres Lozada, and Gollnick, and Ms Sanders. "The role of topical retinoids in acne maintenance therapy" section: Drs Gollnick, Bettoli, Thiboutot, and Leyden, and Ms Sanders. "Management of acne scarring" section: Drs Dréno, Goh, Kubba, Ramos-e-Silva, and Bettoli, and Ms Sanders. "Optimizing adherence with acne therapy" section: Drs Thiboutot, Dréno, Layton, Herane, and Dr Perez, and Ms Sanders. Ms Valerie Sanders is a medical writing consultant to Galderma International. Changes to the first draft and subsequent drafts were generated by each of the authors. All authors reviewed the complete final draft including all sections.

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Industry on Acne Vulgaris (Docket No. 2005D-0340) regarding development of drugs for acne and design of clinical trials in this arena. A subgroup of European members of the alliance formulated a response to recent changes in the European Union regulations for use of oral isotretinoin. As new issues come up, the alliance will continue to advocate for clinicians who treat patients with acne and the patients' rights to optimal treatment. Finally, the Global Alliance has established a World Wide Web site (www.acneglobalalliance.org), which provides information about the management of acne and recent developments in the field.

The first publication in 2003 encompassed current information about acne pathophysiology and comprehensive treatment recommendations. This edition includes updates on pathophysiology and treatment, including our research into treatments that have recently emerged—such as lasers and light therapy—and areas where published data were sparse in 2003 but are now available, including combination therapy, revision of acne scarring, and maintenance therapy. In addition to an updated discussion of acne pathophysiology and treatment, we share in this supplement a new way of looking at acne as a chronic disease, a discussion of the changing role of antibiotics in acne management, and factors that affect adherence to acne treatments. As in the original supplement, we have tried to base recommendations on published evidence as much as possible. However, it should be noted that some recommendations are based primarily on our expert opinion (level V evidence) because of a lack of studies and different designs and methodologies of existing studies. We have strived to clearly acknowledge in text which recommendations are based primarily on opinion, citing them as supported by Level V evidence.

In addition, a number of the clinical trials included in our evaluations of data were performed as registration trials for regulatory approval. We acknowledge that a particular type of patient is selected for study and results may not be generalizable to all patients; regulatory bodies typically address this in the package insert. In acne, the registration trial study inclusion and exclusion criteria often exclude patients with cystic acne (>2 nodules or cysts), truncal acne is often not evaluated, and minimum and maximum numbers of inflammatory and noninflammatory lesions at baseline are specified to give an objective measure of acne severity. To our knowledge, there are no data suggesting that acne in various population subgroups—adolescent, adult, male, female—is different in terms of pathophysiology with the exception of a greater effect of hormones in female patients. Assessment of population differences would be an interesting topic for future studies.

In the case of acne, monotherapy is used relatively rarely despite that regulatory bodies require monotherapy studies for drug approval. Because acne is a multifactorial disease, multiple classes of drugs are typically used in the clinical setting. Indeed, combination therapy is now recommended as the first-line approach for acne.[1] In this publication, the Global Alliance group considered the type and severity of acne in making recommendations. The Global Alliance plans to publish additional articles on the topics of hormonal/antiandrogenic therapy and the current use of oral isotretinoin.

The following definitions were used to evaluate the strength of the evidence for recommendations in the supplement:

- I—Strong evidence from systematic review of multiple well-designed, randomized, controlled trials;
- II—Strong evidence from at least one properly designed, randomized, controlled study of appropriate size;
- III—Evidence from well-designed trials without randomization, single group pre/post, cohort, time series, or matched case-controlled studies;
- IV—Evidence from well-designed nonexperimental studies from more than one center or research group;
- V—Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees.

RECOGNIZING THE CHRONICITY OF ACNE

Editor's note: This section summarizes ideas that were presented in full in a recent article in the *American Journal of Clinical Dermatology*.[2]

It is important for dermatologists to take the lead in educating other clinicians that acne is often a chronic disease and not just a self-limiting disorder of teenagers. For many patients, acne has the following characteristics that have been used to define chronicity[3,4]: a prolonged course, a pattern of recurrence or relapse, manifestation as acute outbreaks or slow onset, and a psychologic and social impact that affects the individual's quality of life. In considering whether acne is a chronic disease, it is interesting to compare it with atopic dermatitis (Table I). The similarities between the conditions are striking and range from underlying pathology (inflammation) to characteristic manifestation (frequently relapsing and recurrent diseases).

CONSENSUS: Acne Should Be Approached as a Chronic Disease

Level of Evidence: V

➢ Characteristics of acne that define chronic diseases:

- Pattern of recurrence or relapse
- Prolonged course
- Manifestation as acute outbreaks or slow onset
- Psychological and social impact

➢ Acne warrants early and aggressive treatment

➢ Maintenance therapy is often needed for optimal outcomes

Why is this important? Because many of our medical colleagues and a significant proportion of the lay public dismiss acne as a natural part of growing up that has few real consequences. Yet considerable evidence shows that acne can be a psychologically damaging condition that lasts years.[5-11] The members of the Global Alliance believe that acne—one of the most common skin diseases treated in routine dermatologic care—should be recognized and investigated as a chronic disease with psychologic sequelae that do not always correlate with the clinician's assessment of severity at one point in time.[5]

There are no definitive longitudinal studies of the natural history of acne; however, in the group's experience approximately 60% of acne cases are self-limiting and can be managed with acute treatment followed by topical maintenance therapy. In other cases, acne is a disease that requires treatment for a prolonged period. Oral isotretinoin—the most effective acne treatment developed to date—is administered during a 20-week period and sometimes must be given in repeated courses.[5] Further, as reviewed later in this supplement, recent well-controlled studies have shown that maintenance therapy is an effective strategy to minimize the risk of relapse.[12-14] In addition, the members of the Global Alliance believe that limiting the duration of active acne by effective treatment may, in turn, reduce the likelihood of physical and emotional scarring. For these reasons, we encourage early and aggressive treatment of acne.

How often do negative outcomes occur after acne? That question is difficult to answer definitively. However, there is good evidence that acne can persist into adult years in as many as 50% of individuals.[7,15-18] Negative psychologic outcomes, including anxiety, depression, and social withdrawal, have all been reported among individuals with acne and acne scars.[7,9,10] Physical scars, persistent hyperpigmentation, or both are not uncommon sequelae of acne and are usually expensive and difficult to treat effectively. The effects of acne can persist for many years, even among individuals who had self-limited adolescent acne.

Table I. Comparison of chronicity in acne and atopic dermatitis

	Acne	Atopic dermatitis
Basic character	Inflammatory	Inflammatory
Duration	>3 mos → 5-30 years	>3 mo → 5-40 years
Genetic influence	Yes, particularly in long-term courses; thought to be polygenic	Yes, thought to be polygenic
Age at onset, y	~10	~1
Self-limiting?	In ~80% of cases by third decade of life	In ~80% of cases by second decade of life
Counseling?	Intervals/years	Intervals/years
Medication	Continuously/ intervals	Continuously/ intervals
Social impact	Yes	Yes
Psychologic impact	Yes	Yes
Postdisease sequelae	Yes	
Physical scarring	Yes	Yes
Psychologic		Yes

Reprinted from Gollnick et al[2] with permission from Wolters Kluwer Health.

Unfortunately, the reason why acne becomes chronic in some patients is not well understood and it is currently difficult to determine which patients will have a chronic course of the disease. Factors that have been linked to a chronic course include stress-related production of adrenal androgens,[19] *Propionibacterium acnes* colonization,[20] familial background,[7] and specific subtypes of acne (conglobata, keloidal, inversa, androgenic, scalp folliculitis, and chloracne).[21,22] The members of the Global Alliance advocate further study to determine the link between these and other characteristics and the development of chronic acne.

In summary, dermatologists are aware that acne is a chronic disease with important ramifications. We are charged in our role as skin experts with the mission of helping other health care professionals and patients to achieve a better understanding of acne and improve awareness of the highly effective treatments that are available. We must also be vigilant in ensuring that insurers and government regulatory bodies are aware of the impact and import of acne. Because the physical and emotional

sequelae associated with acne can last for many years, insurers need to be encouraged to provide reimbursement for acute and maintenance acne treatments that have been proven effective in clinical trials.

UPDATE: PATHOGENESIS OF ACNE

More detailed information regarding the molecular events contributing to the pathogenesis of acne has emerged since 2003. There are 4 primary pathogenic factors, which interact in complex manner to produce acne lesions: (1) sebum production by the sebaceous gland; (2) *P acnes* follicular colonization; (3) alteration in the keratinization process; and (4) release of inflammatory mediators into the skin. Now, cellular culture studies have provided more information about the role of sebaceous lipids and inflammatory mediators including MMPs.

Jeremy et al[23] investigated the initiating events for acne lesions, and found that immune changes and inflammatory responses occur before hyperproliferation of keratinocytes, with a pattern similar to a type IV delayed hypersensitivity response. The immune response is led by $CD4^+$ lymphocytes and macrophages.[23] These researchers hypothesize that the subsequent production of cytokines activates local endothelial cells, up-regulating inflammatory vascular markers (E-selectin, vascular cell adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1], and human leukocyte antigen-DR [HLA-DR]) in the vasculature around the pilosebaceous follicle.[23] They further have postulated that the entire process is initiated by interleukin (IL)-1α up-regulation in response to a relative linoleic acid deficiency caused by excess sebum and perturbation of barrier function within the follicle.[23]

More than a decade ago, an in vitro study by Vowels et al[24] demonstrated the presence of a soluble factor of *P acnes* that induced proinflammatory cytokine production in human monocytic cell lines. Although distinct from lipopolysaccharide, this soluble factor had similar characteristics, in that its activity was dependent on the presence of CD14, a so-called pattern recognition receptor for lipopolysaccharide and other lipid-containing ligands. This *P acnes* product induced the synthesis of tumor necrosis factor-α and IL-1β in the cell lines. Later research showed that the cytokine induction by *P acnes* was occurring through TLR-2.[25] TLR, a mammalian homologue of a drosophila protein known as toll, has emerged as a key regulator of host responses to infection.[26] This transmembrane protein has a cytoplasmic portion that is homologous to the IL-1 receptor and thus could trigger a signaling cascade that activates nuclear factor-κB. A recent in vivo study by Jugeau et al[27] demonstrated that these events occur in inflammatory lesions of patients with facial acne and confirmed the earlier observations of Kim et al[25] in acne lesions. This provided additional evidence that inflammatory cytokines, working via autocrine and paracrine mechanisms through their respective receptors, amplify the signaling pathways that activate the activator protein (AP)-1 transcription factor.[28] Activation of AP-1 induces MMP genes, whose products degrade and alter the dermal matrix.[28] Retinoids are known to inhibit AP-1.[29] Very recent studies indicate that retinoids can induce monocytes to develop into $CD209^+$ macrophages that phagocytose *P acnes* bacteria.[30] These data further substantiate how such currently available treatments as topical retinoids can have anti-inflammatory activity against acne. In addition, they may help to explain why acne can flare after initiation of therapy; for example, disruption of sebocytes may result in release of proinflammatory molecules, leading to the clinical result of increased inflammation in some patients.

More has been learned about the role of seborrhea in acne as well. Sebaceous lipids are at least partly regulated by peroxisome proliferator-activated receptors and sterol response element binding proteins.[31,32] Peroxisome proliferator-activated receptor nuclear receptors act in concert with retinoid X receptors to regulate epidermal growth and differentiation and lipid metabolism.[31] Sterol response element binding proteins mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1.[32]

In parallel, research into the functions of the sebaceous gland has yielded exciting information about the central role these glands play in regulation of skin functions.[33] The sebaceous gland regulates independent endocrine functions of the skin and has a significant role in hormonally induced aging of skin.[34,35] In addition, the sebaceous gland has both direct and indirect antibacterial activities. Sapienic acid, a lipid in sebum, has innate antimicrobial activity and is up-regulated by activation of TLR-2 by skin bacteria.[36,37] Further, the sebaceous gland has ubiquitous expression of antibacterial peptides and proinflammatory cytokines/chemokines; these substances are induced in sebocytes by the presence of bacteria.[38] The sebaceous gland acts as an independent endocrine organ in response to changes in androgens and hormones, and is the control center for a complex regulatory neuropeptide program that acts like the hypothalamus-pituitary-adrenal axis.[33] This aspect of sebaceous gland function is primarily influenced by corticotrophin-releasing hormone, its binding protein, and

What Is New in Acne Pathophysiology

- Inflammatory events have been found to precede hyperkeratinization
- *P acnes* contributes to inflammation via activation of toll-like receptor (TLR) on the membranes of inflammatory cells
- Peroxisome proliferator-activated receptors partly regulate sebum production
- The sebaceous gland is a neuroendocrine-inflammatory organ that likely coordinates and executes a local response to stress and normal functions
- Androgens have influence on follicular corneocytes
- Oxidized lipids in sebum can stimulate production of inflammatory mediators
- Matrix metalloproteinases (MMPs) occur in sebum and diminish with treatment-related resolution of acne lesions

corticotrophin receptors.[39-41] corticotrophin-releasing hormone levels change in response to stress, and its role in regulating sebaceous gland function is likely a link in the brain-skin connection that is thought to explain the relationship between stress and skin disorders with an inflammatory component such as acne. Similarly, substance P,[42] α-melanocyte-stimulating hormone,[43,44] and corticotrophin-releasing hormone-receptor-1[45] are involved in regulating sebocyte activity. In addition, an active role of receptors for highly conserved ectopeptidases such as dipeptidylpeptidase IV and aminopeptidase N in regulation of sebocytes has been reported.[46] The response of skin to stress is a subject of active investigation and may soon suggest new targets for therapeutic interventions.

An additional area of interest that has recently emerged is the action of vitamin D in the skin. Sebocytes are capable of metabolizing and synthesizing the primary vitamin D metabolite 1,25-dihydroxyvitamin D_3.[47] Several lines of evidence suggest that the vitamin D endocrine system is involved in regulating sebocyte function and physiology, including production of sebum. Further, vitamin D analogues may potentially be useful in normalizing sebaceous gland physiology in patients with acne.[33]

Using a human keratinocyte cell line, Ottaviani et al[48] showed that peroxidation of sebum lipids can activate inflammatory mediators, including IL-6 and lipoxygenases. Oxidized squalene can also stimulate hyperproliferative behavior of keratinocytes, suggesting that this lipid may be partly responsible for comedo formation.[48] Zouboulis et al[49,50] have hypothesized that lipoperoxides exert a proinflammatory effect on the pilosebaceous duct. Lipoperoxides produce leukotriene B4, which is a powerful chemoattractant that can recruit both neutrophils and macrophages, and stimulate production of proinflammatory cytokines.[23,49,51]

Papakonstantinou et al[52] investigated the role of MMPs in acne. These enzymes, which include collagenases, gelatinases, stromelysins, and matrilysins, have a prominent role in both inflammatory matrix remodeling and proliferative skin disorders. Sebum includes several MMPs, which are thought to originate in keratinocytes and sebocytes. In addition, oral isotretinoin can reduce concentrations of MMPs in sebum in parallel with clinical improvement.[51]

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves the innate and adaptive immune system and inflammatory events. Treatment that targets both immune system activation and inflammatory pathways is, therefore, desirable. A full discussion of how antiacne agents work at the molecular level is beyond the scope of this text; however, research indicates that many of the agents currently used to treat acne have effects on cellular receptors, inflammatory mediators, and other molecular targets. As more becomes known, new targets for treatment may also be identified.

UPDATE: TREATMENT OF ACNE

Several aspects of acne management have been evolving since the 2003 Global Alliance recommendations.[1] These include the role of antibiotics in treatment, use of lasers and light-based therapies, issues regarding maintenance therapy, and treatment of acne scars. There is increased evidence supporting the recommendation of a combination of a topical retinoid plus an antimicrobial agent as first-line therapy for most patients with acne as a means of targeting multiple pathogenic features and both inflammatory and noninflammatory acne lesions. Studies published since 2003 support the recommendations outlined in the original algorithm, which has undergone minor modification to reflect the addition of new combination products for acne (Fig 1).

The changing role of antibiotics in managing acne

Antibiotic resistance is a significant public health concern in virtually all parts of the world,[58] and the

CONSENSUS: Strategies to Limit Antibiotic Resistance Are Important in Acne Management

Level of Evidence: V

- Treatment regimens that limit, or even reduce, the incidence of bacterial antibiotic resistance are recommended
  - Selection pressure can affect other, more pathogenic bacteria in addition to *P acnes*[53,54]
  - High rates of resistance have been correlated with high outpatient use of antibiotics[55]
- Use of oral antibiotics can lead to resistance in commensal flora at all body sites; topical antibiotics lead to resistance largely confined to skin of treated site[56]
  - Oral antibiotics are recommended for moderate to moderately severe acne[1]
  - Topical antibiotics may be used in mild to moderate acne as long as they are combined with benzoyl peroxide (BPO) and a topical retinoid[1]
  - Limit the duration of antibiotic use[1,57] and assess response to antibiotics and continuing need at 6 to 12 weeks
  - Some countries have regulatory guidance limiting the duration of use of topical antibiotics (alone and in fixed-dose combination products) to 11 to 12 weeks
- Use BPO concomitantly as a leave-on or as a wash
  - BPO for 5 to 7 days between antibiotic courses may reduce resistant organisms on the skin; however, BPO does not fully eradicate potential for resistant organisms
- Avoid using antibiotics (either oral or topical) as monotherapy either for acute treatment or maintenance therapy
- Avoid the simultaneous use of oral and topical antibiotics without BPO, particularly if chemically different

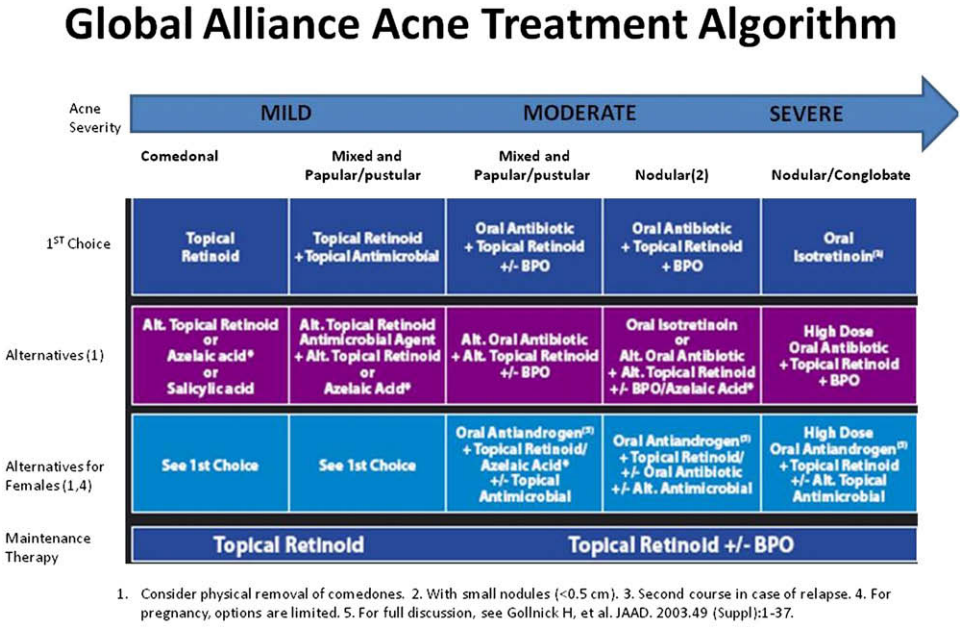


Fig 1. Acne treatment algorithm. *BPO*, benzoyl peroxide. Reprinted from Gollnick et al[1] with permission from the American Academy of Dermatology.

Global Alliance members believe it is appropriate to comment on the role of antibiotic resistance in acne management. Resistance arises from selective pressure on bacteria, and can result from both appropriate and inappropriate uses of antibiotics.[59] Antibiotics were the first effective treatment for acne; although we acknowledge these agents have an important role in acne management, the Global Alliance members agree with recent guidelines and publications that emphasize the need to limit antibiotic use, both frequency and duration, and to add the nonantibiotic antimicrobial agent BPO when long-term antibiotic use is necessary because BPO is a highly efficient bactericidal agent and will minimize the development of resistance at sites of application.[57,58,60,61]

Antibiotic resistance in this setting can encompass both the effect of antibiotic use on *P acnes* and outcomes of acne and the impact of antibiotics

prescribed for acne on other more pathogenic organisms. To date, neither aspect has been extensively studied; there are some data, as will be discussed below. It should be noted that acne does not represent a classic bacterial infection, where resistance to an antibiotic translates directly to treatment failures, in part because antibiotics exert effects in acne that are independent of their antibacterial actions (eg, they have anti-inflammatory actions). Indeed, Eady et al[62] state that "the relationship between resistance and treatment outcomes is perhaps more complex in acne than any other microbial disease for which antibiotics are prescribed." The members of the Global Alliance have evaluated the available evidence in acne, reviewed evidence of the effect of antibiotic use on *P acnes* resistance and transmission of resistance from *P acnes* to other microbes,[59,62,63] and incorporated our collective clinical experience to formulate opinions on what actions dermatologists should take in response to the problem of antibiotic resistance in acne.

Susceptibility breakpoints for *P acnes* have not been well defined; some researchers have used general anaerobic bacteria breakpoints[63-65] and others have set a level of more than 25 mg/L.[62] The correlation between reduced susceptibility and outcome of antibiotic treatment is complex; however, it is clear that propionibacterial growth and multiplication has an important role in acne either through direct microbial effects or more indirect effects on the inflammatory process in skin. Poor outcomes in acne may occur when insufficient antibiotic is delivered to the majority of follicles.[62]

Effect of *P acnes* antibiotic resistance on outcome (level IV evidence). Anecdotally, members of the Global Alliance have heard dermatologists express the opinion that the problem of antibiotic resistance is relevant primarily to pathogenic bacteria and antibiotics used in hospital to treat serious infections. We list here the reasons why we do not agree.

- Resistance is a concern for patients with acne and may manifest as a reduced response, no response, or relapse.[66-68] Because no methodology currently exists to quantify concentrations of topical and/or systemic antibiotics in sebaceous follicles, outcomes studies correlating clinical response with *P acnes* antibiotic sensitivities are the only way to establish the relevance of colonization with insensitive strains. These studies are difficult but some have been done.[62,69] A systematic review of the literature published in 1998 found a "clear association between poor therapeutic response and antibiotic-resistant propionibacteria."[70]
- A significant proportion of patients with acne are colonized with resistant *Propionibacterium* before treatment is initiated.[71] *P acnes* resistance is disseminated primarily by person-to-person contact; study has shown that the prevalence of resistant *P acnes* in household contacts of patients with acne ranged from 41% in Hungary to 86% in Spain.[71] Younger siblings and children of patients with acne may be colonized de novo by resistant strains at an early age. Further, dermatologists are highly likely to have resistant strains of *P acnes* colonizing the face (25 of 39 tested).[71] Because the rationale for using antibiotics in acne is to target *P acnes*, harboring resistant organisms may be logically expected to have an impact on treatment outcome.[66,67]

Potential effect of antibiotic use in acne on other pathogens (level IV evidence). Generally, in medicine, it is agreed that when antibiotics are administered, resistance occurs in both targeted and nontargeted bacteria. In addition, resident flora has a "memory" and retains resistant variants long after antibiotic therapy is discontinued. Finally, resistance gene pools are often shared by pathogens and nonpathogens.[66,72] There is one study of resistant pathogens arising from antibiotic use in acne.[66] Mills et al[66] assessed bacterial resistance in a controlled study of 208 patients with acne treated with topical erythromycin for 12 weeks in a double-blind, randomized, parallel-group fashion followed by a single-blind regression phase during which patients were treated with the antibiotic vehicle only. The prevalence of erythromycin-resistant coagulase-negative staphylococci on the face increased from 87% to 98%; in addition, the density of resistant organisms increased significantly. Similar patterns in both prevalence and density were observed on untreated skin of the back and in the nares. In addition, there was an increase in carriage rate of *Staphylococcus aureus* in the anterior nares in patients treated with erythromycin on the face. The majority of the resistant isolates had high-level resistance, with minimal inhibitory concentrations greater than 128 μ/mL. In addition, there are some studies that show antibiotics commonly used for acne (tetracyclines) can select for resistant strains of non-*P acnes* pathogenic bacteria.[53,54] Raum et al[54] reported that doxycycline used to treat febrile infections was associated with an increase of resistance in *Escherichia coli* from 29% before treatment to 58% during treatment and for a short time after treatment. Lesens et al[53] reported two outbreaks of Pantin-Valentine leukocidin-positive *S aureus* infections among solders in Africa who had been treated with doxycycline for malaria prophylaxis. Although the data showing a connection

Table II. Strategies for limiting antibiotic resistance in *Propionibacterium acnes* and other bacteria

Level of evidence: V

Combine a topical retinoid plus an antimicrobial (oral or topical); this is a rationale choice because of the complementary modes of action that have been shown clinically to result in[1]
- o Increased speed of response
- o Greater clearing
- o Enhanced efficacy against comedones and inflammatory lesions

If the addition of an antibiotic to this regimen is required:

Limit the use of antibiotics to short periods and discontinue when there is no further improvement or the improvement is only slight
- o Oral antibiotics should ideally be used for 3 mo, but 6-8 wk into treatment might be one appropriate time point at which to assess response to antibiotics[57]

Co-prescribe a BPO-containing product or use as washout
- o BPO reduces the likelihood of antibiotic resistant *P acnes* emerging and rapidly reduces the number of sensitive and resistant strains of *P acnes* at the site of application[61]
- o Use BPO either concomitantly or pulsed as an antiresistance agent
- o It may be helpful to use BPO for a minimum of 5-7 days between antibiotic courses

Oral and topical antibiotics should not be used as monotherapy

Concurrent use of oral and topical antibiotics should be avoided, particularly if chemically different
- o Increased risk of bacterial resistance
- o No synergistic actions

Do not switch antibiotics without adequate justification; when possible, use the original antibiotic for subsequent courses if patients relapse

Use topical retinoids for maintenance therapy, with BPO added for an antimicrobial effect if needed

Avoid use of antibiotics for maintenance therapy

BPO, Benzoyl peroxide.

between antibiotics used for acne and increased resistance in bacteria other than *P acnes* are relatively sparse, it is not illogical to surmise that the antibiotics are exerting selection pressure on a variety of flora and not just *P acnes*.

Patients with acne are often treated with multiple antibiotics and their flora is exposed to a significant selective pressure for resistance development. Margolis et al[73] found that patients with acne treated with antibiotics had 2.15 times greater risk of developing an upper respiratory tract infection compared with patients with acne who were not treated with antibiotics. In addition, there have been an increasing number of reports of infections caused by *P acnes,* including arthritis,[74,75] endocarditis,[76] endophthalmitis,[77] and adenitis.[78] The frequency of *P acnes* infections is hard to quantify, because it has long been considered just a contaminant and not a pathogen so has not been rigorously monitored or studied. However, several researchers have termed *P acnes* infections "an emerging clinical entity"[75] and "an underestimated pathogen."[79] In addition, Oprica and Nord,[55] on behalf of the European Study Group on Antimicrobial Resistance in Anaerobic Bacteria, report that among *P acnes* isolates from systemic infections, blood isolates were encountered most frequently followed by isolates from skin and soft-tissue infections and abdominal infections. The Global Alliance members note that resistance in *P acnes* occurs with varying frequency among countries and can be somewhat hard to predict.[55,80,81] In addition, susceptibility testing for *P acnes* is not practical on a routine basis and does not necessarily influence therapeutic decisions. Therefore, we recommend taking steps that are known to limit the potential for antimicrobial resistance (Table II).

Resistance in *P acnes* has not been studied as extensively as resistance in organisms considered to be more pathogenic; however, there are several factors that suggest there may be cause for concern in acne. Prescribing practices for acne have been shown to influence the resistance rate.[82,83] Data from a European surveillance study of *P acnes* were correlated with published data on outpatient antibiotic sales.[55,83] The highest rate of tetracycline resistance (11.8%) was found in Finland, the country with the highest outpatient use of tetracycline. Conversely, no tetracycline resistance was found in Italy, which had the lowest prescription volume of outpatient tetracycline.[55] However, resistance to macrolides was high in Italy (erythromycin 42% and clindamycin 21%), correlating with high sales volumes of macrolides. For the 8 countries included in the analysis, the correlation between sales and resistance was significant for both clindamycin and erythromycin. ($P < .05$).[55]

In addition, new mechanisms of resistance are evolving in *P acnes*.[63,83] In 2005, Oprica et al[63]

reported the existence of several novel resistant genotypes of *P acnes* that were distributed throughout Europe. Data suggest resistance is more common in patients with moderate to severe acne and that patients have multiple resistance strains with different resistance patterns.[64] Spread of resistant strains among family and friends occurs frequently; although some research suggests that resistant isolates disappear after antibiotic treatment is stopped,[59] other research suggests that resistance persists and can be reactivated rapidly.[69,84] Further, it is known that cross-resistance and transfer of resistance characteristics is widespread among bacteria. Finally, although it may be argued that resistance to tetracyclines is not clinically relevant with major pathogenic bacteria, resistance to other antibiotic classes used in acne (more or less frequently depending on the region of the world) such as macrolides and less often quinolones and sulfonamides may be very important.[85,86] In recognition of the foregoing concerns, the regulatory bodies in some countries have mandated a limited duration of use for topical antibiotics either alone or in fixed-dose combination products.

Use of subantimicrobial doses of antibiotics may offer promise, but has not been well studied, particularly in acne. The theoretical basis is that no bacterial killing occurs, so there is no selection of resistant strains.[87] Instead, the primary mechanisms of action of subantimicrobial-dose antibiotics are anti-inflammatory mechanisms (in the United States low-dose doxycycline has been approved for treatment of the inflammation associated with rosacea). This raises the question of how important is bacterial killing in acne? Currently, there is no answer to that question; however, research continues to illuminate the molecular basis for acne and the role of *P acnes* in pathophysiology. Miyachi et al[88] have found cycline antibiotics that reduce leukocyte recruitment by *P acnes* inhibit release of reactive oxygen species, possibly by altering leukocyte metabolism. Additional studies by Akamatsu et al[89,90] have provided supportive evidence about the importance of antioxidant properties with cycline antibiotics. Notably, antibiotics that do not have antioxidant actions, such as penicillin and cephalosporins, are not clinically effective against acne.[88]

It should also be noted that generally bacterial resistance often diminishes or resolves after selective pressure from antibiotics is withdrawn. Data regarding resolution of resistance in *P acnes* are sparse.

Conclusions. As shown in the consensus recommendation at the start of this section, the members of the Global Alliance believe that antibiotic use for acne should be limited. Further, we believe that physicians need to be educated about best practices for managing acne using combination therapy involving a topical retinoid plus an antimicrobial agent and limiting duration of antibiotic therapy/adding BPO. Much remains to be discovered about bacterial resistance in response to antibiotic use for acne. We believe there is a need to gather data about follicular concentrations of antibiotics, because there have been no recent attempts to study this. In addition, studies in larger populations are needed to determine what is the effect of antibiotic therapy for acne on the frequency of pharyngitis, cystitis, colonization of the anterior nares, methicillin-resistant *S aureus* colonization, and cutaneous infections.

Retinoid-based combination therapy for acne

The current understanding of acne pathophysiology indicates that pairing topical retinoids with antimicrobials targets the majority of pathogenic factors more effectively than antimicrobial-focused treatment. As the data reviewed in this article show, this combination results in faster and more complete clearing of acne lesions compared with monotherapy. This means that physicians can now help patients navigate acne-prone years with fewer embarrassing acne lesions and, potentially, prevent the long-term problems of relapse, acne scars, and postinflammatory hyperpigmentation.[91]

Since publication of the original Global Alliance recommendations,[1] numerous clinical studies of topical retinoids in combination with antimicrobial agents either as single agents or in fixed-dose combination products have been published; indeed, there is now evidence from more than 16,000 patients with acne. Because of the large number of studies in this particular aspect of acne management, this review was performed with the methodology of a systematic review. A search of PubMed for clinical trials with the terms "acne vulgaris" and "adapalene," "tazarotene," and "tretinoin" was conducted including publications in the years 1975 to 2008 inclusive; a total of 36 studies were identified that assessed antimicrobial therapy in combination with a retinoid (11 with adapalene, 4 with tazarotene, and 21 with tretinoin).

The rationale for combining topical retinoids and antimicrobial agents. Historically, treatment of acne was directed toward controlling *P acnes* and centered on use of antibiotics. Because acne involves an interplay of 4 major pathogenic factors (excess sebum production; bacterial colonization of the pilosebaceous duct and release of inflammatory mediators; inflammation; and abnormal keratinization within the follicle), acne treatment should be directed toward as many pathogenic

CONSENSUS: Combination Retinoid-based Therapy Is First-line Therapy for Acne

Level of Evidence: I

- The combination of a topical retinoid and antimicrobial agent remains the preferred approach for almost all patients with acne
  - o This combination attacks 3 of the 4 major pathogenic factors of acne: abnormal desquamation, *P acnes* colonization, and inflammation
  - o Retinoids are anticomedogenic, comedolytic, and have some anti-inflammatory effects, whereas BPO is antimicrobial with some keratolytic effects and antibiotics have anti-inflammatory and antimicrobial effects
- The superior efficacy of this combination has been shown in clinical trials involving more than 16,000 patients (reviewed below)
- Fixed-dose combination products with a topical retinoid and an antimicrobial provide improved patient convenience that may translate to improved adherence; those without an antibiotic in the formulation may minimize the development of bacterial resistance (*level IV evidence)*; on a theoretical basis, retinoid-BPO combination products may be the most desirable

factors as possible.[92] More specifically, for reasons explained below, acne management should focus on preventing formation of microcomedones and minimizing the potential for visible acne lesions.

The formation of an acne lesion is thought to begin with the microscopic lesion known as the microcomedo. This lesion, which is not yet clinically visible, forms when excess sebum collects in the follicle and abnormal epithelial desquamation occurs along with proliferation of *P acnes*. The microcomedo is the precursor to all acne lesions, both comedones and papules/pustules. Evaluation of papules has shown the progression of lesions: microcomedones were found in 52% of papule biopsy specimens; in addition, 22% of papules contained an open comedo and 10% contained a closed comedo.[92,93] Clearly, targeting the microcomedo will minimize the visible expression of acne.

Topical retinoids are both comedolytic and anticomedogenic and have been shown to reduce formation of microcomedones and comedones.[94] They also have direct and indirect anti-inflammatory actions. Finally, topical retinoids normalize desquamation, which facilitates penetration of other topical agents.[95] Antibiotics and BPO target *P acnes* and have anti-inflammatory actions; unlike antibiotics, however, BPO has not been associated with the development of bacterial resistance. These antimicrobial agents also have mild keratolytic effects by mechanisms that are different from those of retinoids (they do not regulate the process of hyperkeratinization).[95] Thus, the mechanism of action of topical retinoids and antimicrobials are complementary. This may explain why the combination yields superior results compared with either drug class alone.

Clinical studies supporting retinoid-based combination therapy. The concept of combining a retinoid plus antimicrobial therapy was first investigated in the 1970s.[96-99] Several early small studies showed that the combination of a retinoid plus an antimicrobial—BPO, topical antibiotics, and oral antibiotics—was more effective than monotherapy with the antimicrobial.[96,99,100] For example, Mills et al[96] reported that the combination of tretinoin plus oral tetracycline resulted in a good to excellent response in 67% of patients vs 48% of those treated with tretinoin alone and 41% of those treated with tetracycline alone. Although these early studies are cited as supportive data, this review focuses on the results of newer studies because of the change in standards for clinical trial design in dermatology during the past few decades.

Review of combination therapy studies involving topical retinoids and antimicrobial agents used together shows remarkably consistent results: combination therapy achieves significantly greater and faster acne clearing versus antimicrobial therapy alone.

Topical retinoids with topical antimicrobials. Topical retinoids have been studied with topical antibiotics (clindamycin and erythromycin) and the antimicrobial BPO, and fixed combination antibiotic/BPO products (discussed in section below titled "Fixed-dose combination products").[98-105] Generally, topical combinations are indicated in patients with mild to moderate acne with an inflammatory component.[91]

Adapalene (level II evidence). Wolf et al[105] evaluated the combination of adapalene gel 0.1% plus clindamycin 1% gel versus clindamycin 1% (plus adapalene vehicle) in a 12-week, randomized study (n = 249) of patients with mild to moderate acne. Combination therapy resulted in a more rapid and significantly greater clearance at all study visits.[105]

Level II evidence supports the use of adapalene or tretinoin plus topical antimicrobial agents; we advise against any monotherapy with topical antibiotic and recommend limiting the duration of topical antibiotics, even when used in combination with retinoids, unless BPO is also used (level V evidence).

Tretinoin (level III evidence). Similarly, the combination of tretinoin gel 0.025% plus clindamycin gel 1% provided a numerically superior improvement in acne lesions compared with tretinoin alone and a significantly superior improvement compared with clindamycin alone in 64 patients at 8 weeks of therapy.[102] Shalita et al[104] compared tretinoin 0.1% microsphere with and without BPO 6% cleanser (n = 56) and found a significantly greater reduction in inflammatory acne lesions with combination therapy versus tretinoin alone, but no difference between groups in reduction of noninflammatory acne lesions. Tolerability in the studies was similar between groups.

Comparing retinoids in combination regimens with topical antibiotics (level IV evidence). There have been few head-to-head comparisons of different retinoids in combination regimens. However, Tanghetti et al[106,107] reported results from a randomized, parallel-group, investigator-blinded study of clindamycin 1% gel plus either tazarotene 0.1% cream or tretinoin 0.025% gel in patients with mild to moderate acne (135 patients). The tazarotene regimen was associated with greater improvements in overall disease severity (change on 6-point scale: −1.64 ± 0.97 with tazarotene vs −1.24 ± 0.96 with tretinoin, P = .04), a higher percent of patients with 50% or greater improvement (Fig 2), and better global assessments (67% vs 55% of patients with at least "marked improvement").[107]

Generally, combination therapy involving a topical retinoid and other topical antiacne agents is well tolerated. Cumulative irritancy data suggest that, among the retinoids, adapalene is best tolerated in combination. Studies have compared the cumulative skin tolerance of topical retinoids (adapalene gel 0.1%, tretinoin cream 0.025%, and tretinoin microsphere gel 0.1% and 0.4%) when applied in combination with topical antimicrobial agents (clindamycin 1%, erythromycin 2%, BPO 5%, and erythromycin/BPO gel) in 37 patients with irritancy testing on skin of the upper aspect of the back.[108,109] Adapalene gel was significantly less irritating (P < .001) after repeated application compared with either tretinoin formulation when used in combination with antimicrobial agents.[108]

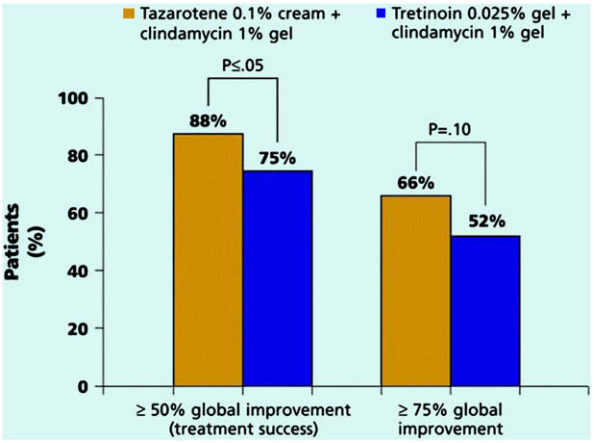


Fig 2. Tazarotene .1% or tretinoin .025% gel plus clindamycin 1% gel. Percentage of patients with greater than or equal to 50% and greater than or equal to 75% improvement at 12 weeks. Reprinted with permission from Tanghetti et al.[106]

Level I evidence supports the use of adapalene plus oral antibiotics in treatment of moderate or moderately severe acne. Level III evidence supports the use of tretinoin and tazarotene plus oral antibiotics.

Topical retinoids plus oral antibiotics. As early as 1972, it was shown that topical tretinoin plus oral tetracycline increased efficacy and provided a faster therapeutic response compared with either agent as monotherapy.[96,101] Topical retinoids plus oral antibiotics are a suitable therapeutic choice for moderate to severe or persistent acne. It is our opinion that oral and topical antibiotics should not be used together because of an increased risk for antibiotic resistance and low likelihood of additional efficacy. Controlled clinical studies have evaluated the combination of topical retinoids with the oral antibiotics tetracycline, doxycycline, and lymecycline.[96,101,110,111]

Adapalene plus oral antibiotics (level I evidence). Two well-controlled studies evaluated the combination of adapalene plus an oral tetracycline (lymecycline and doxycycline).[110,111] Both studies showed that combination therapy was superior in both speed and efficacy versus the antibiotic monotherapy. Significant differences between the groups in total lesion reductions occurred as early as the first postbaseline visit (week 4, P = .04).[111]

A large-scale community-based study has also evaluated adapalene.[112] In the MORE (Measuring Outcomes in a Real-world Experience) Trial, which involved 1662 patients, the most common additional acne agents were oral antibiotics, antibiotic/BPO

Level I evidence supports the use of fixed-dose combination products that incorporate a retinoid/BPO, retinoid/antibiotic, or retinoid plus antibiotic/BPO in the treatment of acne.

products, and topical antibiotics.[112] The results mirror those from controlled clinical trials, and demonstrate that combination therapies involving topical retinoids are significantly more effective than antimicrobial regimens in routine, day-to-day clinical practice.[112] Short-term use of oral antibiotics is also supported by data from Campo et al,[113] who found that the effect of antibiotics reaches a plateau after 3 months. This study emphasizes that the Global Alliance recommendation to limit antibiotic therapy to a period of no more than 3 to 4 months then maintaining therapy with a topical retinoid can be a highly successful strategy in routine clinical practice.

Tretinoin and tazarotene plus oral antibiotics (level III evidence). Tretinoin was studied in the 1970s and 1980s (discussed above) and tazarotene in a large community study in combination with oral antibiotics.[114-118] The open-label BEST (balancing efficacy, speed, and tolerability) study evaluated various tazarotene regimens chosen at the investigator's discretion in 1118 patients with mild to moderate acne.[114-118] The most common additional acne agents were systemic antibiotics, BPO, and topical antibiotics. The results showed that all combination regimens reduced both inflammatory (58%-61%) and noninflammatory (56%-58%) lesions. All therapies were also well tolerated.[114] Leyden et al studied tazarotene in combination with oral minocycline in an open-label study that preceded a randomized blinded maintenance study; the maintenance results are reviewed in the section below. Results from the initial open-label period were not published (JJ Leyden, MD, oral communication, February 20, 2009).

Fixed-dose combination products. Because fixed-dose combination agents are the newest development in acne management, more detailed reviews of the studies supporting these agents are presented. Topical retinoids have also been studied as part of fixed-dose combination formulations with BPO (adapalene 0.1%/BPO 2.5%)[119,120] and with topical antibiotics (tretinoin 0.025%/clindamycin 1.2% gel, tretinoin 0.025%/clindamycin 1% hydrogel, and erythromycin 4%/tretinoin 0.025% gel).[121-126] In addition, retinoids have been paired with antibiotic/BPO fixed-dose combination products.[124,127-131] Consistently across the studies, regimens that included a topical retinoid were more effective than those without.

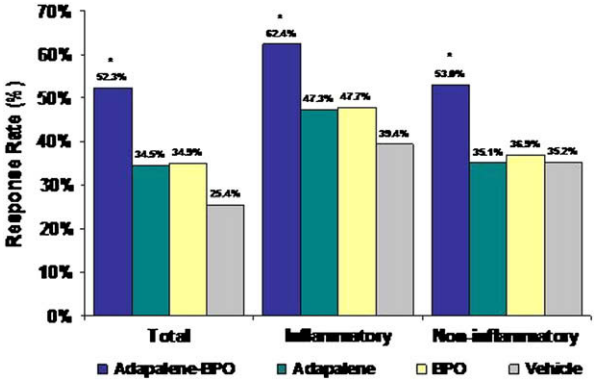


Fig 3. Response rates (percentage of patients with a $\geq$ 50% reduction in lesion counts from baseline) with adapalene/benzoyl peroxide (BPO) product, adapalene monotherapy, BPO monotherapy, or vehicle. *Differences between adapalene-BPO and all other treatments were statistically significant for total (vs adapalene, $P = .001$; vs BPO, $P = .002$; vs vehicle, $P < .001$) inflammatory (vs adapalene, $P = .005$; vs BPO, $P = .005$; vs vehicle, $P = .001$), and noninflammatory lesions (vs adapalene, $P = .001$; vs BPO, $P = .004$; vs vehicle, $P = .012$) at week 12 (intent to treat population, last observation carried forward). Reprinted from Thiboutot et al[119] with permission from the American Acandemy of Dermatology.

Adapalene. *Adapalene/BPO (level I evidence).* In 2007, clinical studies of a once-daily fixed-dose formulation of adapalene gel 0.1% and BPO 2.5% were completed. Currently, adapalene is the only topical retinoid to be formulated with BPO. Adapalene/BPO has greater efficacy than monotherapy, with differences in lesion counts observed after 1 week in clinical studies.[119] It is thought that adapalene and BPO have synergistic actions, because BPO is the most potent bactericidal agent against *P acnes* and adapalene, like other retinoids, is comedolytic and anticomedogenic. Adapalene also has anti-inflammatory and immunoregulating activity; it down-regulates the TLR-2 that is used by *P acnes* to stimulate cytokine production and blocks the AP-1 inflammatory pathway.[29,132] Tenaud et al[132] also have shown that the effect of adapalene on TLR-2 increases CD-1d expression and decreases IL-10 expression by keratinocytes. In theory, these actions could increase interactions between dendritic cells and T lymphocytes, thereby enhancing antimicrobial activity against *P acnes*.[132] Adapalene-BPO targets 3 of 4 pathophysiologic factors and offers antimicrobial activity without antibiotic exposure.

Thiboutot et al[119] conducted a multicenter, randomized, double-blind study of adapalene/BPO in 517 patients with moderate to moderately severe acne. As shown in Fig 3, there were statistically significant differences in response rates ($P < .05$). In

Table III. Median percentage change in lesion counts at week 12 with adapalene/benzoyl peroxide, adapalene, benzoyl peroxide, or vehicle

	Treatment group				*P* value		
	Adapalene/BPO (n = 149) (1)	Adapalene (n = 148) (2)	BPO (n = 149) (3)	Vehicle (n = 71) (4)	(1) vs (2)	(1) vs (3)	(1) vs (4)
Success rate, %	27.5	15.5	15.4	9.9	.008	.003	.002
Lesion count							
Total*	−51.0	−35.4	−35.6	−31.0	<.001	<.001	<.001
Inflammatory	−62.9	−45.7	−43.6	−37.8	<.001	<.001	<.001
Noninflammatory	−51.2	−33.3	−36.4	−37.5	<.001	<.001	<.001

Reprinted from Thiboutot et al[119] with permission from the American Academy of Dermatology.
BPO, Benzoyl peroxide.
*Data of treatment groups are expressed as percentage change.

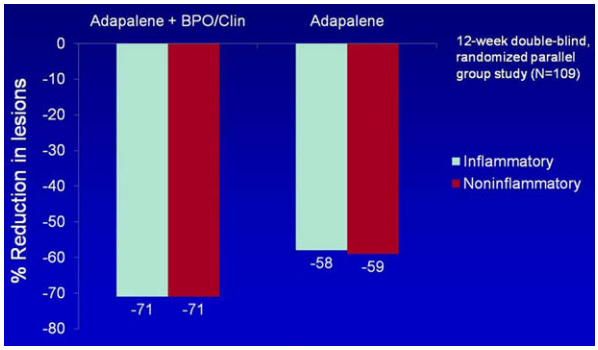


Fig 4. Effect on acne lesion counts of adding retinoid to combination antibiotic/benzoyl peroxide (BPO) product. Adapalene 0.1% + BPO/clindamycin versus adapalene 0.1% alone. From Del Rosso.[130] Reprinted with permission from the *Journal of Drugs in Dermatology*. Copyright 2007.

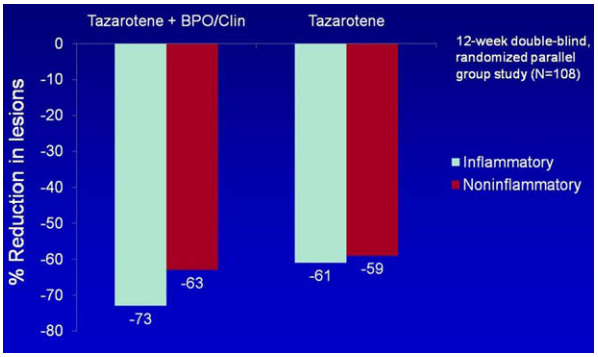


Fig 5. Effect on acne lesions counts of adding retinoid to combination antibiotic/benzoyl peroxide (*BPO*) product. Tazarotene 0.1% + BPO/clindamycin versus tazarotene 0.1% alone. From Tanghetti et al.[128] Reprinted with permission from the *Journal of Drugs in Dermatology*. Copyright 2006.

addition, lesion counts were significantly lower in the group treated with adapalene/BPO compared with either agent alone or placebo, with a statistically significant difference observed as early as week 1 (Table III). Similar efficacy was observed across all patient demographics, including age, sex, and race. The frequency of adverse events and cutaneous tolerability for adapalene/BPO were comparable with that observed with adapalene monotherapy.[119] These results were confirmed in the phase III study of adapalene/BPO (n = 1668).[133] At the 12-week time point, the success rate was significantly higher than the monotherapy arms ($P < .01$ for all comparisons) and the median reduction in total lesions with adapalene/BPO was −61% compared with −50% each for the adapalene and BPO arms and 32% for the vehicle arm ($P < .001$).[133] In addition, adapalene/BPO again demonstrated a significantly more rapid onset of action than other treatment arms.[133]

The once-daily fixed-dose combination formulation of adapalene/BPO has also been evaluated during 12 months in 452 patients with acne.[120] The fixed-dose combination had good safety, with only mild to moderate adverse events that typically occurred in the first 1 to 2 months after initiation of therapy and resolved spontaneously. Discontinuations were infrequent (2%) and cutaneous tolerability was good. Sustained reductions in acne lesions were observed (71%, 76%, and 70% reductions in total, inflammatory, and noninflammatory lesions, respectively).[120]

Adapalene plus antibiotic/BPO products (level III evidence). The regimen of adapalene plus clindamycin/BPO products has also been evaluated. In a multicenter, parallel group study, patients were randomized to one of 3 groups: (1) clindamycin/BPO for 4 weeks followed by clindamycin/BPO plus adapalene gel; (2) monotherapy with adapalene gel for 12 weeks; or (3) clindamycin/BPO plus adapalene gel for the entire 12 weeks.[130] Reductions in lesion counts were greatest in the group that received clindamycin/BPO plus adapalene from the initiation of therapy for the full 12 weeks (Figs 4 and 5); in addition, differences in the reduction of lesions were apparent as early as week 2.[130]

Tazarotene. *Tazarotene plus antibiotic/BPO (level II evidence).* Tazarotene has not currently

been formulated with either a topical antibiotic or BPO in a fixed-dose combination. However, it has been studied in combination with BPO, erythromycin/BPO, and clindamycin.[127,128] Topical tazarotene 0.1% gel as monotherapy was compared with combination therapy in a large (n = 440) investigator-masked, randomized, parallel-group study.[127] Patients received tazarotene or one of the following combination regimens: (1) tazarotene plus BPO 4% gel; (2) tazarotene plus erythromycin 3%/BPO 5% gel; or (3) tazarotene plus clindamycin phosphate lotion. An additional group received monotherapy with clindamycin lotion.[127] Tazarotene plus clindamycin resulted in significantly greater global improvement compared with tazarotene monotherapy. When inflammatory lesions alone were analyzed, tazarotene plus erythromycin/BPO was significantly more effective than other regimens. All combination regimens were associated with fewer adverse events compared with tazarotene monotherapy, although the differences were not statistically significant.[127]

Tanghetti et al[128] published the results of a 12-week study of tazarotene monotherapy versus tazarotene plus a clindamycin/BPO product in 102 patients with moderate to severe inflammatory acne. As shown in Fig 5, *B*, the results from this study were remarkably similar to the results obtained in the study by Del Rosso[130] evaluating the combination of adapalene plus clindamycin/BPO. In addition, tolerability of the combination was good. Tanghetti et al[128] commented that the reduced skin irritation experienced by patients in the combination group might be expected to translate to better satisfaction.

Tretinoin. *Tretinoin plus antibiotic/BPO (level III evidence).* Tretinoin has been studied with combination clindamycin/BPO products and is available in fixed-dose combination products with topical antibiotics (tretinoin/clindamycin, tretinoin/erythromycin). Bowman et al[129] reported the results of a controlled trial comparing 3 treatments: (1) clindamycin/BPO gel; (2) clindamycin/BPO gel plus tretinoin 0.025% gel; and (3) clindamycin/BPO gel plus tretinoin gel 0.025% plus clindamycin. In this study, the triple combination was most effective in reducing inflammatory lesions (69%) followed by clindamycin/BPO (66%), then tretinoin plus clindamycin (52%); noninflammatory lesions also were reduced to the greatest extent by the triple combination (61%), then clindamycin/BPO (57%), and tretinoin plus clindamycin (50%). All 3 treatments were well tolerated, although there were more adverse events in the triple combination group compared with the other groups.[129]

Tretinoin/antibiotic products (level I evidence). In the first report of a multicenter case series, Amblard et al[126] evaluated the efficacy and tolerability of a tretinoin 0.025%/erythromycin 4% formulation. This study of 347 patients with acne showed good efficacy, with clear or marked improvement in 85% of cases. The authors noted that the onset of action was rapid and tolerability was good.[126] Later, Gupta et al[124] evaluated tretinoin 0.025%/erythromycin 4% compared with an antibiotic/BPO combination (erythromycin 3%/BPO 5%) in patients with moderate acne. The treatments had comparable efficacy and both significantly reduced acne lesions. Physicians and patients preferred the erythromycin 3%/BPO 5% product, which had better tolerability.[124]

Several studies have investigated formulations containing clindamycin 1% and tretinoin 0.025%.[121,122,125] Richter et al[122] studied clindamycin 1.2%/tretinoin 0.025% versus tretinoin 0.025% in 145 patients with moderate to severe acne. The combination product was significantly more effective than tretinoin in resolving inflammatory lesions ($P < .05$) and was as effective as tretinoin in reducing noninflammatory and total lesions. The onset of action was faster with the combination product versus tretinoin monotherapy. Cutaneous tolerability was similar with the combination product and tretinoin monotherapy, with significantly less burning.[122] Zouboulis et al[121] conducted a 12-week randomized study to evaluate clindamycin 1%/tretinoin 0.025% versus clindamycin 1% in patients with moderate to severe acne. Again, the combination product was significantly more effective than monotherapy; but in this case, reductions in inflammatory, noninflammatory, and total lesions were all significantly superior ($P < .05$). Onset of action was more rapid with combination therapy as well. Both treatments were well tolerated.[121]

Leyden et al[125] conducted two randomized, double-blind, active-drug and vehicle-controlled studies of a tretinoin/clindamycin fixed combination product. A total of 2219 patients with mild to moderate acne were randomized to treatment with clindamycin 1% (n = 635), tretinoin 0.025% (n = 635), the combination product clindamycin/tretinoin (n = 634), or vehicle (n = 315) during a 12-week period. The results showed that the combination formulation was superior to either agent alone and vehicle in reducing inflammatory lesions ($P < .005$), noninflammatory lesions ($P \leq .0004$), and total lesions ($P < .0001$). In addition, there was a significantly greater proportion of patients at the end of the study with clear or almost clear skin on Investigator Global Assessment ($P < .0001$) in the combination group (37% vs 27% clindamycin, 25% tretinoin, and 14% vehicle).[125] The combination formulation was well

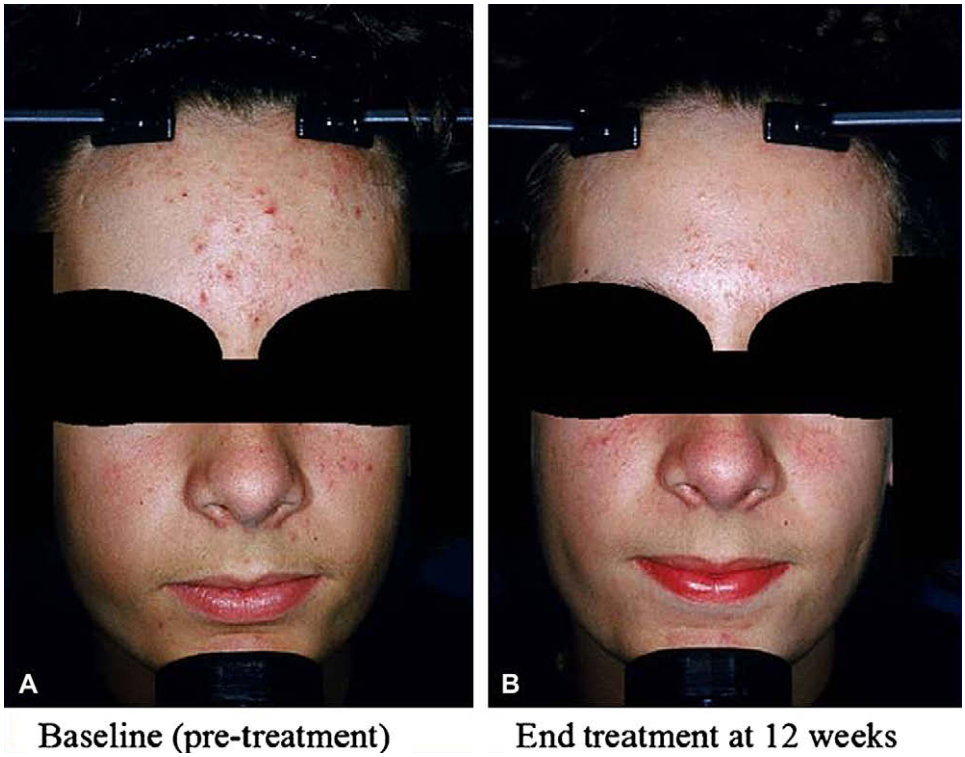


Fig 6. Tretinoin/clindamycin clinical photograph from pivotal 12-week study. **A**, Baseline. **B**, End of treatment. Reprinted with permission from Leyden et al[125] with permission from the American Academy of Dermatology.

tolerated. Fig 6 illustrates a patient from the study.[125] An analysis of 6 controlled safety and efficacy studies conducted with this product in Europe (n = 769) between 1992 and 1997 also showed that the combination of clindamycin/tretinoin was superior to either tretinoin or clindamycin monotherapy both in reducing lesions and in the proportion of patients who had a rating of clear or almost clear at the end of the study.[134]

Community-based studies of tretinoin/antibiotic. In the late 1980s, Korting and Braun-Falco[135] reported that erythromycin 4%/tretinoin 0.025% had good efficacy and tolerability in 1337 patients treated by general practitioners on an open-label basis. The fixed-dose combination treatment effectively reduced acne lesions and was well tolerated, confirming in a general population what had been observed in clinical trials.[135] Of note, patients with light complexions or sensitive skin were advised to apply the treatment every other day, and the authors reported that "tolerability was improved by reducing the applied dose."[135] Although combination products are convenient, tolerability remains an important factor.[91,135] This was followed by a very large (n = 6530) European surveillance study, in which Kreusch and Bextermoller[136] reported that erythromycin 4%/tretinoin 0.025% used alone or in combination with other acne treatments resulted in a clear reduction in both inflammatory and noninflammatory lesions. Tolerability was either good or very good in the majority of cases.[136] Although this study was uncontrolled and did not report lesion count differences based on treatment regimen, the results indicate that the combination product had good effectiveness in the community.

Tolerability of retinoids with clindamycin/BPO. Although head-to-head comparisons of the available retinoids plus clindamycin/BPO combination products are lacking, a cumulative irritancy study has been conducted. Dosik et al[109] evaluated the irritation potential of adapalene gel 0.1%, tazarotene cream 0.05%, and tretinoin microsphere 0.04% in combination with both clindamycin/BPO formulations reported above in the United States.[109] In this study, adapalene resulted in significantly lower irritation compared with tretinoin and tazarotene (all regimens $P < .01$).

Conclusions. Studies continue to demonstrate the use of topical retinoids in combination regimens for acne, thus supporting the Global Alliance recommendation that topical retinoids should be a foundation in acne therapy for virtually all patients

except those with the most severe disease. When used from the initiation of therapy, topical retinoids significantly increase the speed of resolution of acne lesions. Retinoids target the microcomedo—the initial step in comedogenesis and formation of subsequent acne lesions. When inflammatory lesions are present, an antimicrobial agent such as BPO or an antibiotic should be added to provide synergy and faster clearing.

Because of concerns regarding development of antibiotic-resistant bacteria, it is our opinion that antibiotics should be discontinued as soon as inflammatory lesions begin to resolve, usually within 3 to 4 months; if this is not possible, BPO or a BPO/antibiotic combination product should be added. The topical retinoid should be continued as maintenance, alone or in combination with BPO. Antibiotic resistance is a significant public health issue worldwide. Use of antibiotics in acne increases selective pressures on a wide range of microbial flora (particularly when oral antibiotics are used), not just *P acnes*. There is some debate as to whether resistance in *P acnes* should constitute a clinical concern. It is the consensus of the Global Alliance that prolonged antibiotic use can contribute to problems that are clinically relevant, including the development of resistant staphylococci. Thus, the group continues to recommend that antibiotic use for acne be limited in duration. However, there are some patients who experience an acne flare when oral antibiotics are discontinued, despite continuing use of topical retinoids; and there are some cases where long-term oral antibiotic therapy is required as an alternative to use of oral isotretinoin.

The advent of fixed-dose combination products should result in improved convenience for patients and, as a result, increased adherence. These agents have been shown to enhance both efficacy and speed of action. Because they target multiple pathophysiologic factors, they have broader disease effectiveness. However, products or regimens that include topical antibiotics without BPO (eg, the fixed-dose retinoid/antibiotic formulations) have the potential to increase bacterial resistance. The combination of a topical retinoid plus BPO is a logical formulation, because it targets 3 of 4 pathophysiologic factors and the antimicrobial portion—BPO—is rapidly bactericidal without evidence of bacterial resistance. With retinoid/antibiotic combinations, either BPO should be added (we recommend a wash or leave-on product) or therapy should be changed to a retinoid with or without BPO once resolution of inflammatory lesions is apparent. Similarly, antibiotic/BPO preparations are not ideal in maintenance therapy because of concerns regarding the potential for antibiotic resistance over the long term.

In summary, the use of combination therapies involving a topical retinoid from the initiation of therapy has been confirmed to improve treatment outcomes by achieving superior reductions in lesion counts and faster resolution of lesions. It is sensible to treat acne as quickly and efficiently as possible to achieve the best possible patient outcomes, thus improving patient satisfaction, limiting expense and the development of sequelae such as scarring.

Does enough evidence now exist for using lasers and lights to treat inflammatory acne?

In recent years, light-based treatments for acne have gained some popularity. A range of treatments are being investigated, including visible light, specific narrowband light, intense pulsed light (IPL), pulsed dye laser (PDL), and photodynamic therapy (PDT) with or without photosensitizing agents. Early data suggest that these treatments offer greatest utility when used as an adjunct to medical therapy or for patients who refuse or cannot tolerate medical therapy.

In 2003, the published literature about light-based therapies was very sparse; therefore, the topic was not covered in depth in the 2003 Global Alliance recommendations.[1] We present here an overview of the currently available medical literature about light-based treatments for acne treatment (the use of lasers in acne scarring is treated later in this supplement). Although progress has been made in the study of light-based treatment of acne, to date, the existing clinical studies have often lacked controls and included only small numbers of patients. In addition, very few studies have compared light-based treatments with standard and well-validated pharmaceutical treatments and none with the current recommended therapy for most types of acne—combination therapy with a topical retinoid plus one or more antimicrobial agents.[1,137] Further, little information is available about long-term effects of therapy. Much remains to be determined about the optimal device, dosing, and frequency of administration for these procedures in active acne.

Approval of drugs versus devices. The US FDA has approved several optical devices for the treatment of active acne. However, clinicians must be aware that the approval process for devices is significantly different from that for drugs. Regulatory clearance of a device should not be considered to denote the same degree of safety and efficacy that is now expected with regulatory clearance of a drug.

To be approved for marketing, a pharmaceutical agent must be tested in pharmacokinetic studies, toxicology and teratogenicity studies, and carefully

CONSENSUS: More Data Are Needed to Define the Role of Laser and Light Therapy in Acne

Level of Evidence: V

- Available optical devices target *P acnes* or the sebaceous gland
  - o In vivo effects on *P acnes* have not been shown; are there other unknown mechanisms of action?
- The regulatory approval process for devices is much less stringent than the familiar clinical testing process required for approval of drugs
  - o Cannot assume safety and efficacy have been proven with devices based on regulatory approval
- Existing studies are of variable quality
- Clinical data on use of optical therapies are emerging and suggest that both may offer benefit in acne; currently the evidence is not sufficiently robust to recommend any device be used as monotherapy in acne
- Optimal strategies, frequencies, and device settings remain to be clarified

controlled multicenter clinical efficacy and safety studies involving hundreds to a few thousand patients. In contrast, it is the norm for devices to be approved without randomized clinical trial efficacy data involving clinical outcomes. Device manufacturers typically have to provide evidence of technical reliability and reasonable safety data, and may be able to rely on mechanistic end points (eg, altering sebaceous gland structure or reducing *P acnes* levels) for efficacy. Further, the approval of some devices can be achieved through a grandfathering process that involves showing that the new device is substantially equivalent to an existing approved device.

Use of devices for indications that have not been FDA approved (off-label use) has been recognized by the FDA as a barrier to the initiation of randomized clinical efficacy trials. In some cases, the manufacturer, which typically sponsors clinical efficacy trials, may have a diminished motivation to spend thousands of dollars on clinical trials because physicians are already using the product in the desired manner. These issues are not likely to change in the near future, and it is important for clinicians to be aware of the differences in approval processes.

Scientific rationale in active acne: Targets of light-based therapies. In general, light-based treatments have two primary therapeutic targets: (1) reduction of *P acnes* levels; and (2) disruption of sebaceous gland function (Table IV). Light may also have anti-inflammatory properties via action on inflammatory cytokines.[138-141]

Reduction of P acnes. As part of its normal metabolism, *P acnes* produces light-sensitive porphyrin compounds (protoporphyrin, uroporphyrin, and coproporphyrin III).[137,142] These porphyrins absorb visible light at several wavelengths, including blue and red light wavelengths between 400 and 700 nm (Fig 7).[142] Absorption of light excites the porphyrin compound, causing formation of singlet oxygen and reactive free radicals. Oxygen radicals are thought to damage lipids in the cell wall of *P acnes*, destroying the organism.[143] Similar to the effect of antibacterial agents, reduction in *P acnes* levels by light therapy may play a role in improving acne lesions. Many light sources may affect *P acnes*, including narrowband light sources, IPL devices (broadband light), KTP lasers (532 nm), PDLs (585-595 nm), and various orange/red light lasers or light sources (610-635 nm); these light sources have wavelengths that correspond to an absorption peak of *P acnes* porphyrins. Longer wavelengths penetrate more deeply into the skin, but are less effective at activating porphyrins.

Bacterial destruction may also be enhanced by use of a photosensitizer with light therapy.[144] Ashkenazi et al[145] showed that addition of aminolevulinic acid (ALA) dramatically reduced bacterial viability in vitro compared with untreated cultures (7 vs 2 orders of magnitude).[137] There have been conflicting reports of the effects on *P acnes* in vivo. Horfelt et al[146] reported no reduction in *P acnes* measurements in skin surface biopsy specimens after PDT treatment of patients with acne, whereas Yung et al[147] found that a single application of methyl aminolevulinate (MAL) or hexyl aminolevulinate plus light transiently reduced the density of *P acnes* from bacterial skin samples. Horfelt et al[146] speculated that PDT may have a mechanism of action in acne other than eradication of *P acnes*, and Yung et al[147] suggested that "the prolonged antiacne effect of PDT relies on factors independent of bacterial density."

Although it is known that light sources can target bacteria, a robust bactericidal action has not been shown with *P acnes* in vivo.[148,149] Because there has been no in vivo demonstration of an antimicrobial effect, more research is needed to elucidate the mechanism of action in acne. Treatments that affect *P acnes*, including antibacterial agents and light sources, generally are effective only when used

Table IV. Targets of light-based treatments for acne

UVA/UVB	*P acnes*
Blue light	*P acnes*
Blue/red light combination	*P acnes*
Pulsed dye laser	*P acnes*/sebaceous gland
KTP laser	*P acnes*/sebaceous gland
ALA and photodynamic therapy	Sebaceous gland
Infrared lasers	Sebaceous gland

From Mariwalla and Rohrer.[142] Copyright 2005. Reprinted with permission of John Wiley & Sons, Inc.
ALA, Aminolevulinic acid; *KTP*, potassium-titanyl-phosphate; *P acnes*, *Propionibacterium acnes*; *UV*, ultraviolet.

chronically; relapse occurs soon after cessation. In acne, therefore, light-based treatments that primarily target *P acnes* probably should be combined with agents that affect comedogenesis, such as the topical retinoids that inhibit formation of both comedones and the microcomedo (precursor of all acne lesions).

Disruption of sebaceous gland function. Light-based therapies can also target sebocytes and the sebaceous glands.[137,150] Destruction of the sebaceous gland is possible, but may be detrimental to the normal function of skin; lasers that have a temporary effect on the sebaceous gland may be preferred.[151] This concern, along with pain associated with long-wavelength laser therapy, currently limit treatments that target the sebaceous gland. A painless treatment that temporarily disrupts sebaceous gland function should provide significant benefit in acne.

Free oxygen radicals generated by application of photosensitizers may damage the gland and eliminate or reduce sebum excretion for prolonged periods of time; this shows the potential for PDT.[151] However, a study of MAL PDT using sebum measurement found that this treatment was associated with a limited effect on sebum secretion.[152] More study is needed to fully determine the effects of photosensitizers on the sebaceous glands.

Indocyanine green (ICG) is a topical agent that preferentially accumulates in the sebaceous glands, but may also be harmful to the epidermis.[150] This agent plus a long-pulsed 810-nm diode laser has been shown on biopsy specimen to produce selective necrosis of the sebaceous glands.[153] The same study also showed reduction in *P acnes* concentrations, which can occur as a secondary effect of reduced sebum as has been shown with systemic isotretinoin therapy.[153,154] Bhardwaj et al[150] suggest that the combination of ICG plus laser causes both photodynamic and photothermal effects.

Finally, long-wavelength near- and mid-infrared lasers (eg, 1320-1540 nm) target the sebaceous gland.

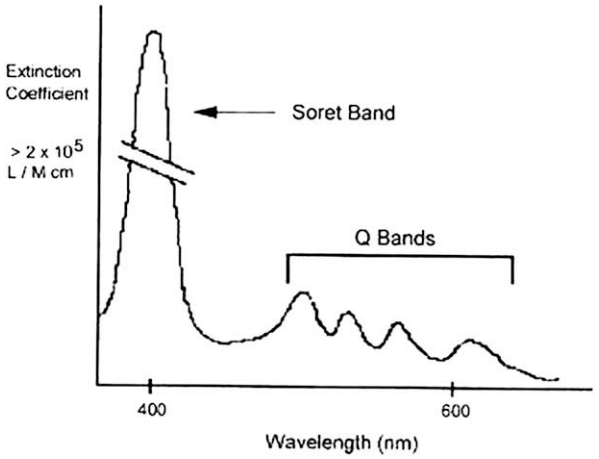


Fig 7. Light absorption of porphyrins; highest peak is around 400 to 420 nm, with smaller peaks between 500 and 700 nm. Blue light (415 nm) was used in several light-source systems because of this absorption spectrum. *L/M cm*, Light/mass per centimeter; *Q band*, radiofreguency band of 36 to 46 gigahertz. From Mariwalla and Rohrer.[142] Copyright 2005. Reprinted with permission of John Wiley & Sons, Inc.

Heating the sebaceous gland with these lasers results in a decrease in glandular size and sebum output.[137] With typical safe pulses of near infrared light (1064-nm laser), only modest heating of the sebaceous gland occurs.[137] Longer wavelengths cause thermolysis while preserving the epidermis.[155] Recently, Ross[137] speculated that these lasers do not irreparably heat the sebaceous glands but rather damage the gland by heating water in the surrounding tissue. The long wavelength near- and mid-infrared lasers that are available are associated with pain, particularly when used in facial areas.

Disruption of sebaceous gland function may be associated with a longer duration of action versus reduction of *P acnes*. However, because there are very few data about the long-term effects of light-based therapies in clinical practice, validation of this theory awaits controlled clinical trials. Additional factors to consider with treatments that target the sebaceous gland include the degree of damage to the gland and the extent to which it recovers.

Evidence supporting use of light-based treatment in acne. Generally, it is agreed that well-designed clinical studies include randomization, a sample size large enough to make statistical inferences, controls such as inclusion/exclusion criteria and control groups, treatment per protocol, and blinding. Studies of light-based treatments in acne should be evaluated with these design factors in mind.

Narrowband light treatments. There is some evidence for the efficacy of blue light in the treatment of

Table V. Studies on the use of blue light for mild to moderate acne vulgaris

Study and design	Treatment	No. of treatments	Results	Follow-up, mo
Controlled				
Tzung et al,[163] randomized split face in facial acne (n = 31)	2×/wk for 4 wk; Split face, with half of face serving as control	8	Significant improvement with light vs no treatment ($P < .001$); worsening of nodulocystic nodules with light treatment	1
Papageorgiou et al,[164] randomized open label in mild-moderate acne (n = 107)	4 Groups: (1) blue light; (2) mixed blue and red light; (3) cool white light; (4) 5% BPO	Daily for 12 wk (15 min for light therapy)	76% Improvement in inflammatory lesions with blue-red light mix, 58% improvement in comedones; blue-red light statistically superior to all other treatments at most evaluations	3
Elman and Lask,[158] 3 small studies combined (n = 46 total) split face, dose response; full face, open label; and split face, double blind	High-intensity (405-420 nm) for 8-15 min 2×/wk	8	Overall 80% response with significant reduction (59%-67%) of inflammatory lesions; prolonged remission for 8 wk after therapy; no adverse events or discomfort reported	2
Uncontrolled				
Tremblay et al,[160] open label in mild-moderate acne (n = 45)	High-intensity blue light (415 nm and 48 J/cm^2) for 20 min 2×/wk	8-16	Significant improvement on global improvement scoring system; 9 patients completely cleared; 50% of patients highly satisfied with treatment	2
Morton et al,[161] open label in mild-moderate acne (n = 30)	LED light source (409-419 nm at 40 mW/cm^2) for 10-20 min	8	Reduction in inflammatory lesions apparent at wk 5, statistically significant at wk 8; little effect on comedones; well tolerated	3
Omi et al,[162] open label in facial acne (n = 28)	High-intensity (405-420 nm) for 15 min 2×/wk	8	65% Improvement in acne lesions; no bacterial changes on PCR or culture	2-3
Kawada et al,[159] open label of mild-moderate acne (n = 30)	High-intensity (407-420 nm) for 15 min 2×/wk	10	64% Reduction of acne lesions; dryness reported by two patients, no treatment discontinuations	2.5
Shalita et al,[156] open label of mild-moderate acne (n = 35)	High-intensity (407-420 nm) for 8-15 min 2×/wk	8	Overall improvement in 80% of patients; 68% reduction in inflammatory lesions; no side effects reported	1

BPO, Benzoyl peroxide; *LED*, light emitting diode; *PCR*, polymerase chain reaction.

acne (Table V); however, acne clearing is variable among patients and relapse rates are high after therapy is discontinued.[137,143,156-164] There have been 8 studies of blue light for treatment of mild to moderate acne. All but one study were open label and most involved relatively small numbers of patients (typically 30-50/study). Further, the available studies used different treatment regimens, so it is difficult to determine the optimal duration of light exposure and number of treatments. Four studies used a split-face design, randomization, or blinding.[157,163,164] Only one study[164] had an active comparator arm—BPO

There is level IV evidence for the efficacy of blue light in the treatment of mild to moderate acne; it should be noted that acne clearing is variable among patients and relapse rates are high after therapy is discontinued.

5%—and it was a therapy that would rarely be used alone in treatment of acne according to current recommendations for treatment.

The effect of blue light was greatest on inflammatory lesions. One study had active comparators (BPO and mixed blue-red light); this study indicated that the mixed blue-red light was superior to blue light or BPO.[164] Another randomized study (n = 25) suggested blue light was superior to topical 1% clindamycin; however, the efficacy of both treatments was relatively modest (34% for light and 14% for clindamycin).[165] Currently, there are not enough data to support clinical recommendations about narrowband light systems.

Laser therapy. Lasers have become very popular in the past few years for treatment of a variety of skin conditions, from photoaging to acne. Like narrowband light sources, lasers may be used with or without exogenous photosensitizers.[166]

The 1450-nm diode laser (level V evidence). Small studies have reported positive results with the 1450-nm diode laser system for acne treatment.[155,167] A study of back acne suggested that lesion counts were reduced for a prolonged period (24 weeks).[155] This laser treatment has been associated with pain (particularly in perioral areas or areas with high concentrations of inflammatory lesions) and erythema and hyperpigmentation in some patients.[167] The device settings have varied between studies, making it difficult to determine the optimal regimen. Further, concomitant use of pharmaceutical treatments was allowed in one study, making it difficult to interpret results.

The 585-nm PDL (level V evidence). A 585-nm PDL that targets oxyhemoglobin has also been investigated for treatment of acne in two randomized controlled studies using the same device settings, with mixed results. Seaton et al[168] reported that inflammatory lesion counts were reduced by 49%. In an editorial accompanying the study of Seaton et al,[168] Webster[169] correlated the degree of success with the laser to that achieved with BPO. Soon after, however, Orringer et al[170] reported no significant improvement in acne. Both articles reported that the treatment was well tolerated, with some reduction in fluence occasionally needed because of discomfort during treatment.[168,170]

Level IV evidence supports use of PDT in acne; whereas existing studies suggest promise, conclusions are not possible because of the varying regimens and methodologies used.

Light therapy plus photosensitizers: PDT. Three agents, ALA, MAL, and ICG, have been investigated for PDT of acne (Table VI). ALA is a prodrug that converts in situ into protoporphyrin IX, a very active porphyrin activated by blue, red, or green light.[137,145,171] ALA is relatively hydrophilic and has limited ability to penetrate cellular membranes and interstitial spaces.[172] MAL is an ester of ALA that has also been used as a sensitizer in treatment of acne and other dermatologic diseases.[146,171,172] MAL was investigated because of its lipophilicity, which was expected to translate to greater penetration into target lesions.[171] Indeed, Fritsch et al[173] found that MAL was more selective than ALA for abnormal skin lesions. The accumulation into glands depends on both vehicle and application time; significant accumulation with ALA and MAL occurs within 3 to 4 hours.[137] PDT has been implemented with continuous wave light sources, IPL, and PDL.

Several studies have reported on the use of PDT in treating acne (Table VI).[146,151,166,171-183] Areas treated with a photosensitizer plus light show significantly greater improvement in acne severity and significant decreases in *P acnes* populations and sebum production relative to control areas.[151] In addition, results have been sustained for 10 weeks after a single treatment and up to 20 weeks after multiple treatments.[151] Adverse effects that may occur during and immediately after treatment include acne flare, erythema (sometimes persistent), hyperpigmentation, exfoliation, edema, pain, burning, and itching.

ICG dye, another photosensitizer currently being investigated for PDT of acne, absorbs light strongly at approximately 800 nm and is selectively concentrated in sebaceous glands when applied topically in a microemulsion.[153] Lloyd and Mirkov[153] treated patients with an application of an ICG microemulsion followed by exposure to a 50-millisecond pulsed diode laser with 4-mm spot size emitting 810-nm light with a total fluence of 40 J/cm^2. Although the patient population was not described, treatment was applied to a 10- × 10-cm area and followed by 24-hour occlusion. The treatment improved acne symptoms (although the degree of improvement was not reported) and produced histologically visible damage to sebaceous cells, with no noticeable adverse effects.[153]

Table VI. Studies on the use of pulsed dye laser for acne vulgaris

Study	Agent	Incubation time (h)	No. of treatments	Light source	Results	Follow-up, mo
Itoh et al[174] (n = 13, intractable acne with history of several years' treatment with various agents); open-label, uncontrolled study	ALA	4	1	Halogen (600-700 nm)	New lesions reduced 1, 3, 6 mo after treatment; improved facial appearance; temporary edematous erythema, epidermal exfoliation; acne lesions returned in 6 mo	6
Gold et al[175] (n = 20, moderate-severe acne); open-label, uncontrolled study	ALA	1	4	IPL	12/15 Patients responded to therapy; 50% reduction in lesions at end of final treatment; 68% reduction 4 wk after final treatment; 72% reduction at 12 wk; no adverse events or recurrences	1,3
Goldman and Boyce[176] (n = 22, mild-moderate acne); open-label, uncontrolled study	ALA	0.25	2	Blue	32% (ALA PDT) vs 25% (light only) improvement; 68% (ALA PDT) vs 40% (light only) reduction in papule counts; no significant adverse events	0.5
Gold et al[177] (n = 19, moderate-severe inflammatory acne)	ALA	0.25-0.5	4	Pulsed light source 420-950 nm	55% Reduction in inflammatory lesions; 38% reduction in noninflammatory lesions	2
Hongcharu et al[151] (n = 22, mild-moderate back acne); randomized to single or multiple treatment, open-label study	ALA	3 with occlusion	1 or 4	Broadband (550-700 nm)	Significant inflammatory acne flare 3-4 d posttreatment in all ALA-PDT—treated patients, "statistically significant improvement in acne" (percentage change not reported)	4.5
Taub[178] (moderate-severe acne)	ALA	0.25-0.5	2-4	Blue or 580-1000 nm with RF	1.75 Average improvement*; 11 of 12 patients with improvement had 50% improvement and 5 had >75% improvement; temporary erythema, peeling	4
Alexiades-Armenakas[166] (mild-severe acne)	ALA	0.75	Mean 2.9, range 1-6	LP PDL (595 nm)	Clearance in all patients	Mean 6.4, range 1-13
Horfelt et al[179] (n = 30 moderate-severe acne); prospective, randomized, blinded placebo-controlled multicenter study	MAL	3	2	Red (635 nm)	63% Reduction in inflammatory lesion counts at 6 wk (vs 28% placebo); 54% reduction at 12 wk (vs 20% placebo); pain, erythema, and skin swelling	3
Wiegell and Wulf[171] (n = 15, mild-moderate inflammatory acne); randomized, controlled, investigator-blinded study	ALA vs MAL	3	1	Red (635 nm)	59% Median reduction in inflammatory lesions in both treatment groups; more severe adverse events with ALA	3

Wiegell and Wulf[180] (n = 36, moderate-severe acne); randomized, controlled, investigator-blinded study	MAL (n = 21), control—no treatment (n = 15)	3	2	Red	68% Reduction in inflammatory lesions (MAL) vs no change in control (P = .0023); no reduction in noninflammatory lesions; moderate-severe pain in all active treatment patients, 7 patients did not receive second treatment because of adverse events	3
Yeung et al[181] (n = 30, moderate acne); randomized, split-face open-label study	MAL	0.5	4	IPL (530-750 nm)	At 12 wk, 65% reduction in inflammatory lesions vs 88% in control group; 38% reduction in noninflammatory vs 15% increase in control; 25% of patients in PDT group withdrew because of adverse events	3
Horfelt et al[146] (n = 15, mild-severe acne); open, unblinded study	ALA	3	1	Red light (dose-response study: varying doses based on anatomic area and severity of acne)	Percentage improvement not reported, by patient assessment, 8 improved after treatment; hyperpigmentation and pain more common with higher doses of light	2.5
Taub[182] (n = 22, moderate-severe acne); randomized, open-label study	ALA	3	3	IPL (600-850 nm or 580-980 nm) + RF or blue light (417 nm)	Responses to IPL greatest and more consistent than RF-IPL or blue light	3
Haedersdal et al[183] (n = 15, mild-moderate acne); split-face, open-label study	MAL	3	3	Long-pulsed dye laser	PDT improved both inflammatory and noninflammatory lesions to a greater degree than laser alone	3

ALA, 5 Aminolevulinic acid; *ELOS*, Electro-Optical Synergy (Syneron Medical Ltd, Yokneam, Israel); *IPL*, intense pulsed light; *LP PDL*, long-pulsed, pulsed dye laser; *MAL*, methyl aminolevulinate; *PDT*, photodynamic therapy; *RF*, radiofrequency.
*Acne improvement on a scale of 0-4.

With PDT therapy, it is very important to educate patients about the need for sun avoidance/protection after treatment for up to 48 hours. As the techniques are refined, a variety of ALA concentrations and formulations, application times, vehicles, and light sources may emerge, with a goal of achieving selective accumulation of the photosensitizer in the sebaceous gland and not in the epidermis.[137]

Light therapy plus medical therapy (level IV evidence). To date, a few trials have evaluated laser and light therapy in combination with medical therapy. As indicated by the study of Friedman et al[167] discussed above, this is likely to be an effective clinical approach, because the light therapy may speed resolution while the medical therapy prevents development of new lesions.[137,184] Also, the efficacy of pharmaceutical treatment of acne is well established; it is our opinion that adding light-based therapy as an adjunct to medical therapy makes sense until these new treatments have been better validated.

A randomized controlled study[185,186] used a 532-nm variable pulsed laser with topical therapy in 175 patients with acne. Patients were randomized to receive laser treatment alone (n = 25), laser treatment plus cleansers and topical antiacne agents (topical retinoids and salicylic acid) after completing 6 laser treatments (n = 25), or laser treatment with cleanser and topical acne therapy for the entire study duration (n = 125). The results showed that combination therapy involving both laser treatment and topical therapy was most effective. The time to response was slower in the group treated with laser therapy alone; in addition this group had faster relapse rates compared with patients using combination therapy. Of those treated with both medical and laser therapy, more than 50% of patients maintained results for longer than 4 months without requiring another treatment.[185,186]

A second study[186] evaluated a combination radiofrequency (RF)-IPL device in 50 patients with mild to moderate inflammatory acne involving the face, chest, back, and arms. Patients were treated with the RF-IPL weekly for up to 6 sessions; settings were 12 to 20 J/cm^2 optical fluence and 16 to 20 J/cm^2 RF fluence. Patients also were treated with topical agents (topical retinoids and salicylic acid) and cleansers, with a goal of targeting comedones. Noticeable improvement was reported in 80% to 90% of patients after the second treatment, with significant improvement in lesion counts after the fourth treatment (70%-80% reduction in inflammatory lesions).[186]

Summary. The current literature consists mainly of small uncontrolled studies with a body of evidence that is miniscule compared with that compiled with medical treatments of inflammatory acne.[187] In 2008, Haedersdal et al[187] conducted a systematic review of the topic of optical treatments in acne and found 16 randomized controlled trials altogether spread among 6 different types of interventions (PDT, IPL, infrared lasers, broad-spectrum light sources, PDLs, and KTP lasers). Given that each type of intervention has multiple available devices and protocols, it is clear there is a very limited evidence base for any of the treatments. Nonetheless, it seems that the use of lasers and light therapy alone or with photosensitizers offer promise. In the available studies, remission tends to be incomplete and relapses frequent. Long-term remissions have only been reported with photosensitizers in combination with deeply penetrating red light; however, this regimen is associated with significant side effects. Therapies that target *P acnes* (if any demonstrate an in vivo effect) will need to be administered on a regular basis or be used in conjunction with medical therapy. Treatments that target sebaceous glands offer the potential for long-term results.

Narrowband light therapies are typically well tolerated and conveniently administered; however, these treatments seem to target primarily inflammatory lesions. Again, this argues for use in combination with medical treatments, such as topical retinoids, that have anticomedogenic and comedolytic effects. Other light-based therapies are less well tolerated and are associated with pain and photosensitizing reactions.

In our opinion, some laser and light therapies for acne may not be as useful in patients with darker skin tones because ultraviolet penetration is partially filtered by melanin. Therefore, if the therapeutic rationale is that the light source penetrates into the skin to exert an effect on acne, then benefit is as not likely in individuals with dark pigmentation. Specific studies in patients with dark skin tones are needed.

Laser procedures vary widely in cost but are generally quite expensive. In many cases, light-based therapies are not covered by health insurance; thus, cost may be a limiting factor for widespread use of these new treatments.[137] Postprocedure care is important to optimize outcomes, and should include retinoids to maintain results, moisturizers, and sunscreens plus depigmenting agents as needed to prevent hyperpigmentation.

There is an important need for scientific evaluation of light-based therapies for acne based on evidence collected from clinical trials during a long period of time and compared with pharmaceutical regimens. Also, training programs regulated by

CONSENSUS: Topical Retinoids Should Be First-line Agents in Acne Maintenance Therapy

Level of Evidence: V

- Data from controlled studies show topical retinoid therapy can maintain improvement achieved with combination therapy
- Topical retinoids are a logical choice for maintenance therapy
  - o Target microcomedo and prevent formation of both comedones and inflammatory lesions
  - o Do not create selective pressure on bacteria
  - o No known additional safety issues with long-term use versus short-term use
- These recommendations are for patients with mild to moderately severe acne; a different approach may be required for patients with more severe acne or extensive truncal acne
- Long-term use of antibiotics should be avoided

medical boards should be created to help insure the most appropriate use of these devices. Use by untrained physicians and nonmedical personnel should be rigorously discouraged on a national level.

Although some recommendations for clinical use of light-based therapies have been given here, the members of the Global Alliance agree that more data are needed before the role of lasers and light treatments in inflammatory acne can be assessed. Before any of these technologies can be viewed as standard treatments for acne, they need to mature and be tested in large, well-designed clinical trials and by experience in normal clinical practice.

The role of topical retinoids in acne maintenance therapy

Clinicians who treat patients with acne know that acne lesions typically recur for years.[2,188] Also, lesions return soon after cessation of active treatment.[189] Therefore, maintenance therapy to reduce the potential for recurrence of visible lesions is an attractive option. However, maintenance therapy in acne has only recently been the subject of controlled studies.

In the decades since the efficacy of antibiotics against acne became known, these agents have commonly been used for prolonged periods in patients with acne. But in recent years, there has been increasing concern about long-term use of antibiotics because of the increasing worldwide prevalence of drug-resistant pathogens.[57] In addition, an improved understanding of acne pathophysiology has suggested to acne experts that antibiotics may not be the best class of therapy in terms of mechanism of action for maintenance. Antibiotics do not prevent the development of microcomedones, the subclinical precursors to both inflammatory and noninflammatory acne lesions. In contrast, topical retinoids do target microcomedones and macrocomedones and are comedolytic. Thielitz et al[189] used cyanoacrylate strips from the face to evaluate the effect of topical retinoid therapy on the development of closed comedones and microcomedones (Fig 8).[1] As shown, microcomedones significantly decreased during therapy but rebounded almost immediately after discontinuation of the topical retinoid. In contrast, reductions in comedo counts continued during the 4-week follow-up after cessation of therapy; this probably reflects normal skin turnover.[1,189] However, the presence of microcomedones signals that acne lesions develop even while older lesions resolve.

Theoretically, therefore, topical retinoids might be preferred as maintenance therapy because topical retinoids have the ability to prevent the development of new acne lesions and to resolve existing lesions.[1] When discussing maintenance in acne, it is important to emphasize the lack of definitions surrounding the topic. For example, is a therapy only to be considered maintenance if the acne has completely cleared? Or is there a level of clearing that can be considered adequate for beginning maintenance therapy? The members of the Global Alliance have discussed the issue of definitions and terminology, but have not reached a clear consensus. Depending on the severity of inflammation, an additional antimicrobial agent may be needed and the Global Alliance recommends BPO or a BPO-antibiotic combination product as the first-line antimicrobial for maintenance with topical retinoids because BPO is a highly effective agent against *P acnes* and has not been shown to induce bacterial resistance.[1]

Until recently, there has been no study of maintenance therapy in acne; several controlled clinical trials have now been published that provide favorable evidence of the benefits of topical retinoid monotherapy as maintenance. This is an excellent beginning, but the members of the Global Alliance believe there is a need for more studies to determine optimal maintenance regimens. Other issues

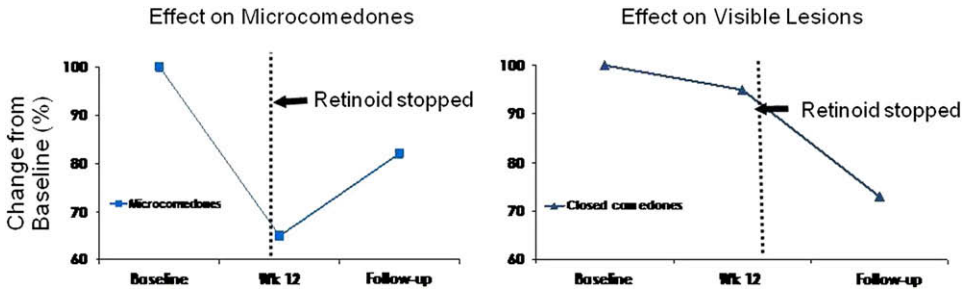


Fig 8. Effect of topical retinoid therapy on closed comedones and microcomedones. Data from Thielitz et al.[189] Reprinted from Gollnick et al[1] with permission from the American Academy of Dermatology.

that should be addressed include creating a standardized definition of successful maintenance, determining the most appropriate patient populations for maintenance therapy, and identifying the ideal length of observation of patients. The studies available to date have used different types of patients, different initial therapies (but always a combination of a topical retinoid and an antibiotic), and, most importantly, different methods of analyzing the maintenance phase. The high rate of patients who were successfully maintained on vehicle in some studies may in part reflect the difference in threshold for success/failure or perhaps a reservoir or residual effect from the initial therapy. In future studies, it would be useful to present data on the proportion of patients who were able to maintain a defined level of improvement (eg, 50% from baseline).

Clinical studies of topical retinoids as maintenance therapy. To date, adapalene regimens have been most extensively studied as maintenance in acne.[12,14,94,190] One clinical trial evaluating tazarotene[13] and one study involving maintenance with tretinoin after oral tetracycline and tretinoin topical treatment have been published.[191] Long-term use of adapalene has been studied, both with adapalene 0.3% and adapalene 0.1%/BPO 2.5%.[120,192] The recent maintenance therapy studies are summarized in Table VII.

In the majority of these studies, topical retinoid monotherapy has been evaluated after an initial 12-week period of combination therapy involving a topical retinoid plus an oral or topical antibiotic. Bettoli et al[193] also studied the use of a topical retinoid after oral isotretinoin therapy. The studies have ranged from 3 to 12 months; however, the two longest studies (6 and 12 months, respectively) did not include a control arm.[12-14,94,190,191,193]

Adapalene. There have been 4 controlled and two uncontrolled studies of adapalene gel 0.1% as maintenance therapy (Table VII).[12,14,94,190] In addition, one study assessed the effect of adapalene gel 0.1% on microcomedones and two others evaluated the long-term use of adapalene gel 0.3% and the novel combination product adapalene gel 0.1%/BPO 2.5%.[94,120,192]

There is now level II evidence (multiple controlled studies) to support use of topical retinoid monotherapy as maintenance in acne. To minimize antibiotic resistance, long-term therapy with antibiotics is not recommended (level V evidence). If antimicrobial effect is desired, addition of BPO to topical retinoid therapy is preferred (level V evidence).

The first controlled study of adapalene gel 0.1% evaluated the effects of adapalene gel 0.1% versus no therapy for 12 weeks as maintenance therapy in 241 patients with moderate to moderately severe acne.[12] Adapalene maintenance therapy was associated with a significant and continuing reduction in lesion counts ($P < .01$ through weeks 20-24) (Fig 9).[12] Rebound of acne lesions was apparent within 4 to 8 weeks after cessation of therapy in the group receiving no maintenance therapy. This study did not report data on the proportion of patients who were successfully maintained.[12]

Second, Thiboutot et al[14,111] reported a 16-week, randomized, vehicle-controlled maintenance study, also conducted as follow-up to a controlled combination therapy study. At the end of the acute phase study, patients in the combination therapy group achieved a median 61% reduction in total lesions, 65% reduction in inflammatory lesions, and 60% reduction in noninflammatory lesions.[111] Those in the doxycycline monotherapy group had reductions of 45.3% in total lesions, 58.5% in inflammatory lesions, and 40.5% in noninflammatory lesions.[111] Patients who achieved at least a moderate improvement were allowed to enroll in the maintenance

therapy study; this included 82% of patients from the combination study.[111] At time of entry into the maintenance phase, patients had achieved a degree of clearing similar to that seen in routine clinical practice when maintenance therapy would be considered:

- All patients had severe acne at combination study baseline.
- When they were enrolled in the maintenance study, there were no patients with severe acne: only 28% of patients had moderate acne and 72% of patients had mild or minimal acne or were clear.

During the maintenance phase of the study, adapalene was significantly superior to vehicle in maintaining improvement (Fig 10); vehicle was associated with a maintenance effect in about half of the patients, although this was significantly ($P < .001$) less than the effect of adapalene.[14] A subsequent analysis was conducted to determine the percentage of patients who maintained the acute-phase treatment effect at various levels while in the second phase of the study. As shown in Fig 11, more than half of patients were able to maintain 90% of their clearing while on adapalene maintenance therapy. The post hoc analysis also showed that maintenance of at least 50% reduction in lesions was significantly more frequent in adults (>20 years of age, $P = .035$), but there was no relationship between successful maintenance and sex or race. In addition, the number of acne lesions at baseline was correlated with successful maintenance therapy, with success more likely with increasing number of lesions before treatment.[152] Patients completed a 5-question survey about satisfaction with treatment; there were significantly more patients in the adapalene group who indicated they were satisfied or very satisfied with effectiveness (75% vs 58%, $P = .001$) and overall maintenance (76% vs 65%, $P = .01$).[14]

In a third study, which was also vehicle controlled, 12-week maintenance therapy was given after either combination adapalene-lymecycline or lymecycline plus gel vehicle.[8] Success rates were significantly greater (85% vs 64%, $P = .0049$) in patients receiving adapalene versus those receiving vehicle.[190] Assessments of global severity at the end of the study showed mild acne in more patients treated with adapalene (82.2% vs 68.3%) and moderate acne in fewer patients treated with adapalene (17.8% vs 31.7%) compared with vehicle. The local cutaneous tolerability was excellent for both groups, with most patients experiencing either mild or no irritation.[190] In all studies, there was a pattern of gradual rebound of acne lesions in patients who were untreated or treated with vehicle, whereas acne lesion counts remained stable or decreased in patients treated with adapalene.

In the fourth controlled study, Thielitz et al[94] evaluated the effect of maintenance therapy with adapalene gel 0.1% on microcomedones counts assessed by cyanoacrylate stripping. In this single-center study, eligible patients had mild to moderate acne with at least 250 microcomedones/cm^2 at the screening visit. Cyanoacrylate strip sampling was performed at baseline, week 8, and week 20. Both adapalene regimens (once daily or every other day compared with vehicle) were significantly superior ($P < .05$) in reducing microcomedones counts versus vehicle.[94] As shown in Fig 12, this study very closely replicates the results obtained by Thielitz et al[189] in 2001.

Bettoli et al[193] evaluated the use of adapalene as maintenance after discontinuation of oral isotretinoin in 74 patients. In this 12-month study, 6.7% of patients had a recurrence of acne defined as an increase in acne severity by greater than or equal to 0.5 on the Leeds scale or patient request for treatment.[193] This compares favorably with published reports of acne recurrence after isotretinoin therapy (range 12%-39%).[194-199]

Results from long-term studies. Two long-term studies have been conducted that were not specifically designed as maintenance studies but provide additional evidence supporting the concept of maintenance therapy, because acne is often a chronic, relapsing disease.[120,192] The efficacy and safety of adapalene gel 0.3% was evaluated in a 12-month, open-label study (551 patients enrolled); 167 of patients completed the 12-month study.[192] Patients applied adapalene gel 0.3% once daily to the face for 12 months. By the end of the study, total lesions were reduced by 76.5%, inflammatory lesions by 77%, and noninflammatory lesions by 78.3% (Fig 13).[192] Similarly, Pariser et al[120] evaluated the long-term efficacy and safety of the adapalene 0.1%/BPO 2.5% fixed-combination product in a 12-month study of 452 patients with acne. Clinically significant improvements in acne were apparent as early as week 1; at study end, the reductions in total lesions were 71%, in inflammatory lesions were 76%, and in noninflammatory lesions were 70%.[120] Adapalene/BPO was well tolerated, with mild to moderate adverse events occurring in the early part of the study and resolving with continued use of the study medication.[120]

Tazarotene. In a randomized, parallel-group study, Leyden et al[13] evaluated the efficacy of 3 maintenance regimens involving tazarotene gel 0.1%. Patients with an improvement of greater than or equal to 75% during the combination treatment

Table VII. Overview of maintenance therapy studies

Study	Design	Treatments	Efficacy	Safety
Adapalene				
Zhang et al[12] (N = 241)	Randomized, controlled, 12-wk study in moderate-moderately severe acne To enter, at least moderate improvement needed during earlier 12-wk treatment study	**Maintenance phase** • Adapalene gel 0.1% once daily (N = 122) • No treatment (N = 119) **Earlier treatment phase** • Adapalene gel 0.1% once daily + clindamycin solution 1% twice daily • Clindamycin solution 1% • 12 wk	**Change in total lesion counts** • Adapalene: −41.6% • No treatment: +92% $P < .01$ Change in inflammatory lesion counts • Adapalene: −41.7% • No treatment: +97.1% Change in inflammatory lesion counts • Adapalene: −40.8% • No treatment: +87.7% **Global assessment** • Adapalene: further improved, much improved/clear in 67.2% of patients • No treatment: improvement in 4.2% of patients	**Adverse events:** Adapalene was well tolerated
Thiboutot et al[14] (N = 253)	Randomized, investigator-blinded, parallel group, vehicle-controlled, 16-wk study in severe acne To enter, at least moderate improvement needed during earlier 12-wk treatment study	**Maintenance phase** • Adapalene gel 0.1% once daily (N = 126) • Adapalene gel vehicle once daily (N = 127) **Earlier treatment phase** • Adapalene gel 0.1% + doxycycline 100 mg • Doxycycline 100 mg + gel vehicle • 12 wk	**Maintenance success (sustained 50% improvement in lesion counts)** 75% in Adapalene group vs 54% in vehicle group ($P < .001$) **Global assessment success (clear/almost clear)** • Adapalene: 27% • Vehicle: 16% $P = .005$ **Lesion counts at end point** Significantly lower with adapalene vs vehicle (total, $P = .005$; inflammatory, $P = .01$; noninflammatory, $P = .02$)	**Tolerability** Excellent in both groups Worst scores <1 (mild) at all time points during study
Alirezai et al[190] (N = 136)	Randomized, investigator-blinded, parallel-group, vehicle-controlled 12-wk study in moderate to moderately severe acne	**Maintenance phase** • Adapalene gel 0.1% once daily (N = 73) • Adapalene gel vehicle once daily (N = 63)	**Maintenance success (sustained 50% improvement in total lesion counts)** • Adapalene: 85%	**Tolerability** Excellent in both groups Worst scores <1 (mild) at all time points during study

	To enter, at least moderate improvement	Earlier treatment phase • Adapalene gel 0.1% + lymecycline 300 mg, both once daily • Lymecycline 300 mg + gel vehicle, both once daily • 12 wk	• Vehicle: 64% $P = .0049$ Global severity Stable in adapalene group, worsened in vehicle group	Discontinuation rate • Adapalene: 6.8% • Vehicle: 20.6%
Thielitz et al[94] (N = 49)	Single-site exploratory study with randomized, investigator-blinded and vehicle-controlled 12-wk maintenance phase To enter, successful completion of earlier combination therapy 8-wk study	**Maintenance phase** • Adapalene gel 0.1% once daily (N = 16) • Adapalene gel 0.1% every other day (N = 16) • Vehicle once daily (N = 17) **Earlier treatment phase** • Adapalene gel 0.1% + BPO 2.5%, both once daily • 8 wk	**Percent change in microcomedo count at end of maintenance phase compared with baseline** Adapalene every other day: −53.5% Adapalene once daily: −50.6% Vehicle: −42.1% $P < .05$	**Good tolerability**
Tazarotene Leyden et al[13] (N = 110)	Randomized, parallel-group, double-blinded 12-wk study To enter, ≥ 75% improvement from baseline at end of combination therapy phase	**Maintenance phase** • Tazarotene gel 0.1% once daily (N = 36) + placebo • Minocycline 100 mg twice daily (N = 37) + vehicle • Tazarotene gel 0.1% once daily + minocycline 100 mg twice daily (N = 37) **Earlier treatment phase (N = 189)** • Tazarotene gel 0.1% + minocycline 100 mg twice daily • 8 wk	**All regimens equally effective:** • 81%-87% of Patients with ≥ 50% improvement from baseline • 54%-70% of Patients with ≥ 75% improvement from baseline NS **Reductions in lesion counts** Noninflammatory • Tazarotene: 60% • Minocycline: 52% • Tazarotene + minocycline: 64% Inflammatory • Tazarotene: 54% • Minocycline: 66% • Tazarotene + minocycline: 66% NS	**All regimens were well tolerated** **Maximum scores none for burning and pruritus and trace for peeling, erythema, and dryness**

BPO, Benzoyl peroxide; *NS*, not significant.

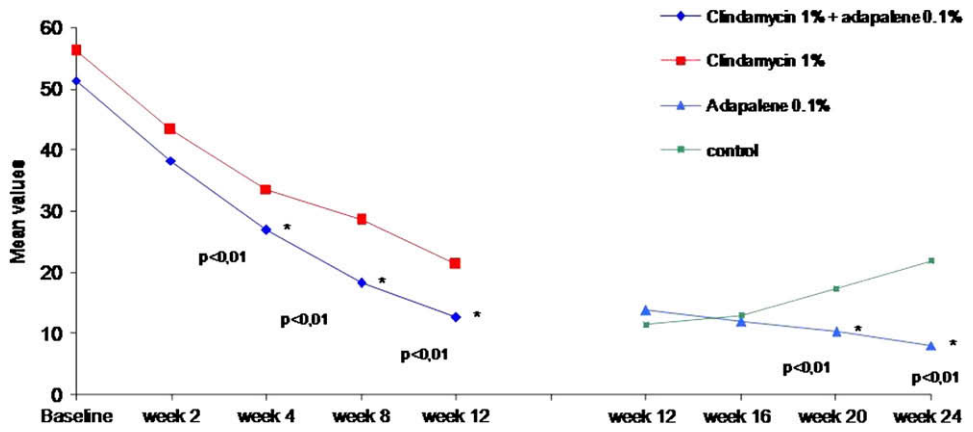


Fig 9. Change in lesion counts during initial treatment and maintenance phases. *$P < .01$. Reprinted from Zhang et al[12] with permission of the publisher (Taylor & Francis Group, http://www.informaworld.com).

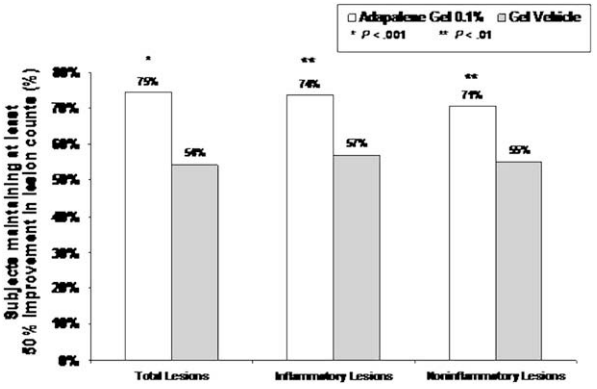


Fig 10. Maintenance rates (percent of patients maintaining ≥ 50% of improvement in lesion counts) with adapalene gel 0.1% or gel vehicle. *$P < .05$; **$P < .001$. Reprinted with permission from Thiboutot et al[14] copyright © 2006 American Medical Association. All rights reserved.

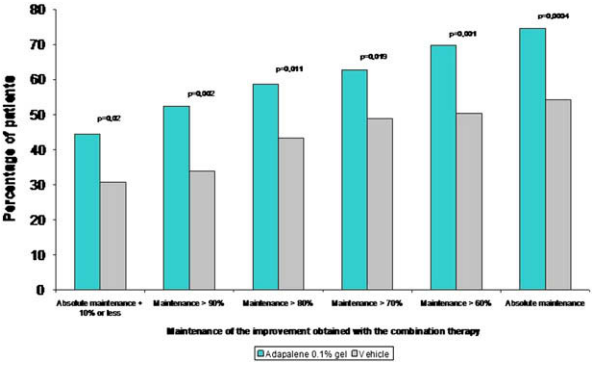


Fig 11. Maintenance success stratified by degree of maintenance and treatment regimen in acute and maintenance treatment periods.

phase were randomized to 12 weeks of maintenance therapy with tazarotene plus placebo capsules (n = 36), minocycline plus tazarotene vehicle (n = 37), or tazarotene plus minocycline (n = 37).[13] A total of 83% of patients both completed the acute phase and had the required degree of clearing to enter the maintenance phase (n = 114). All 3 regimens effectively maintained the improvement achieved during the initial open-label combination treatment (Fig 14). There were no significant differences between groups for several variables, including: mean overall disease score, percent of patients with greater than or equal to 50% or greater than or equal to 75% global improvement from baseline (around 80% and from 54%-70%, respectively), reduction in acne lesions from baseline, or percent of patients with good or excellent maintenance (eg, those who maintained their lesion count reduction throughout the second 12-week phase). However, regimens containing minocycline were slightly better in maintaining a good response with inflammatory lesions. No statistically significant differences were found.[13]

Maintenance studies should indicate the degree to which clinical improvement is preserved. In this study, the proportion of patients who maintained greater than or equal to 50% global improvement from baseline were: 81% in the tazarotene group, 81% in the minocycline group, and 87% in the combination therapy group.[13] Further, more than 75% global improvement from baseline was reported in 54% of those in the tazarotene group, 68% in the minocycline group, and 70% in the combination therapy group.[13]

Tolerability was acceptable with all regimens; in the initial treatment phase, the most common adverse events included burning (3%), peeling (3%), and erythema (2%). During the maintenance phase, there were no adverse events considered probably related to study medication.[13]

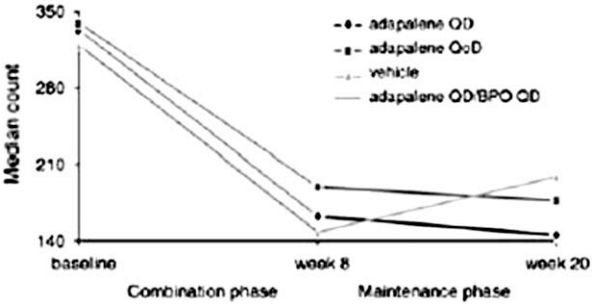


Fig 12. Median microcomedone counts. Difference in change at week 20 from baseline was statistically significantly in favor of both adapalene groups versus vehicle. *BPO*, Benzoyl peroxide; *QD*, once daily; *QoD*, every other day. Reprinted with permission from Thielitz et al,[94] published by Wiley-Blackwell Publishing.

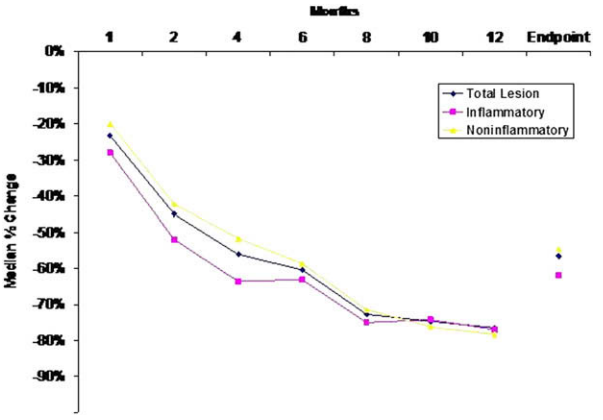


Fig 13. Change in lesion counts during 12 months of adapalene 0.3% therapy. From Weiss et al.[192] Reprinted with permission from the *Journal of Drugs in Dermatology*. Copyright 2008.

Achieving best results with maintenance therapy (level of evidence: V). For a successful long-term treatment, any acne maintenance therapy must be tolerable, appropriate for the patient's lifestyle, and convenient. As discussed above, the effectiveness of topical retinoids against existing lesions and subclinical precursor lesions provides the rationale for using this class of drug as maintenance in addition to the avoidance of long-term antibiotic use. Topical retinoids are available in a variety of concentrations and formulations; these should be selected for optimal comfort and compatibility with the patient's daily routine. Use of a gentle cleanser and a noncomedogenic moisturizer can help protect the skin barrier and minimize irritation.

Education about the pathophysiology of acne can enhance the likelihood that a patient will adhere to maintenance therapy. Understanding how acne lesions arise and the goal of preventing microcomedo formation can encourage the patient to treat asymptomatic skin and to adhere to the treatment strategy. Discussing other positive effects of topical retinoid use, such as skin-repairing effects on collagen structure in the papillary dermis and on postinflammatory hyperpigmentation, may be useful with adult patients. However, the psychosocial benefits of clearer skin may be the most compelling reason for consistent maintenance therapy. Finally, explaining that acne is for many people a chronic disease that requires acute and maintenance therapy for remission may also be helpful for many patients.

The natural history of acne suggests that maintenance therapy should continue during a period of months to years depending on the patient's age. Exploration of the patient's previous experience with acne medications and current use of cosmetics can be useful in selecting the best agent, formulation,

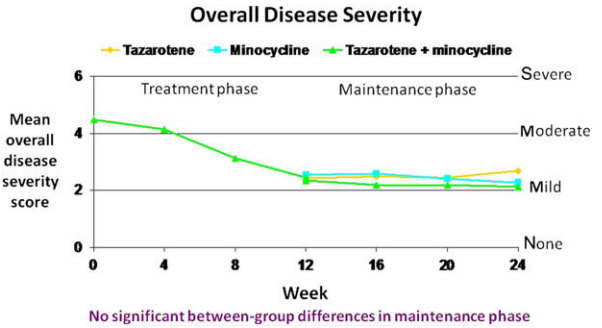


Fig 14. Topical retinoid versus oral antibiotic or combination maintenance therapy. Reprinted with permission from Elsevier Inc from "Maximizing Results in the Treatment of Acne and Improving Facial Appearance" (*Skin and Allergy News*. 2005;36:8-10).

and regimen needed to maintain the beneficial effects of acne treatment.

Conclusions. Maintenance therapy to minimize the likelihood of relapse after initial successful treatment of acne is important, given the chronic nature of the disease. Use of a topical retinoid as monotherapy to maintain acne remission is a relatively new concept for many clinicians. However, the results of the clinical studies discussed in this article show that topical retinoids are a good choice for maintenance, as suggested by their mechanism of action and shown by clinical data. Successful maintenance regimens must minimize development of new clinical lesions, be well tolerated, and have a low potential for evoking bacterial resistance; all of these criteria are met by topical retinoids.

The majority of studies reported to date have lasted 3 to 4 months and show a trend toward continuing improvement with topical retinoid maintenance therapy and relapse when patients stop treatment. Clinical experience indicates that a longer

duration of maintenance therapy is likely to be beneficial for many patients. Ongoing research will help to define the optimal duration of therapy and, perhaps, refine patient selection. Some patients with significant inflammation may need to be treated with a combination of retinoid and antimicrobial agent. This should be further studied.

The fact that microcomedones are subclinical and not apparent to the naked eye underscores the need to apply topical therapies to the entire affected area. This, in turn, suggests that any agent used for maintenance therapy must be well tolerated. The current studies are well done and interesting; however, future studies should include comparison of several maintenance regimens in different patient populations.

Management of acne scarring

Scars are a visible and, often, indelible reminder of acne. This dreaded outcome of acne has a wide variety of manifestations, from barely visible to severely disfiguring, and can be a consequence of even relatively mild acne; further, it is currently not possible to predict which patient may scar and which may not. Scarring can also arise from inflammatory lesions or from self-manipulation. Although acne scars create significant concerns for patients and clinicians alike, there is currently no standardized approach to management. This is, in part, a result of the variable presentation of acne scars, which can range from deep pitted ice-pick scars to large raised hypertrophic scars. Management approaches include various types of resurfacing (chemical peels, lasers, and lights), use of dermal fillers, and surgical methods such as dermabrasion, subcision, and punch excision. Individual scar characteristics, including color, texture, and morphology, determine the treatment choice.[200]

The occurrence and incidence of scarring is not well understood. Goodman[201] has reported an 11% frequency of acne scars in men and 14% in women based on clinical examination by dermatologists; however, patient interview by Poli et al[18] showed that 49% of individuals thought they had acne scarring. Layton et al[202] studied 185 patients with acne and found some degree of facial scarring in 95% and a higher likelihood of truncal scarring in men versus women ($P < .05$). Layton et al[202] also showed a correlation between the severity of scars and the duration of delay between the onset of acne lesions and the start of treatment, emphasizing the need for early aggressive therapy.

The considerable variation in scarring that occurs in different individuals suggests that some people are more prone to scarring than others. Scarring frequently results from severe inflammatory nodulocystic acne but may also result from more superficial inflamed lesions.[21] Severity is related to both the depth in the dermis/pilosebaceous unit where inflammation and wound healing occur and the duration of inflammation. Erythema and pigmentation changes represent epidermal damage whereas atrophic, hypertrophic, and keloidal scars indicate dermal damage.[201] (An in-depth discussion of pigmentation changes is beyond the scope of this article and is not presented here.) Currently, there is no predictive tool to identify patients who are likely to develop acne scars.

Causes and types of scarring. The skin contour and color are most often altered in acne scars. Light that strikes skin with contour changes causes visible shadows; scars with steep rims have significant shadows and are most conspicuous whereas those with shallow or beveled rims reflect less shadow and are less noticeable.[21] Color changes in acne scars can include red, white, or brown; these changes often diminish over time but do not always completely resolve.[201]

Causes of scars. Scars form at the site of tissue injury and may be hypertrophic or atrophic. Injury to the skin initiates a cascade of wound healing events, which progresses through 3 stages: inflammation, granulation tissue formation, and matrix remodeling.[203-205] Numerous cells, growth factors, cytokines, and components of the extracellular matrix (mainly MMPs and inhibitors of MMPs) are involved in the process.

The first step in wound healing is coagulation and inflammation. Blanching occurs secondary to vasoconstriction for hemostasis. After the blood flow has been stopped, vasodilation and resultant erythema replace vasoconstriction. Melanogenesis may also be stimulated. This step has an important role in the development of postacne erythema and hyperpigmentation. A variety of blood cells, including granulocytes, macrophages, and lymphocytes, are activated and release inflammatory mediators, which ready the site for granulation tissue formation.[203,205]

In the second step, damaged tissues are repaired and new capillaries are formed. New production of collagen by fibroblasts begins approximately 3 to 5 days after the wound is created. Early on, the new skin composition is dominated by type III collagen, with a small percentage (~20%) of type I collagen. However, the balance of collagen types shifts in mature scars to be similar to that of unwounded skin, with approximately 80% of type I collagen.[203,205] Keratinocytes proliferate and migrate to the site, closing the wound and eliminating the fibrin clot.

CONSENSUS: Early, Appropriate Treatment Is Best to Minimize Potential for Acne Scars

Level of Evidence: V

- Scarring is often the primary concern of a patient with acne
- Classification systems have been developed and now help to standardize discussions about acne scars
- The treatment approach is usually determined by the scar characteristics and may involve resurfacing, surgical revision, and use of dermal fillers; in many cases, topical retinoids are a useful adjunct to procedures in management of scarring
- Two key modifiable factors are linked to acne scars: a time delay between onset of acne and effective treatment and the extent/duration of inflammation
- Early appropriate treatment that is continued for as long as necessary is the best way to prevent acne scarring
- The progression of scarring despite aggressive traditional treatment is a primary rationale for use of oral isotretinoin

In the third step, which has a long duration (weeks or months), fibroblasts and keratinocytes produce enzymes including those that determine the architecture of the extracellular MMPs and tissue inhibitors of MMPs. An imbalance in the ratio of MMPs to tissue inhibitors of MMPs results in the development of atrophic or hypertrophic scars. Notably, retinoids bind to apolipoprotein and inhibit MMP production in acne lesions. These agents may thus shift the balance of MMP:tissue inhibitors of MMP back toward normal and reduce the likelihood of scar development.[28]

When the healing response is too exuberant, a raised nodule of fibrotic tissue forms; inadequate response results in diminished deposition of collagen factors and formation of an atrophic scar. Pigmentary and vascular changes caused by acne are often temporary; however, changes in texture caused by disruption of collagen are often permanent.[205]

By examining biopsy specimens of acne lesions from the back of patients with severe scars and without scars, Holland et al[206] found that the inflammatory reaction at the pilosebaceous gland was stronger and had a longer duration in patients with scars versus those without; in addition, the inflammatory reaction was slower in those with scars versus patients who did not develop scars. They found a direct link between inflammation and the development of scarring, suggesting that treating early inflammation in acne lesions may be the best method to prevent acne scarring.

Types of acne scars. There are two general types of acne scars, defined by tissue response to inflammation: (1) scars caused by increased tissue formation and (2) scars caused by loss of tissue.[207]

Hypertrophic scars. Hypertrophic and keloidal scars are associated with excess collagen deposition and decreased collagenase activity. Hypertrophic scars are typically pink, raised, and firm, with thick hyalinized collagen bundles that remain within the borders of the original site of injury.[205] The histology of hypertrophic scars is similar to that of other dermal scars.[203] In contrast, keloids form as reddish-purple papules and nodules that proliferate beyond the borders of the original wound; histologically, they are characterized by thick bundles of hyalinized acellular collagen arranged in whorls. These scars may occur a long time after the original injury or even without an obvious history of preceding injury. Keloidal scars are more common in darker-skinned individuals. Both hypertrophic and keloidal scars may cause pruritus.[203,205] Hypertrophic acne scars and acne-associated keloids occur predominantly on the torso (upper and mid aspect of back, sterna and clavicular areas, shoulders and deltoids, and occasionally over the jaw angles). In contrast, atrophic acne scars occur predominantly on the face and rarely, if ever, on the back.

Atrophic scars. Atrophic acne scars are more common than keloids and hypertrophic scars. Jacob et al[207] have proposed an acne scar classification scheme that divides atrophic scars into 3 types: icepick, rolling, and boxcar (Fig 15). They suggest that the most important features of scars are width, depth, and 3-dimensional architecture.[207]

- *Icepick:* Narrow (<2 mm), punctiform, deep scars are known as icepick scars. With this type of scar, the opening is typically wider than the deeper infundibulum (forming a "V" shape). Icepick scars are often too deep to be managed with conventional resurfacing options.
- *Rolling:* Dermal tethering of the dermis to the subcutis characterizes rolling scars, which are usually wider than 4 to 5 mm. These scars give a rolling or undulating appearance to the skin ("M" shape). Successful treatment of rolling scars will eliminate the subdermal tether.
- *Boxcar:* Round or oval scars with well-established vertical edges are known as boxcar scars. These

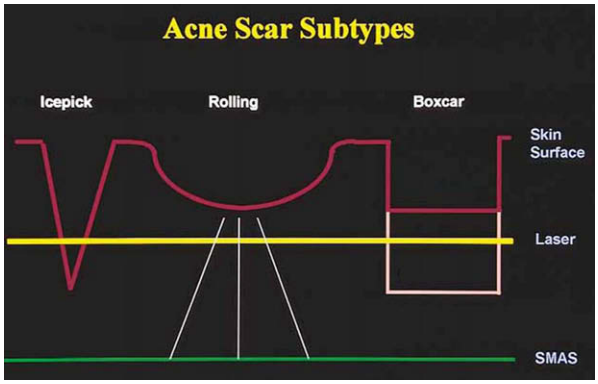


Fig 15. Novel classification system of 3 basic scar types: icepick, rolling, and boxcar (superficial and deep). *Yellow reference line* denotes depth of ablation and resurfacing capability of carbon-dioxide laser. *Green line* represents superficial musculoaponeurotic system (*SMAS*) to which fibrous bands adhere, creating rolling scars. Reprinted from Jacob et al[207] with permission from the American Academy of Dermatology.

scars tend to be wider at the surface than an icepick scar and do not have the tapering V shape. Instead, they can be visualized as a "U" shape with a wide base. Boxcar scars can be shallow or deep.[207]

Note, however, that acne scars are sometimes mixed and are not always amenable to simple classification.

Dréno et al[208] created a grading scale to quantify the severity of acne scars (Fig 16). This scale, known as the ECCA scale (échelle d'évaluation Clinique des cicatrices d'acné), is designed for use in clinical practice with a goal of standardizing discussions about treatment of scars.[208,209] Goodman and Baron[209] also developed a quantitative global acne scarring assessment tool. Like the ECCA scale, Goodman score assigns points depending on the type of scar and the number of scars present. This system assigns fewer points to macular and mild atrophic score compared with moderate to severe atrophic scores. Hypertrophic scars are assigned points based on the area of skin involvement.

Treatment of scarring (level IV evidence). The objective of scar treatment is to give the skin a more acceptable physical appearance. Resurfacing techniques destroy the epidermis and allow re-epithelialization with collagen remodeling. They include chemical peeling, dermabrasion, laser abrasion, selective photothermolysis, RF, and electrosurgery. Surgical techniques include excision, punch elevation, and subcision. Dermal fillers may be used to plump up atrophic scars, and makeup may be used to conceal scars. For best results, a combination of techniques and procedures may be needed. In addition, treatment of scars may be focused on a single scar; surgical techniques or fillers may be suitable approaches in this case—or to the entire area of involvement—when chemical peels, laser therapy, or dermabrasion may be the treatment of choice. Sometimes treatments will need to be used sequentially. In this case, treatments targeted at individual scars should precede treatments that resurface the entire area. In addition, the later resurfacing should be attempted only after full recovery of any individually treated scars. Topical retinoids can be used with procedures to enhance healing, maintain results, and treat and prevent pigmentary changes.[210,211]

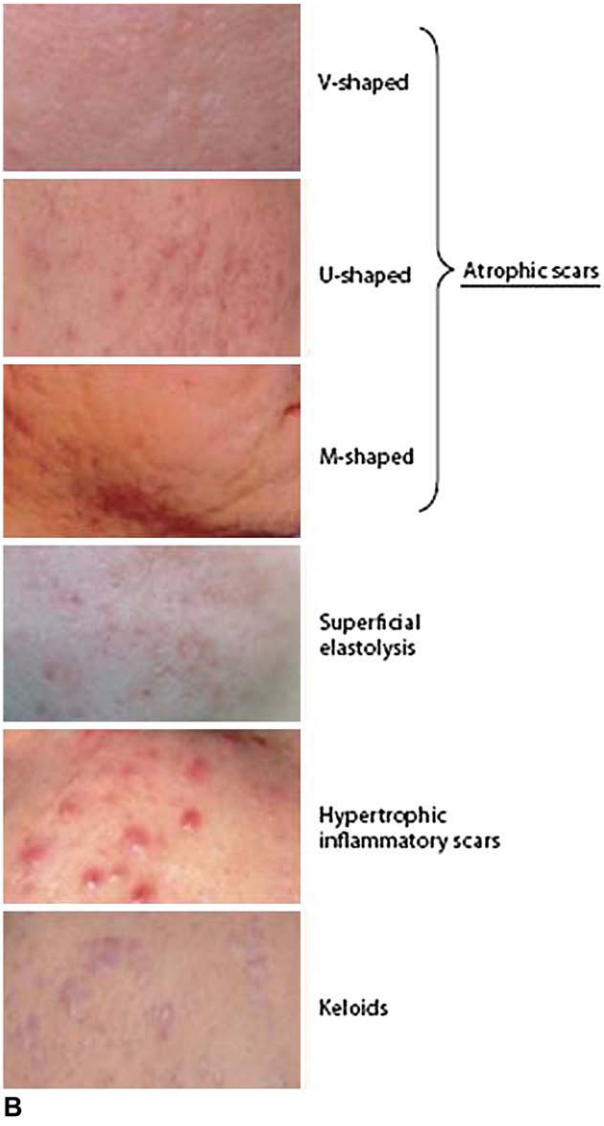
Nonsurgical/resurfacing techniques.

Dermabrasion/microdermabrasion (level IV evidence). Dermabrasion can provide effective treatment for acne scars; however, it is associated with significant pain and recovery time.[207] In addition, a small group of patients develop hypertrophic scarring after dermabrasion, and pigmentary alterations, hypertrophic or keloidal scarring, and milia formation can occur.[207,211] Dermabrasion usually fails to improve icepick or deep boxcar scars. Microdermabrasion is well tolerated but of limited benefit in acne scarring. In a study of 10 patients with acne scarring, use of microdermabrasion with a topical retinoid was associated with a mild but definite improvement.[210] Use of microneedle arrays (derma rollers) is becoming popular in some areas of Asia to treat shallow acne scars. The microneedle array consists of fine needles mounted on a cylinder; the cylinder is rolled over target areas to lightly wound the skin. Although it has not been rigorously studied, this technique may provide an abrasive effect that is similar to microdermabrasion. Fig 17 shows results after two sessions at 2-week intervals.

Chemical peels (level IV evidence). Medium-depth chemical peels are most useful for correcting small depressed scars; this approach should not be used for ice pick scars or deep fibrotic scars. Repeated light peels with Jessner solution, 20% to 35% trichloroacetic acid (TCA), or glycolic acid peels can improve mild scars.[201] Home regimens of peels plus topical retinoids also offer a small benefit for patients with shallow, mild scarring.[201] However, for many patients with acne scars, improvement from chemical peel is unsatisfactory.[201] Lee et al[212] reported a technique called chemical reconstruction of skin scars, which incorporates focal application of TCA applied by a sharp stick to icepick and deep boxcar scars. The procedure is associated with good clinical response in the majority of patients (82%

Description	Weighting factor (a)	Semi-quantitative score (b)	Grading (a × b)
V-shaped atrophic scars, diameter of less than 2 mm, and punctiform	15	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	/_____/
U-shaped atrophic scars, diameter of 2–4 mm, with sheer edges	20	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	/_____/
M-shaped atrophic scars, diameter of more than 4 mm, superficial and with irregular surface	25	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	/_____/
Superficial elastolysis	30	0 = absent 1 = mild 2 = moderate 3 = intense	/_____/
Subgrading 1			/_____/
Hypertrophic inflammatory scars, scars of less than 2 years of age	40	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	/_____/
Keloid scars, hypertrophic scars, of more than 2 years of age	50	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	/_____/
Subgrading 2			/_____/
Global score (subgradings 1 + 2)			/_____/

A



B

Fig 16. **A**, The échelle d'évaluation Clinique des cicatrices d'acné (ECCA) grading scale. Total score is directly correlated with scar severity. **B**, Types of acne scars assessed by ECCA grading scale. Reprinted from Dréno et al[208] with permission from S. Karger AG, Basel.

treated with 65% TCA and 94% treated with 100% TCA), but should be performed with caution in dark-skinned individuals because of the high risk of prolonged postinflammatory hyperpigmentation.[212] Medium-depth topical peels with glycolic acid or TCA may be used alone or in combination with other techniques such as optical treatments or injection of dermal fillers.[207] Deep peels (phenol) may also be an option, but are more rarely used because of the downtime required for healing and the potential for complications and adverse events.

Laser treatment (level IV evidence). Lasers of various wavelength and intensity may be used to recontour scar tissue and reduce the redness of skin around healed acne lesions.[205] The choice of optimal laser system and settings depends on the characteristics of scarring present.[203] For example, low-energy fluencies should be used for less fibrotic scars in sensitive skin areas such as the chest, but it should also be noted that the efficacy is generally low. Table VIII presents criteria that should be considered when deciding to use laser revision of scars.[203]

Ablative lasers (level IV evidence). Ablative lasers emit high energy densities at extremely short pulses to vaporize target tissue with limited damage to nontargeted surrounding skin; they offer better control of resurfacing compared with dermabrasion.[200,213] The clinical results are a

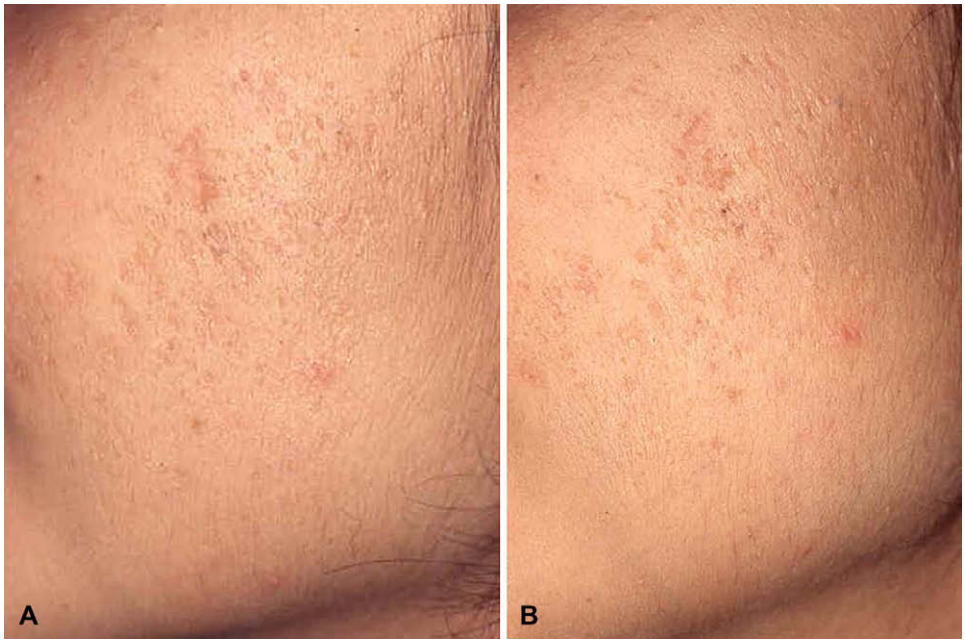


Fig 17. Effect of microneedle array treatment on shallow boxcar acne scars. Before (**A**) and after (**B**) two sessions at 2-week intervals. Clinical photographs courtesy of Drs Vandana Chatrath and Raj Kubba.

Table VIII. Patient characteristics for optimal laser efficacy (level V evidence)

- Skin phototype—darker skin tones require lower energy densities
- Concurrent infection/inflammation—avoid laser treatment to affected area
- Medication use—discontinue anticoagulants (for pulsed dye laser)
- Earlier treatment—note presence of background dyspigmentation
- Expectations and compliance—assess whether realistic and agreeable to treatment
- Nonfibrotic scars

Reprinted with permission from Alster and Zaulyanov,[203] published by Wiley-Blackwell Publishing.

result of collagen shrinkage and remodeling. The carbon-dioxide (CO_2) laser can achieve improvements of approximately 50% to 80% in atrophic scars. With this laser, epidermis and papillary dermal tissue is vaporized to depths of 20 to 60 μm with thermal necrosis zones of an additional 20 to 50 μm.[213]

Pulsed erbium-doped yttrium-aluminum-garnet (Er:YAG) lasers are more selective for water than the CO_2 laser; the Er:YAG laser improves tissue vaporization and reduces residual thermal damage.[213] The short-pulsed Er:YAG laser typically ablates 10 to 20 μm of tissue per pass with a thermal necrosis zone of an additional 15 μm or less. This laser is better tolerated than the CO_2 laser (producing less erythema), but has less efficacy. It may be best used for mild atrophic scars, because the clinical effects are similar in that setting to the CO_2 laser but recuperation is faster.[205,213] Modulated or dual-mode (short and long pulsed) Er:YAG systems may achieve greater improvement in scars.[213] Ablative resurfacing carries the potential for adverse effects including erythema, edema, and serous discharge. Potential complications include infection, acne or milia formation, and dyspigmentation.

Nonablative lasers (level IV evidence). The risks associated with ablative laser resurfacing have driven investigation of less invasive laser resurfacing methods. Of the variety of devices used to treat atrophic scars, the most popular are the 1320-nm neodymium:yttrium-aluminum-garnet and 1450 diode lasers. These devices combine epidermal surface cooling with deep penetrating energy to target water-containing tissue that can produce thermal injury in the dermis without affecting the epidermis. Three monthly treatments are typically given, and clinical improvement continues for approximately 3 to 6 months after the last treatment. Mild overall improvement has been reported with these lasers.[213-216] A comparison of the efficacy of the 1450-nm diode laser versus the 1320-nm neodymium:yttrium-aluminum-garnet laser for atrophic facial scars in 20 patients with mild to moderate scars suggested better clinical results with the 1450-nm laser.[213] Side effects are generally mild.

It has been suggested that best results may be achieved when these lasers are combined with another modality such as surgery or chemical peels.[205] Carniol et al[217] reported on the combination of a 1450-nm mid-infrared laser plus 30% TCA peels as treatment of atrophic rolling and boxcar scars in 9 patients. Four monthly laser treatments were followed by two bimonthly treatments with 30% TCA; blinded evaluators and the patients rated the results. Improvement was greater when the chemical peels were added.[217]

Use of the vascular-specific 585-nm PDL may achieve clinical and textural improvement in established erythematous and hypertrophic scars.[218-220] Several mechanisms of action have been proposed to explain the clinical effects of PDL: induction of tissue hypoxia and associated collagenesis, heating of collagen fibers to break disulfide bonds and realign the collagen, photothermolysis of vasculature, and stimulation of mast cell factors that affect collagen metabolism.[205] Vascular-specific lasers should used with caution in patients with darker skin, because of lower absorption of the laser energy and the risk of destroying melanin.[203]

Fractional laser treatment (level IV evidence). In 2007, Alster et al[221] reported results of a study of 53 patients with mild to moderate atrophic facial acne scars treated with 1550-nm erbium-doped fiber laser. This system produces microthermal zones of tissue coagulation; dermal collagen is denatured, leading to significant neocollagenesis, epidermal coagulated tissue is shed, and keratinocytes migrate to the site.[222] In the study of Alster et al,[221] response was assessed at each monthly treatment visit and at 6 months posttreatment by independent investigators. There was an average clinical improvement of 51% to 75% in most patients after 3 treatments, and the improvement scores increased with each treatment. Most patients experienced transient erythema and edema, but there was no report of dyspigmentation, ulceration, or scarring.[221] The procedure is painful, and topical anesthetics should be used along with forced air cooling to increase patient comfort.[222] A variety of ablative fractional resurfacing lasers are now available and the initial impression is that these lasers may be more effective than nonablative fractional lasers for acne scars. However, side effects may also be more of a concern with the ablative fractional lasers. Confirmation of the role of these relatively new procedures awaits more data.

Surgical techniques. There are 3 primary surgical techniques for acne scars: excision (with or without graft), punch elevation, and subcision.

Punch excision and elevation (level V evidence). Scattered individual ice-pick scars may be removed by punch excision of each scar. The scar is excised down to the layer of subcutaneous fat; the resulting hole in the skin is then repaired with sutures or with a small skin graft. Punch excision may be used for icepick and narrow, deep boxcar scars.[207] The tool should be carefully sized to the inner diameter of the scar.[207] This is a relatively easy technique that usually produces a good result; in some cases, secondary widening of the scar occurs.

Punch elevation uses partial lateral round excision of the borders of the scar, leaving the deep part of the scar adherent to the fat layer. After the scar has been isolated from the surrounding skin, it is elevated enough to be slightly raised against the bordering tissue. During healing, the tissue retracts and a level surface is achieved. There is no risk of skin color or texture mismatch. Elevation should only be used on boxcar scars with sharp edges and normal-looking bases.[207]

Subcision (level IV evidence). Subcision, or subcutaneous incision, may be used for rolling or depressed scars (Fig 18).[207,223,224] This technique releases fibrotic strands that tether the scar to underlying tissue. A sharp needle is inserted under the skin with the blade parallel to the skin surface, then moved in a sweeping motion to cut the subcutaneous fibrotic strands.[223,224] Associated pooling of blood in the subcutaneous space probably reduces the likelihood of new tethers forming. Temporary bruising and swelling are expected, but complications such as acneiform cystic lesions from disruption of sinus tracts are rare.[201]

Additional improvement may be achieved when surgical techniques are combined with resurfacing procedures.[207]

Fillers (level V evidence). Scars may be filled with collagen injections, artificial dermal fillers, or autologous fat transfer. Collagen may be used to fill certain types of superficial and deep soft scars, particularly those with gently sloping walls, but is not a preferred option for ice-pick scars and should not be used in fibrotic scars. Collagen injections achieve a temporary improvement (3-6 months). Autologous fat transfer may be a therapeutic choice for deep contour defects and the effect lasts approximately 6 to 18 months. Dermal fillers have variable duration of effect (6-12 months), depending on the agent chosen. Injection of filler must be repeated to maintain the effect and it is an expensive treatment option. However, dermal fillers are safe, with a low risk of inflammatory reactions.[201]

Adjunctive treatment (level V evidence). Preparing the skin before procedures and

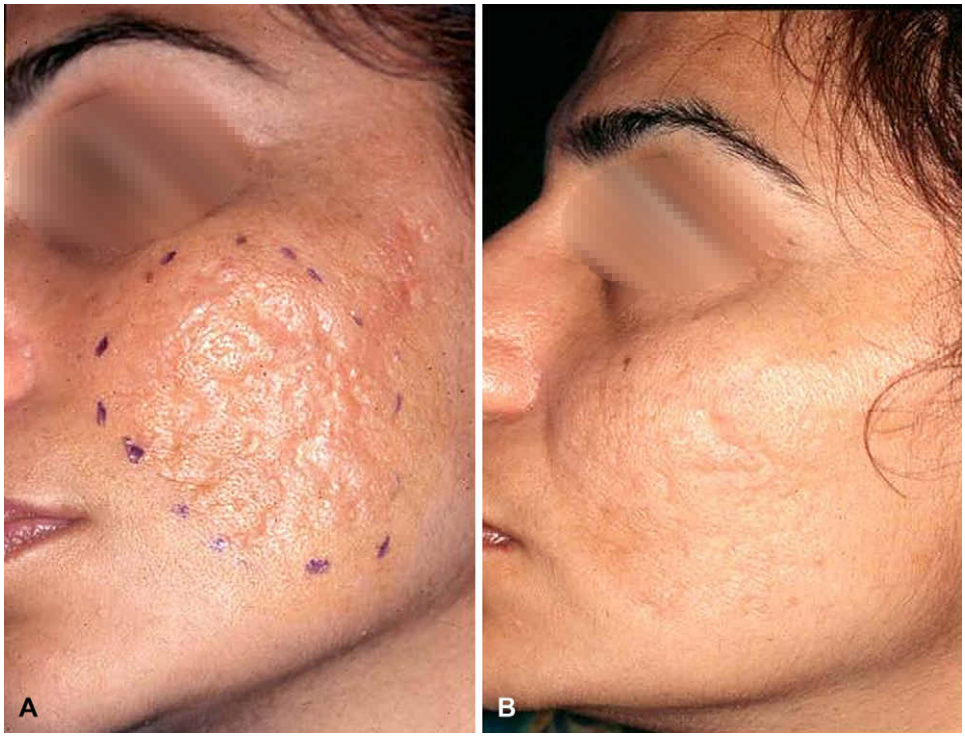


Fig 18. Effect of subcision on acne scars. Before (**A**) and after (**B**) two treatments. Clinical photographs courtesy of Drs Vandana Chatrath and Raj Kubba.

postprocedure strategies can be used to improve and maintain results. Topical retinoids are a good adjunct to resurfacing techniques because procedures that remove the epidermis involve dermal wound healing and re-establishment of the epidermal barrier.[225] Retinoid therapy increases the synthesis of mucopolysaccharides, collagen, and fibronectin and decreases collagenase production. In addition, retinoid therapy shortens the healing time after cosmetic invasive procedures.[225] In a study of dermabrasion in acne scarring, use of a topical retinoid for 2 weeks before the procedure resulted in complete healing within 5 to 7 days versus 7 to 11 days in the control group.[226] In addition, there were fewer postprocedure complications in patients who were pretreated with the retinoid.[225,226] Similar benefits have been reported for retinoid pretreatment before chemical peel.[225,227]

Posttreatment use of moisturizers, sunscreens, and retinoids is also useful. Retinoids can help to maintain results, whereas the moisturizers and sunscreens can have a preventive effect for development of postinflammatory hyperpigmentation.

Treatment of keloids (level IV evidence). A recent meta-analysis and review of the literature on treatment of keloids and hypertrophic scars included 27 different treatments ranging from surgical excision to topical preparations such as bleomycin and fluorouracil.[228] The results showed a 70% chance for some improvement with treatment and no statistically significant difference between treatments.[228] Because so many modalities have been used for hypertrophic and keloidal scars, a complete discussion is beyond the scope of this article.

A wide variety of treatments have been directed against hypertrophic scars. Surgical excision was used early on, but is associated with a very high recurrence rate. Radiation therapy has also been used, alone and in combination with surgical excision. The response rates in published studies of radiation therapy vary widely; in addition, the carcinogenic risk associated with this treatment limits its routine use as treatment of benign scars.[228] Optical treatments offer good potential, with PDL emerging as a good option.[228] The 585-nm PDL has been used with good results to treat hypertrophic scars and keloids, reducing erythema, pliability, bulk, and dysesthesia with few side effects.[200] Thick keloids may respond best to PDL plus intralesional corticosteroid or 5-fluorouracil injections.[200,229] Cryotherapy has been used, but may be undesirable to patients because of the potential for hypopigmentation and postoperative pain. Injection of corticosteroids is also a therapeutic option that some consider a mainstay of treatment.[228] Pressure and occlusive dressings can be used alone or with

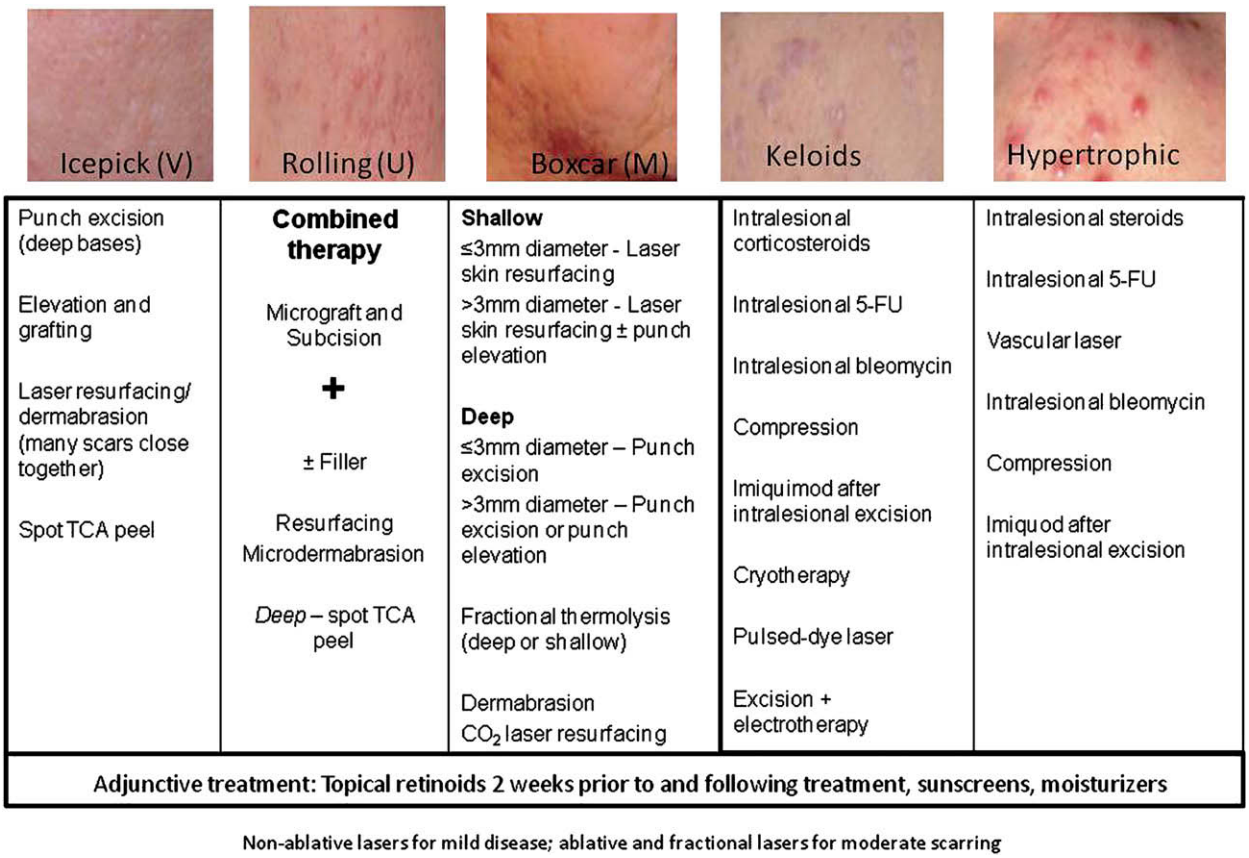


Fig 19. Treatment options for acne scars. *CO_2*, Carbon dioxide; *FU*, fluorouracil; *TCA*, trichloroacetic acid.

surgical excision and act by an unknown mechanism. Interferon, fluorouracil, and bleomycin have all been used in hypertrophic and keloidal scars and may reduce recurrence. To date, no optimal treatment has been identified and investigation into pharmacologic agents and other treatment modalities is encouraged.[228]

Prevention of scarring. The occurrence of scarring is hard to predict. At present, the best method of preventing or limiting scarring is to treat acne early to minimize the extent and duration of inflammation. Patients seeking treatment of acne should be educated that scarring is a permanent sequelae that can occur and that it is more likely with long-term inflammation. In addition, the importance of adherence with treatment to minimize the potential for scarring should be emphasized.

Summary. Acne scars arise as a result of the inflammatory response to acne lesions. Data show that the degree and duration of inflammation are directly related to the likelihood of scarring. Thus, the best method of managing acne scars is to prevent them by treating acne early and continuing therapy for as long as necessary. There are a variety of scars and treatment options that can be used to achieve significant cosmetic improvement (Fig 19), but it must be noted that none of the currently available treatments achieve complete resolution of the scar. Combining treatment methods may provide additional improvement compared with one method alone.

OPTIMIZING ADHERENCE WITH ACNE THERAPY

Acne medications should be started soon after the appearance of acne lesions to minimize the potential for physical and emotional scarring. This is especially important because the clinical severity of acne does not correlate well with the impact on the patient; thus, the patient may feel significant embarrassment, anger, or other psychologic disturbance even when disease is mild.[230-232] Several studies have demonstrated that the impact of acne on the quality of life of adult patients is related to patient's self-assessment of the severity of disease, rather than to the physician's objective clinical assessment.[5,233,234] The therapeutic goals in acne are to resolve existing lesions, prevent scarring, and suppress the development of new

Terminology: Compliance or adherence?

For many years, the term "compliance" was used; recently, "adherence" has assumed prominence. What is the difference?

Although there is no single agreed-on definition, "compliance" suggests that the patient is taking medication as ordered, highlighting a power imbalance between the physician and patient and emphasizing the patient's obedience.

"Adherence," in contrast, refers to the patient's willingness to implement a health care plan and suggests the plan was formulated and agreed on by the patient in concert with the physician.[238]

In addition, the term "persistence" may be used to describe long-term use of a medication. The term "adherence" is intended to be nonjudgmental, a statement of fact rather than of blame.[235]

lesions. Successful management of acne involves choosing the right medications and helping the patient to use the medications as directed. Medication adherence has a prominent role in the success of therapy. For example, data show that discontinuing topical retinoid therapy is associated with a rapid increase in microcomedones, which in turn give rise to clinical acne lesions.[189]

Between 1960 and 1975, a large number of scientific articles examined medication adherence (compliance) in a variety of disease states and care settings; more modern reviews of these studies consistently showed that unpredictable and disappointing responses to therapy were quite frequently a result of poor adherence.[235,236] The studies also suggested that the patient behaviors comprising adherence are complex and can be affected by many variables. In general, research has estimated that 20% to 50% of patients do not take medication as directed.[237] The Global Alliance reviewed the literature about adherence in acne and provides some recommendations to help clinicians encourage better adherence.

There is level III evidence indicating adherence in acne is poor; there is a need for clinicians to be aware of the problem of adherence and have an actionable strategy for improving adherence among their patients.

Studies of adherence in acne

Although there have been relatively few formal studies of medication adherence in acne, data suggest it is poor overall and experts have theorized that poor adherence may be a major contributor to treatment failures.[236,239,240] Adherence can be evaluated either directly, as in the case of monitoring radiolabeled chemicals in blood, or indirectly via questionnaires or interviews.

The indirect method of assessing adherence has been used most frequently in acne studies. In 1985, Flanders and McNamara[241] reported that adherence with over-the-counter BPO was 48% in college-aged patients (n = 42) despite educational strategies to improve compliance. Of patients with dermatologic conditions, 44% (n = 396) reported that they did not exactly follow their doctor's prescription in a 2002 study.[239] Most recently, a surprising 70% of adolescents with acne said they adhered closely to a prescribed treatment regimen in a telephone survey that was not conducted in a medical setting. The authors speculated that "patients have a less strict definition of adherence than doctors."[230] One study, by Zaghloul et al,[242] used both direct (pill counts/tube weights) and indirect (interview) methods to assess adherence; they reported a 65% adherence rate.

In addition to not using medications as directed, patients with acne are also likely to miss appointments. McEvoy et al[243] reported that just 28% of patients kept all 4 scheduled follow-up visits during a 6-month period; worse, 19% did not return at all after the first visit. Notably, the likelihood of keeping appointments was associated with demographic factors such as age and race, along with payment method, but not in this study with knowledge of acne or its treatment.[243] However, McEvoy et al[243] noted that appointment keeping should not be used as a surrogate marker of compliance because some patients continue self-treating but do not keep appointments and others may not keep an appointment as a result of clearing of acne to the point where they no longer believe professional treatment is needed.

Researchers have also attempted to determine what patient beliefs might influence adherence in acne. One study reported that although 90% of patients had used over-the-counter medications for acne, more than 75% thought that these medications had only a slight effect or no effect on their disease.[243] In addition, many patients have indicated that their acne improved at a slower or far slower rate than they expected.[243] Studies have suggested

Table IX. Factors associated with adherence

	Factor	Effect on adherence
Patient demographic factors[242]	Older age	↑
	Being married	↑ vs Single
	Female	↑ vs Male
	Smoking	↓
	Drinking alcohol	↓
	Unemployed	↓
Medication characteristics[242,247]	Out-of-pocket cost	↓ With ↑ costs
	Oral isotretinoin	↑ vs Other regimens
	Gel formulations	↑ vs Other topical antiacne formulations
	Once-daily formulations	↑ vs BID
	Convenient formulations (eg, no need to refrigerate)	↑
Patient preferences[239,242,247]	Satisfaction with treatment	↑
	Pleased with physician	↑
	Shame/embarrassment	↑
	Psychiatric morbidity (anxiety/depression)	↓

BID, Twice a day.

that most patients with acne expect significant results of treatment to be apparent within 4 to 6 weeks.[244,245]

Factors associated with adherence in acne

Several studies have investigated the impact of factors that are associated with adherence in acne, and there is some guidance available to help clinicians determine which patients may have good adherence and which may need extra support with their acne therapy. It has been known for years that the frequency of administration is negatively correlated with adherence; in a study of an orally administered drug, 87% of patients took their once-daily dose on schedule whereas only 39% were able to adhere to 4 times per day dosing.[236,246] Similarly, the total number of medications taken and medication costs can affect adherence.[246]

Table IX shows factors that have been associated with good or poor adherence in acne; however, it should be remembered that studies have been few in number and have typically involved small numbers of patients. A few patient demographic characteristics have been linked to medication-taking behavior. Zaghloul et al[242] found a negative correlation between age and medication adherence.[242] In addition, female patients were more adherent than male patients (71% vs 60%, $P < .0001$) and married persons had better adherence than single individuals. There is some evidence that smoking and drinking alcohol may affect adherence in acne. Zaghloul et al[242] reported that medication adherence was 68% among nonsmokers and 44% among smokers ($P < .0001$ and abstinence from alcohol was associated with better adherence than drinking alcohol (88% vs 56%, $P < .0001$). With the last two variables, there were no rigorous attempts to quantify how much the respondent smoked or drank and these data may be open to some interpretation. Finally, lack of employment was significantly correlated with medication adherence (22% for unemployed vs 65% for employed subjects, $P < .0001$).[242]

> Level IV evidence suggests that certain factors may be associated with better or worse adherence. However, there is no clear definition of which patients are less likely to adhere with treatment. Clinicians need to proactively ask patients about adherence, particularly if the therapeutic response is less than expected.

The impact of psychiatric factors on adherence have been investigated in several studies.[239,242] Renzi et al[239] reported that treatment adherence was strongly correlated with satisfaction (relative risk 2.31, $P = .002$ vs not satisfied); factor analysis also showed that satisfaction with the physician's manner had a large bearing on overall satisfaction. High levels of shame and embarrassment were also associated with better adherence (relative risk 2.13, $P = .05$), presumably serving as motivating factors for patients to take their medication. However, there was a negative correlation between psychiatric morbidity and adherence.[239] Zaghloul et al[242] also found that worse scores on the Dermatology Quality of Life Index were associated with poor adherence (r −0.87).

Table X. Adherence questionnaire

Oral treatment	
• Have you used the drug?	**Yes**
• Did you tolerate the drug well?	**Yes**
• Did you forget to take the drug at any time during the treatment period?	**No**
• Did the drug improve your acne?	**Yes**
Sensitivity = 0.61, specificity = 0.56	
Topical treatment	
• Do you remember the name of the last drugs you took?	**Yes**
• Did you tolerate the drug well?	**Yes**
• Did you stop using the drug because you thought it would do more harm than good?	**No**
• Was the drug useful for you?	**Yes**
Sensitivity = 0.47, specificity = 0.8.	

Reprinted from Pawin et al[248] with permission from S. Karger AG, Basel.

Several treatment-related factors can play a role in adherence, including costs, particular drug regimens, and patient preferences. Paying for prescription was associated with worse medication adherence.[242] Oral isotretinoin therapy has been associated with better adherence than topical therapy (71% vs 35% in the study of Zaghloul et al[242]); however, adherence decreases in patients who require repeated courses of oral isotretinoin (60%). To correctly frame the results, it should be noted that the majority (81%) of patients in the study of Zaghloul et al[242] were taking oral isotretinoin; factors affecting adherence may be somewhat different with traditional topical and oral acne therapies. Kellett et al[247] and others studied patient preferences with topical acne therapies, and found that patients preferred gel formulations that could be applied once daily and stored at room temperature.

New tool to assess adherence validated

Recently, a tool was developed to help clinicians evaluate the adherence of patients with acne with topical and oral antiacne treatments (Elaboration d'un outil d'evaluation de l'observance des traitements medicamenteux [ECOB]).[248] Two questionnaires (a self-administered questionnaire for patients and a dermatologist-directed questionnaire) were created and tested in a cohort of 246 patients with acne consulting a dermatologist at a follow-up visit. Of these, 91 (37%) were taking both oral and topical treatment, 84 (34%) were using oral isotretinoin, and 71 (29%) were being treated with topical therapy only. Patients were considered good compliers if they reported they had followed the treatment regimen according to the dermatologists' prescription or could give the correct name of the treatment (or correct color of the packaging). They were categorized as bad compliers if they said they followed their treatment regimen sometimes, stopped treatment without following dermatologist advice, or had the wrong name/wrong package color.[248]

Good compliance was present in 54% of patients treated with topical therapy, and 95% of patients treated with oral isotretinoin. Among those treated with a combination of oral and topical therapies, patients were more likely to be compliant with oral versus topical therapy (81% vs 59%). Sensitivity and specificity analysis showed that two very brief sets of questions and answers could reliably predict adherence (Table X).[248]

The ECOB adherence assessment tool can be administered in less than 1 minute, and as such poses minimal constraints during a consultation. It can help the dermatologist optimize the therapeutic treatment of patients with acne, and could contribute to a better understanding of the underlying causes of therapeutic failure in individual patients.

A large international study was then conducted using the mini-questionnaire to validate its use in daily practice. This study was also designed to evaluate adherence to acne treatment in different countries throughout the world and factors that influence adherence. Ultimately, the goal is to help create a profile of patients who are likely to have poor adherence so that clinicians can focus their educational efforts and optimize outcomes. In this study (n = 3339), combination therapy involving both topical and systemic treatments was the most common therapeutic regimen (52%) followed by topical therapy (25%), oral isotretinoin (22%), and systemic treatment that was not isotretinoin (1%). Retinoids and antibiotics were the most common therapeutic classes used.

Interim results using the ECOB adherence scale revealed that a total of 59% of patients had poor adherence to the combination of systemic and topical treatments; analyzed by type of treatment within a combination regimen, fewer patients had poor compliance to topical versus systemic treatment (43% vs 49%, respectively). Of patients, 46% taking oral isotretinoin had poor compliance; this is lower than cited above, but may reflect inclusion of patients who were using repeated courses of isotretinoin and those on low-dose isotretinoin. Among patients treated with topical therapy, the rate of poor adherence was 39%. Analysis of topical therapy showed that poor adherence was most common for the class of retinoids (50%), followed by topical antibiotics (44%) and BPO (40%).

According to patient questionnaire results, patients believed they were not very knowledgeable about acne (53% had little or no knowledge) or its treatment (63% had little or no knowledge). The severity of acne was not correlated with the likelihood of adherence in this study; however, the presence of side effects and acne scarring were both associated with a higher rate of poor adherence. In accordance with other studies, adherence was better in patients who believed that their acne had improved (63% in those who rated improvement as much or very much). Both quality of life and satisfaction with treatment were also associated with adherence.

Global Alliance recommendations

Assessing adherence (level V evidence). The membership of the Global Alliance to Improve Outcomes in Acne believes it is very important to regularly assess adherence in patients with acne by asking open-ended questions regarding their acne regimen. Evaluation of a large medical database that included almost 6 million individuals showed that, on average, patients with acne fill two acne prescription refills per year, which is not nearly enough to adhere to any prescribed regimen.[249] Yet in the same database, those who demonstrated good adherence with acne medication had significantly better overall health status (P = .026) compared with nonadherent individuals.[249] Because adherence is not a discreet activity at one time point, the best approach to improving adherence may involve a combination of nonpharmacologic interventions plus simple and effective drug regimens.[249,250] It has been shown that simply asking about adherence can identify more than 50% of cases of nonadherence.[250] In the short term, achieving good adherence is a relatively easy task; achieving good adherence in a chronic remitting condition such as acne requires changing patients health behaviors.

The Global Alliance recommends assessment of adherence via verbal interview or use of a simple tool such as the ECOB questionnaire at each visit for patients with acne (level V Evidence)

Actions physicians can take to improve adherence

Focus on counseling and education, whether done directly by the physician or by office staff and physician extenders. First, it is important to recognize that patients may have a limited understanding of the terms used in acne. Lucero et al[251] analyzed terms to describe acne used by patients and found that most patients had a limited understanding of language for acne lesions. They suggested that use of clinical photographs may help patients to understand discussion of acne lesions and improve results when using quality-of-life assessment instruments.[251] In addition, dermatologists should know that information about acne is most often obtained from family physicians (71%), mass media, and friends or relatives.[245] However, the majority of patients who gained acne information this way believed that it was inadequate.[245] Studies consistently show that patients expect acne to be treated within 1 to 2 months.[245] Taking the time to educate patients in the beginning of treatment can help them cope with medication side effects and have proper expectations for treatment.

Be sure to show the patient how much medication to use and how it is applied to the skin. Patients who are not taught to apply topical therapy to the entire face typically spot treat, and have been shown to use approximately one third of the medication used by patients with education (0.34 vs 0.9 g).[252] Again, spending some extra time at the initial visit can save time in the long run and increase the possibility of good outcomes.[253]

Address the reasons why patients do not take their treatment. Zaghloul et al[242] found that the main reasons for missing treatments were being fed up, forgetful, and too busy. Each clinician treating patients with acne should develop a few strategies to help patients manage their schedules and routines in a manner that will facilitate medication adherence.

Assess quality of life, because there is evidence it can affect adherence. Initially, this can be done in the patient interview. When there is a suggestion that quality of life is negatively impacted, a more formal assessment tool can be used. Renzi et al[239] showed that shame and embarrassment, as measured on the Skindex-29 emotions scale, were associated with adherence behavior.

Evaluate the likelihood of psychiatric morbidity. If present, institute appropriate management of anxiety and depressive disorders. Consult with the patient's primary care physician or psychiatric professionals if the comorbid condition seems to be more than can be appropriately managed in a busy dermatologic practice.

Consider using medication reminders (text messages), self-monitoring with diaries, rewards for adherence, support groups, and telephone follow-up. These techniques have been associated with improved adherence in nondermatologic diseases.[253] This may be an area of interest for future research.

Use available resources. National dermatologic associations and, sometimes, pharmaceutical companies have good educational resources available. Often,

selected information from several different sources can be combined into an educational tool that matches an individual dermatologist's philosophy.

Summary

Problems with adherence in acne are well accepted, although few rigorous studies have been done to quantify existing problems. The factors that influence adherence are less well known, and are currently the focus of a large-scale international study using the validated ECOB questionnaire. This study, which involves 3339 patients, is designed to evaluate the prevalence of good adherence to various types of acne drugs, identify the factors that influence adherence, and build a profile of patients who are likely to have poor adherence. In addition, the goal is to facilitate the development of sensitive and specific tools to improve adherence in routine practice.

Acne medications are very efficacious, but only when patients use them correctly. It is vital to take a few seconds to assess adherence in routine practice, and take appropriate steps to enhance adherence; it is hoped that in the future there will be additional tools available to assist clinicians in these tasks. Strategies to improve adherence may entail altering the medication regimen or patients' behaviors. The reward is likely to be greater patient satisfaction with both the physician and the overall treatment regimen.

REFERENCES

1. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne: a report from Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol 2003; 49(Suppl):S1-37.
2. Gollnick H, Finlay AY, Shear N, Global Alliance to Improve Outcomes in Acne. Can we describe acne as a chronic disease? If so, how and when? Am J Clin Dermatol 2008;9:279-84.
3. Centers for Disease Control and Prevention. Classifications of diseases and functioning and disability. In: Classifications of diseases and functioning and disability. Vol 2008. National Center for Health Statistics; 2001 definition of disability reference. Available at http://www.cdc.gov/nchs/icd9.htm. Accessed February 23, 2009.
4. O'Halloran J, Miller GC, Britt H. Defining chronic conditions for primary care with ICPC-2. Fam Pract 2004;21:381-6.
5. Niemeier V, Kupfer J, Demmelbauer-Ebner M, Stangier U, Effendy I, Gieler U. Coping with acne vulgaris: evaluation of the chronic skin disorder questionnaire in patients with acne. Dermatology 1998;196:108-15.
6. Thiboutot DM, Lookingbill DP. Acne: acute or chronic disease? J Am Acad Dermatol 1995;32(Suppl):S2-5.
7. Goulden V, McGeown CH, Cunliffe WJ. The familial risk of adult acne: a comparison between first-degree relatives of affected and unaffected individuals. Br J Dermatol 1999;141:297-300.
8. Tan J. The Canadian acne epidemiological survey: baseline demographics and interim analysis [abstract]. J Am Acad Dermatol 2004;50:15.
9. James WD. Clinical practice: acne. N Engl J Med 2005;352: 1463-72.
10. Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 1999;140:273-82.
11. Cunliffe WJ. Acne and unemployment. Br J Dermatol 1986; 115:386.
12. Zhang JZ, Li LF, Tu YT, Zheng J. A successful maintenance approach in inflammatory acne with adapalene gel 0.1% after an initial treatment in combination with clindamycin topical solution 1% or after monotherapy with clindamycin topical solution 1%. J Dermatolog Treat 2004;15:372-8.
13. Leyden J, Thiboutot DM, Shalita AR, Webster G, Washenik K, Strober BE, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Arch Dermatol 2006;142:605-12.
14. Thiboutot DM, Shalita AR, Yamauchi PS, Dawson C, Kerrouche N, Arsonnaud S, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. Arch Dermatol 2006;142:597-602.
15. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. J Am Acad Dermatol 1999;41:577-80.
16. Collier CN, Harper JC, Cafardi JA, Cantrell WC, Wang W, Foster KW, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol 2008;58:56-9.
17. Poli F, Pernet AM, Verschoore M. Epidemiological study on adult acne [abstract]. J Am Acad Dermatol 2007;56: AB13.
18. Poli F, Dréno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. J Eur Acad Dermatol Venereol 2001;15:541-5.
19. Kligman A. Postadolescent acne in women. Cutis 1992;48: 218-22.
20. Till AE, Goulden V, Cunliffe WJ, Holland KT. The cutaneous microflora of adolescent, persistent and late-onset acne patients does not differ. Br J Dermatol 2000;142:885-92.
21. Plewig G, Kligman A. Acne and rosacea. 3rd ed. New York: Springer; 2000.
22. Cunliffe WJ, Gollnick HPM. Acne: diagnosis and management. London: Taylor and Francis; 2001.
23. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121:20-7.
24. Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by a soluble factor of *Propionibacterium acnes:* implications for chronic inflammatory acne. Infect Immun 1995;63:3158-65.
25. Kim J, Ochoa MT, Krutzik SR, Takeuchi O, Uematsu S, Legaspi AJ, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002;169: 1535-41.
26. Kapetanovic R, Cavaillon JM. Early events in innate immunity in the recognition of microbial pathogens. Expert Opin Biol Ther 2007;7:907-18.
27. Jugeau S, Tenaud I, Knol AC, Jarrousse V, Quereux G, Khammari A, et al. Induction of toll-like receptors by *Propionibacterium acnes*. Br J Dermatol 2005;153:1105-13.
28. Kang S, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. Am J Pathol 2005;166:1691-9.
29. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. J Eur Acad Dermatol Venereol 2001;15(Suppl):5-12.

30. Liu PT, Phan J, Tang D, Kanchanapoomi M, Hall B, Krutzik SR, et al. CD209(+) macrophages mediate host defense against *Propionibacterium acnes*. J Immunol 2008;180:4919-23.
31. Trivedi NR, Cong Z, Nelson AM, Albert AJ, Rosamilia LL, Sivarajah S, et al. Peroxisome proliferator-activated receptors increase human sebum production. J Invest Dermatol 2006; 126:2002-9.
32. Smith TM, Cong Z, Gilliland KL, Clawson GA, Thiboutot DM. Insulin-like growth factor-1 induces lipid production in human SEB-1 sebocytes via sterol response element-binding protein-1. J Invest Dermatol 2006;126:1226-32.
33. Zouboulis CC, Baron JM, Bohm M, Kippenberger S, Kurzen H, Reichrath J, et al. Frontiers in sebaceous gland biology and pathology. Exp Dermatol 2008;17:542-51.
34. Zouboulis CC, Chen WC, Thornton MJ, Qin K, Rosenfield R. Sexual hormones in human skin. Horm Metab Res 2007;39: 85-95.
35. Zouboulis CC. The human skin as a hormone target and an endocrine gland. Hormones (Athens, Greece) 2004;3:9-26.
36. Wille JJ, Kydonieus A. Palmitoleic acid isomer (C16:1delta6) in human skin sebum is effective against gram-positive bacteria. Skin Pharmacol Appl Skin Physiol 2003;16:176-87.
37. Georgel P, Crozat K, Lauth X, Makrantonaki E, Seltmann H, Sovath S, et al. A toll-like receptor 2-responsive lipid effector pathway protects mammals against skin infections with gram-positive bacteria. Infect Immun 2005;73:4512-21.
38. Boehm KD, Yun JK, Strohl KP, Elmets CA. Messenger RNAs for the multifunctional cytokines interleukin-1 alpha, interleukin-1 beta and tumor necrosis factor-alpha are present in adnexal tissues and in dermis of normal human skin. Exp Dermatol 1995;4:335-41.
39. Zouboulis CC, Bohm M. Neuroendocrine regulation of sebocytes—a pathogenetic link between stress and acne. Exp Dermatol 2004;13(Suppl):31-5.
40. Ziegler CG, Krug AW, Zouboulis CC, Bornstein SR. Corticotropin releasing hormone and its function in the skin. Horm Metab Res 2007;39:106-9.
41. Slominski AT, Botchkarev V, Choudhry M, Fazal N, Fechner K, Furkert J, et al. Cutaneous expression of CRH and CRH-R: is there a "skin stress response system?" Ann N Y Acad Sci 1999;885:287-311.
42. Toyoda M, Morohashi M. New aspects in acne inflammation. Dermatology 2003;206:17-23.
43. Bohm M, Schiller M, Stander S, Seltmann H, Li Z, Brzoska T, et al. Evidence for expression of melanocortin-1 receptor in human sebocytes in vitro and in situ. J Invest Dermatol 2002; 118:533-9.
44. Zhang L, Anthonavage M, Huang Q, Li WH, Eisinger M. Proopiomelanocortin peptides and sebogenesis. Ann N Y Acad Sci 2003;994:154-61.
45. Zouboulis CC, Seltmann H, Hiroi N, Chen W, Young M, Oeff M, et al. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. Proc Natl Acad Sci U S A 2002;99:7148-53.
46. Thielitz A, Ansorge S, Bank U, Tager M, Wrenger S, Gollhick H, et al. The ectopeptidases dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN) and their related enzymes as possible targets in the treatment of skin diseases. Front Biosci 2008;13:2364-75.
47. Zouboulis CC. Isotretinoin revisited: pluripotent effects on human sebaceous gland cells. J Invest Dermatol 2006;126: 2154-6.
48. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes: a possible role in acne vulgaris. J Invest Dermatol 2006;126:2430-7.
49. Zouboulis CC. Leukotrien-antagonisten bie atopischen Erkrankungen und Akne. Akt Dermatol 2003;29:419-25.
50. Zouboulis CC, Saborowski A, Boschnakow A. Zileuton, an oral 5-lipoxygenase inhibitor, directly reduces sebum production. Dermatology 2005;210:36-8.
51. Alestas T, Ganceviciene R, Fimmel S, Muller-Decker K, Zouboulis CC. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. J Mol Med 2006;84:75-87.
52. Papakonstantinou E, Aletras AJ, Glass E, Tsogas P, Dionyssopoulos A, Adjaye J, et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. J Invest Dermatol 2005;125:673-84.
53. Lesens O, Haus-Cheymol R, Dubrous P, Verret C, Spiegel A, Bonnet R, et al. Methicillin-susceptible, doxycycline-resistant Staphylococcus aureus, Cote d'Ivoire. Emerg Infect Dis 2007; 13:488-90.
54. Raum E, Lietzau S, von Baum H, Marre R, Brenner H. Changes in *Escherichia coli* resistance patterns during and after antibiotic therapy: a longitudinal study among outpatients in Germany. Clin Microbiol Infect 2008;14:41-8.
55. Oprica C, Nord CE. European surveillance study on the antibiotic susceptibility of Propionibacterium acnes. Clin Microbiol Infect 2005;11:204-13.
56. Eady EA, Cove JH. Topical antibiotic therapy: current status and future prospects. Drugs Exp Clin Res 1990;16:423-33.
57. Dréno B, Bettoli V, Ochsendorf F, Perez-Lopez M, Mobacken H, Degreef H, et al. European recommendations on the use of oral antibiotics for acne. Eur J Dermatol 2004;14:391-9.
58. Del Rosso JQ, Leyden JJ. Status report on antibiotic resistance: implications for the dermatologist. Dermatol Clin 2007;25:127-32.
59. Nord CE, Oprica C. Antibiotic resistance in Propionibacterium acnes: microbiological and clinical aspects. Anaerobe 2006; 12:207-10.
60. Eady EA, Bojar RA, Jones CE, Cove JH, Holland KT, Cunliffe WJ. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. Br J Dermatol 1996;134:107-13.
61. Eady EA, Farmery MR, Ross JI, Cove JH, Cunliffe WJ. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. Br J Dermatol 1994;131:331-6.
62. Eady AE, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? Implications of resistance for acne patients and prescribers. Am J Clin Dermatol 2003;4:813-31.
63. Oprica C, Lofmark S, Lund B, Edlund C, Emtestam L, Nord CE. Genetic basis of resistance in Propionibacterium acnes strains isolated from diverse types of infection in different European countries. Anaerobe 2005;11:137-43.
64. Oprica C, Emtestam L, Lapins J, Borglund E, Nyberg F, Stenlund K, et al. Antibiotic-resistant *Propionibacterium acnes* on the skin of patients with moderate to severe acne in Stockholm. Anaerobe 2004;10:155-64.
65. Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT. Comparative in vitro activities of retapamulin (SB-275833) against 141 clinical isolates of *Propionibacterium* spp., including 117 *P acnes* isolates. Antimicrob Agents Chemother 2006;50:379-81.
66. Mills O Jr, Thornsberry C, Cardin CW, Smiles KA, Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. Acta Derm Venereol 2002;82:260-5.

67. Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AI, O'Neill C, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomized controlled trial. Lancet 2004; 364:2188-95.
68. Leyden JJ, McGinley KJ, Cavalieri S, Webster GF, Mills OH, Kligman AM. *Propionibacterium acnes* resistance to antibiotics in acne patients. J Am Acad Dermatol 1983;8:41-5.
69. Eady EA. Bacterial resistance in acne. Dermatology 1998;196: 59-66.
70. Cooper AJ. Systematic review of *Propionibacterium acnes* resistance to systemic antibiotics. Med J Aust 1998;169: 259-61.
71. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, Bettoli V, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003;148:467-78.
72. Levy RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. Arch Dermatol 2003;139:467-71.
73. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of acne may be associated with upper respiratory tract infections. Arch Dermatol 2005;141:1132-6.
74. Levy PY, Fenollar F, Stein A, Borrione F, Cohen E, Lebail B, et al. *Propionibacterium acnes* postoperative shoulder arthritis: an emerging clinical entity. Clin Infect Dis 2008;46: 1884-6.
75. Berthelot P, Carricajo A, Aubert G, Akhavan H, Gazielly D, Lucht F. Outbreak of postoperative shoulder arthritis due to Propionibacterium acnes infection in nondebilitated patients. Infect Control Hosp Epidemiol 2006;27:987-90.
76. Delahaye F, Fol S, Celard M, Vandenesch F, Beaune J, Bozio A, et al. *Propionibacterium acnes* infective endocarditis: study of 11 cases and review of literature [French]. Arch Mal Coeur Vaiss 2005;98:1212-8.
77. Bagyalakshmi R, Madhavan HN, Therese KL. Development and application of multiplex polymerase chain reaction for the etiological diagnosis of infectious endophthalmitis. J Postgrad Med 2006;52:179-82.
78. Chanet V, Romaszko JP, Rolain JM, Beytout J. *Propionibacterium acnes* adenitis [French]. Presse Med 2005;34:1005-6.
79. Jakab E, Zbinden R, Gubler J, Ruef C, von Graevenitz A, Krause M. Severe infections caused by *Propionibacterium acnes*: an underestimated pathogen in late postoperative infections. Yale J Biol Med 1996;69:477-82.
80. Eady EA, Gloor M, Leyden JJ. *Propionibacterium acnes* resistance: a worldwide problem. Dermatology 2003;206:54-6.
81. Tan HH, Goh CL, Yeo MG, Tan ML. Antibiotic sensitivity of *Propionibacterium acnes* isolates from patients with acne vulgaris in a tertiary dermatological referral center in Singapore. Ann Acad Med Singapore 2001;30:22-5.
82. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851-3.
83. Ross JI, Snelling AM, Eady EA, Cove JH, Cunliffe WJ, Leyden JJ, et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. Br J Dermatol 2001;144:339-46.
84. Espersen F. Resistance to antibiotics used in dermatological practice. Br J Dermatol 1998;139(Suppl):4-8.
85. Bhambri S, Del Rosso JQ, Desai A. Oral trimethoprim/sulfamethoxazole in the treatment of acne vulgaris. Cutis 2007;79: 430-4.
86. Matsuzaki K, Omika K, Hasegawa M, Sato Y, Kobayashi I. Antibacterial activity of nadifloxacin against *Staphylococcus* and *Propionibacterium* isolated from patients with dermatological infections [French]. Jpn J Antibiot 2006;59:316-20.
87. Bikowski JB. Subantimicrobial dose doxycycline for acne and rosacea. Skinmed 2003;2:234-45.
88. Miyachi Y, Yoshioka A, Imamura S, Niwa Y. Effect of antibiotics on the generation of reactive oxygen species. J Invest Dermatol 1986;86:449-53.
89. Akamatsu H, Nishijima S, Takahashi M, Ushijima T, Asada Y. Effects of subminimal inhibitory concentrations of erythromycin, tetracycline, clindamycin, and minocycline on the neutrophil chemotactic factor production in *Propionibacterium acnes* biotypes 1-5. J Dermatol 1991;18:247-51.
90. Akamatsu H, Asada M, Komura J, Asada Y, Niwa Y. Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. Acta Derm Venereol 1992;72:178-9.
91. Weiss JS, Shavin JS. Topical retinoid and antibiotic combination therapy for acne management. J Drugs Dermatol 2004;3: 146-54.
92. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. Br J Dermatol 1988;118: 651-9.
93. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some etiological, clinical and therapeutic strategies. Dermatology 2003;206:11-6.
94. Thielitz A, Sidou F, Gollnick H. Control of microcomedone formation throughout a maintenance treatment with adapalene gel, 0.1%. J Eur Acad Dermatol Venereol 2007;21: 747-53.
95. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol 2003; 49(Suppl):S200-10.
96. Mills OH Jr, Marples RR, Kligman AM. Acne vulgaris: oral therapy with tetracycline and topical therapy with vitamin A. Arch Dermatol 1972;106:200-3.
97. Christiansen JV, Gadborg E, Ludvigsen K, Meier CH, Norholm A, Pedersen D, et al. Topical vitamin A acid (Airol) and systemic oxytetracycline in the treatment of acne vulgaris: a controlled clinical trial. Dermatologica 1974;149:121-8.
98. Hurwitz S. The combined effect of vitamin A acid and benzoyl peroxide in the treatment of acne. Cutis 1976;17: 585-90.
99. Handojo I. The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. Int J Dermatol 1979;18:489-96.
100. Mills OH Jr, Kligman AM. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. Acta Derm Venereol 1978;58:555-7.
101. Kligman AM, Mills OH, McGinley KJ, Leyden JJ. Acne therapy with tretinoin in combination with antibiotics. Acta Derm Venereol Suppl (Stockh) 1975;74:111-5.
102. Rietschel RL, Duncan SH. Clindamycin phosphate used in combination with tretinoin in the treatment of acne. Int J Dermatol 1983;22:41-3.
103. Swinyer LJ, Swinyer TA, Britt MR. Topical agents alone in acne: a blind assessment study. JAMA 1980;243:1640-3.
104. Shalita AR, Rafal ES, Anderson DN, Yavel R, Landow S, Lee WL. Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. Cutis 2003;72: 167-72.
105. Wolf JE Jr, Kaplan D, Kraus SJ, Loven KH, Rist T, Swinyer LJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. J Am Acad Dermatol 2003;49(Suppl):S211-7.
106. Tanghetti E, Dhawan S, Torok H, Kircik L. Tazarotene 0.1% cream plus clindamycin 1% gel versus tretinoin 0.025% gel

plus clindamycin 1% in the treatment of facial acne vulgaris. In: Tazarotene 0.1% cream plus clindamycin 1% gel versus tretinoin 0.025% gel plus clindamycin 1% in the treatment of facial acne vulgaris, Dermatol Online J 2007;13:1.
107. Tanghetti E. Comparison of the tolerability and efficacy of tazarotene 0.1% cream used in a combination regimen with clindamycin 1% gel versus tretinoin 0.025% gel used in a combination regimen with clindamycin 1% gel for the treatment of acne vulgaris [abstract]. J Am Acad Dermatol, 2007;56:AB14.
108. Brand B, Gilbert R, Baker MD, Poncet M, Greenspan A, Georgeian K, et al. Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. J Am Acad Dermatol 2003;49(Suppl):S227-32.
109. Dosik JS, Gilbert RD, Arsonnaud S. Cumulative irritancy comparison of topical retinoid and antimicrobial combination therapies. Skinmed 2006;5:219-23.
110. Cunliffe WJ, Meynadier J, Alirezai M, George SA, Coutts I, Roseeuw DI, et al. Is combined oral and topical therapy better than 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(Suppl):S218-26.
111. Thiboutot DM, Shalita AR, Yamauchi PS, Dawson C, Arsonnaud S, Kang S, et al. Combination therapy with adapalene gel 0.1% and doxycycline for severe acne vulgaris: a multicenter, investigator-blind, randomized, controlled study. Skinmed 2005;4:138-46.
112. Campbell JL Jr, Weiss JS. The results of the MORE trial: overview. Cutis 2006;78:5-11.
113. Campo MS, Zulaga A, Escobar P. A comparative study on the effectiveness of lymecycline and adapalene versus minocycline and adapalene in the treatment of acne vulgaris. Proceedings of the 20th World Congress of Dermatology. Paris, France, July 1-5, 2002. P0005.
114. Shalita A. Topical tazarotene: the BEST (balancing efficacy, speed, and tolerability) in acne trial. Cutis 2004;74:4-8.
115. Rodriguez D, Davis MW. The BEST study: results according to prior treatment. Cutis 2003;71:27-34.
116. Weiss J, Shavin J, Davis MW. Overall results of the BEST study following treatment of patients with mild to moderate acne. Cutis 2003;71:10-7.
117. Shavin J, Weiss J. Implications of the BEST study. Cutis 2003; 71:35-6.
118. Weiss J, Shavin J, Davis MW. Improving patient satisfaction and acne severity in patients with mild to moderate acne: the BEST study. Cutis 2003;71:3-4.
119. Thiboutot DM, Weiss J, Bucko A, Eichenfield L, Jones T, Clark S, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J Am Acad Dermatol 2007;57:791-9.
120. Pariser DM, Westmoreland P, Morris A, Gold MH, Liu Y, Graeber M. Long-term safety and efficacy of a unique fixed-dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% for the treatment of acne vulgaris. J Drugs Dermatol 2007;6:899-905.
121. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazard F, Stuhlert A. A multicenter, single-blind, randomized comparison of a fixed clindamycin phosphate/-tretinoin gel 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.
122. Richter JR, Forstrom LR, Kiistala UO, Jung EG. Efficacy of the fixed 1.2% clindamycin phosphate, 0.025% tretinoin gel formulation (Velac) and a proprietary 0.025% tretinoin gel formulation (Aberela) in the topical control of facial acne. J Eur Acad Dermatol Venereol 1998;11:227-33.
123. Queille-Roussel C, Poncet M, Mesaros S, Clucas A, Baker M, Soloff AM. Comparison of the cumulative irritation potential of adapalene gel and cream with that of erythromycin/tretinoin solution and gel and erythromycin/isotretinoin gel. Clin Ther 2001;23:205-12.
124. Gupta AK, Lynde CW, Kunynetz RA, Amin S, Choi K, Goldstein E. A randomized, double-blind, multicenter, parallel group study to compare relative efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. J Cutan Med Surg 2003;7:31-7.
125. Leyden JJ, Krochmal L, Yaroshinsky A. Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris. J Am Acad Dermatol 2006;54:73-81.
126. Amblard P, Bazex A, Beylot C, Civatte J, Garrel J, Grupper C, et al. The association tretinoin-erythromycin base: a new topical treatment for acne; results of a multicentric trial on 347 cases (authors transl) [French]. Sem Hop 1980;56:911-5.
127. Draelos ZD, Tanghetti EA. Optimizing the use of tazarotene for the treatment of facial acne vulgaris through combination therapy. Cutis 2002;69:20-9.
128. Tanghetti E, Abramovits W, Solomon B, Loven K, Shalita A. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel-group trial. J Drugs Dermatol 2006; 5:256-61.
129. Bowman S, Gold M, Nasir A, Vamvakias G. Comparison of clindamycin/benzoyl peroxide, tretinoin plus clindamycin, and the combination of clindamycin/benzoyl peroxide and tretinoin plus clindamycin in the treatment of acne vulgaris: a randomized, blinded study. J Drugs Dermatol 2005;4:611-8.
130. Del Rosso JQ. Study results of benzoyl peroxide 5%/clindamycin 1% topical gel, adapalene 0.1% gel, and use in combination for acne vulgaris. J Drugs Dermatol 2007;6: 616-22.
131. Kircik L. Community-based trial results of combination clindamycin 1%—benzoyl peroxide 5% topical gel plus tretinoin microsphere gel 0.04% or 0.1% or adapalene gel 0.1% in the treatment of moderate to severe acne. Cutis 2007;80:10-4.
132. Tenaud I, Khammari A, Dréno B. In vitro modulation of TLR-2, CD1d and IL-10 by adapalene on normal human skin and acne inflammatory lesions. Exp Dermatol 2007;16:500-6.
133. Stein-Gold L, Tan J, Werschler W. Adapalene-benzoyl peroxide, a unique fixed dose combination gel for the treatment of acne: a North American, multicenter, randomized, double-blind, controlled, phase III trial in 1,668 patients. Arch Dermatol. In press.
134. Yaroshinsky A, Leyden J. The safety and efficacy of clindamycin (1%), as clindamycin phosphate and tretinoin (0.025%) for the treatment of acne vulgaris: a combined analysis of results from six controlled safety and efficacy trials conducted in Europe [abstract]. J Am Acad Dermatol 2004;50: P23.
135. Korting HC, Braun-Falco O. Efficacy and tolerability of combined topical treatment of acne vulgaris with tretinoin and erythromycin in general practice. Drugs Exp Clin Res 1989;15: 447-51.
136. Kreusch J, Bextermoller R. Efficacy and tolerability of a topical erythromycin/tretinoin combination preparation in acne

treatment: post-marketing surveillance study involving over 6500 patients. Curr Med Res Opin 2000;16:1-7.
137. Ross EV. Acne, lasers, and light. Adv Dermatol 2005;21:1-32.
138. Cunliffe WJ, Goulden V. Phototherapy and acne vulgaris. Br J Dermatol 2000;142:855-6.
139. Young S, Bolton P, Dyson M, Harvey W, Diamantopoulos C. Macrophage responsiveness to light therapy. Lasers Surg Med 1989;9:497-505.
140. Taub AF. Procedural treatments for acne vulgaris. Dermatol Surg 2007;33:1005-26.
141. Shnitkind E, Yaping E, Geen S, Shalita AR, Lee WL. Anti-inflammatory properties of narrow-band blue light. J Drugs Dermatol 2006;5:605-10.
142. Mariwalla K, Rohrer TE. Use of lasers and light-based therapies for treatment of acne vulgaris. Lasers Surg Med 2005;37: 333-42.
143. Elman M, Lebzelter J. Light therapy in the treatment of acne vulgaris. Dermatol Surg 2004;30:139-46.
144. Peng Q, Moan J, Warloe T, Nesland JM, Rimington C. Distribution and photosensitizing efficiency of porphyrins induced by application of exogenous 5-aminolevulinic acid in mice bearing mammary carcinoma. Int J Cancer 1992;52:433-43.
145. Ashkenazi H, Malik Z, Harth Y, Nitzan Y. Eradication of *Propionibacterium acnes* by its endogenic porphyrins after illumination with high intensity blue light. FEMS Immunol Med Microbiol 2003;35:17-24.
146. Horfelt C, Stenquist B, Larko O, Faergemann J, Wennberg AM. Photodynamic therapy for acne vulgaris: a pilot study of the dose-response and mechanism of action. Acta Derm Venereol 2007;87:325-9.
147. Yung A, Stables GI, Fernandez C, Williams J, Bojar RA, Goulden V. Microbiological effect of photodynamic therapy (PDT) in healthy volunteers: a comparative study using methyl aminolevulinate and hexyl aminolevulinate cream. Clin Exp Dermatol 2007;32:716-21.
148. Guffey JS, Wilborn J. In vitro bactericidal effects of 405-nm and 470-nm blue light. Photomed Laser Surg 2006;24: 684-8.
149. Seaton ED, Mouser PE, Charakida A, Alam S, Seidon PM, Chu AC. Investigation of the mechanism of action of nonablative pulsed-dye laser therapy in photorejuvenation and inflammatory acne vulgaris. Br J Dermatol 2006;155:748-55.
150. Bhardwaj SS, Rohrer TE, Arndt K. Lasers and light therapy for acne vulgaris. Semin Cutan Med Surg 2005;24:107-12.
151. Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol 2000;115: 183-92.
152. Galderma LLP. Data on file.
153. Lloyd JR, Mirkov M. Selective photothermolysis of the sebaceous glands for acne treatment. Lasers Surg Med 2002;31: 115-20.
154. Leyden JJ, McGinley KJ. Effect of 13-*cis*-retinoic acid on sebum production and *Propionibacterium acnes* in severe nodulocystic acne. Arch Dermatol Res 1982;272:331-7.
155. Paithankar DY, Ross EV, Saleh BA, Blair MA, Graham BS. Acne treatment with a 1,450 nm wavelength laser and cryogen spray cooling. Lasers Surg Med 2002;31:106-14.
156. Shalita AR, Harthy Y, Elman M. Acne phototherapy using UV free high intensity narrow band blue light—3 center clinical study. Proc SPIE 2001;4244:61-73. Available at: http://spie.org/x648.html?product_id=427830. Accessed February 23, 2009.
157. Elman M, Slatkine M, Harth Y. The effective treatment of acne vulgaris by a high-intensity, narrow band 405-420 nm light source. J Cosmet Laser Ther 2003;5:111-7.
158. Elman M, Lask G. The role of pulsed light and heat energy (LHE) in acne clearance. J Cosmet Laser Ther 2004;6:91-5.
159. Kawada A, Aragane Y, Kameyama H, Sangen Y, Tezuka T. Acne phototherapy with a high-intensity, enhanced, narrow-band, blue light source: an open study and in vitro investigation. J Dermatol Sci 2002;30:129-35.
160. Tremblay JF, Sire DJ, Lowe NJ, Moy RL. Light-emitting diode 415 nm in the treatment of inflammatory acne: an open-label, multicentric, pilot investigation. J Cosmet Laser Ther 2006;8:31-3.
161. Morton CA, Scholefield RD, Whitehurst C, Birch J. An open study to determine the efficacy of blue light in the treatment of mild to moderate acne. J Dermatolog Treat 2005;16: 219-23.
162. Omi T, Bjerring P, Sato S, Kawana S, Hankins RW, Honda M. 420 nm Intense continuous light therapy for acne. J Cosmet Laser Ther 2004;6:156-62.
163. Tzung TY, Wu KH, Huang ML. Blue light phototherapy in the treatment of acne. Photodermatol Photoimmunol Photomed 2004;20:266-9.
164. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. Br J Dermatol 2000;142:973-8.
165. Gold MH, Rao J, Goldman MP, Bridges TM, Bradshaw VL, Boring MM, et al. A multicenter clinical evaluation of the treatment of mild to moderate inflammatory acne vulgaris of the face with visible blue light in comparison to topical 1% clindamycin antibiotic solution. J Drugs Dermatol 2005;4:64-70.
166. Alexiades-Armenakas M. Laser-mediated photodynamic therapy. Clin Dermatol 2006;24:16-25.
167. Friedman PM, Jih MH, Kimyai-Asadi A, Goldberg LH. Treatment of inflammatory facial acne vulgaris with the 1450-nm diode laser: a pilot study. Dermatol Surg 2004;30:147-51.
168. Seaton ED, Charakida A, Mouser PE, Grace I, Clement RM, Chu AC. Pulsed-dye laser treatment for inflammatory acne vulgaris: randomized controlled trial. Lancet 2003;362:1347-52.
169. Webster GF. Laser treatment of acne. Lancet 2003;362:1342.
170. Orringer JS, Kang S, Hamilton T, Schumacher W, Cho S, Hammerberg C, et al. Treatment of acne vulgaris with a pulsed dye laser: a randomized controlled trial. JAMA 2004; 291:2834-9.
171. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. J Am Acad Dermatol 2006;54:647-51.
172. Nestor MS, Gold MH, Kauvar AN, Taub AF, Geronemus RG, Ritvo EC, et al. The use of photodynamic therapy in dermatology: results of a consensus conference. J Drugs Dermatol 2006;5:140-54.
173. Fritsch C, Homey B, Stahl W, Lehmann P, Ruzicka T, Sies H. Preferential relative porphyrin enrichment in solar keratoses upon topical application of delta-aminolevulinic acid methylester. Photochem Photobiol 1998;68:218-21.
174. Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy of acne vulgaris with topical delta-aminolevulinic acid and incoherent light in Japanese patients. Br J Dermatol 2001;144: 575-9.
175. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA. Treatment of sebaceous gland hyperplasia by photodynamic therapy with 5-aminolevulinic acid and a blue light source or intense pulsed light source. J Drugs Dermatol 2004;3(Suppl): S6-9.
176. Goldman MP, Boyce SM. A single-center study of aminolevulinic acid and 417 NM photodynamic therapy in the treatment of moderate to severe acne vulgaris. J Drugs Dermatol 2003;2:393-6.

177. Gold MH, Biron JA, Boring M, Bridges TM, Bradshaw VL. Treatment of moderate to severe inflammatory acne vulgaris: photodynamic therapy with 5-aminolevulinic acid and a novel advanced fluorescence technology pulsed light source. J Drugs Dermatol 2007;6:319-22.
178. Taub AF. Photodynamic therapy for the treatment of acne: a pilot study. J Drugs Dermatol 2004;3(Suppl):S10-4.
179. Horfelt C, Funk J, Frohm-Nilsson M, Wiegleb Edstrom D, Wennberg AM. Topical methyl aminolevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. Br J Dermatol 2006;155:608-13.
180. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolevulinate: a blinded, randomized, controlled trial. Br J Dermatol 2006;154:969-76.
181. Yeung CK, Shek SY, Bjerring P, Yu CS, Kono T, Chan HH. A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. Lasers Surg Med 2007;39:1-6.
182. Taub AF. A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris. J Drugs Dermatol 2007;6:1010-6.
183. Haedersdal M, Togsverd-Bo K, Wiegell SR, Wulf HC. Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: a randomized controlled trial. J Am Acad Dermatol 2008;58:387-94.
184. Sigurdsson V, Knulst AC, van Weelden H. Phototherapy of acne vulgaris with visible light. Dermatology 1997;194:256-60.
185. Nataloni R. Laser treatment comparable to oral antibiotics: 532 nm laser addresses multiple acne pathogens. In: Dermatology Times. Danvers (MA): Advanstar Communications; 2003.
186. Wilson F. Light-based therapies battle acne without side effects: response is quicker than with oral antibiotics; improvement is equivalent. In: Dermatology Times. Danvers (MA): Advanstar Communications. 2004.
187. Haedersdal M, Togsverd-Bo K, Wulf HC. Evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris. J Eur Acad Dermatol Venereol 2008;22:267-78.
188. Stone AC. Facing up to acne. Pediatr Nurs 1982;8:229-34.
189. Thielitz A, Helmdach M, Ropke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br J Dermatol 2001;145:19-27.
190. Alirezai M, George SA, Coutts I, Roseeuw DI, Hachem JP, Kerrouche N, et al. Daily treatment with adapalene gel 0.1% maintains initial improvement of acne vulgaris previously treated with oral lymecycline. Eur J Dermatol 2007;17:45-51.
191. Gould DJ, Cunliffe WJ. The long-term treatment of acne vulgaris. Clin Exp Dermatol 1978;3:249-52.
192. Weiss JS, Thiboutot DM, Hwa J, Liu Y, Graeber M. Long-term safety and efficacy study of adapalene 0.3% gel. J Drugs Dermatol 2008;7(Suppl):S24-8.
193. Bettoli V, Mantovani L, Borghi A. Adapalene 0.1% cream after oral isotretinoin: evaluation of the acne recurrence incidence. Rhodes: Medimond Monduzzi Editore International Proceedings, Division - 15th Congress of the European Academy of Dermatology and Venereology, 2006. Available at: http://www.medimond.com/proceedings/moreinfo/20061004.htm. Accessed February 23, 2009.
194. Bettoli V, Lombardi AR, Pazzaglia M, Virgili A. Isotretinoina ed acne grave: esperienza personale in tema di recidive dopo un lungo periodo di follow-up. G Ital Dermatol Venereol 1998; 133:333-6.
195. Cavicchini S, Caputo R. L'isotretinoina sistemica nella terapia delle diverse forme di acne: esperienza personale su indicazioni, schemi terapeutici e monitoraggio clinic e di laboratorio. G Ital Dermatol Venereol 1996;131(Suppl):1-15.
196. Lehucher-Ceyrac D, Weber-Buisset MJ. Isotretinoin and acne in practice: a prospective analysis of 188 cases over 9 years. Dermatology 1993;186:123-8.
197. Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? Br J Dermatol 1993;129:297-301.
198. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. Br J Dermatol 1993;129:292-6.
199. Harms M, Masouye I, Radeff B. The relapses of cystic acne after isotretinoin treatment are age-related: a long-term follow-up study. Dermatologica 1986;172:148-53.
200. Tanzi EL, Alster TS. Laser treatment of scars. Skin Therapy Lett 2004;9:4-7.
201. Goodman GJ. Management of post-acne scarring: what are the options for treatment? Am J Clin Dermatol 2000;1: 3-17.
202. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol 1994;19: 303-8.
203. Alster T, Zaulyanov L. Laser scar revision: a review. Dermatol Surg 2007;33:131-40.
204. Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg 2005;31:674-86.
205. Nouri K, Alster TS, Ballard CJ. Laser revision of scars. In: Laser revision of scars. Available at: http://www.emedicine.com/derm/topic519htm. Accessed February 23, 2009.
206. Holland DB, Jeremy AH, Roberts SG, Seukeran DC, Layton AM, Cunliffe WJ. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. Br J Dermatol 2004;150:72-81.
207. Jacob CI, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. J Am Acad Dermatol 2001;45:109-17.
208. Dréno B, Khammari A, Orain N, Noray C, Merial-Kieny C, Mery S, et al. ECCA grading scale: an original validated acne scar grading scale for clinical practice in dermatology. Dermatology 2007;214:46-51.
209. Goodman GJ, Baron JA. Postacne scarring—a quantitative global scarring grading system. J Cosmet Dermatol 2006;5: 48-52.
210. Bhalla M, Thami GP. Microdermabrasion: reappraisal and brief review of literature. Dermatol Surg 2006;32:809-14.
211. Jacyk WK, Mpofu P. Adapalene gel 0.1% for topical treatment of acne vulgaris in African patients. Cutis 2001;68:48-54.
212. Lee JB, Chung WG, Kwahck H, Lee KH. Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method. Dermatol Surg 2002;28:1017-21.
213. Tanzi EL, Alster TS. Comparison of a 1450-nm diode laser and a 1320-nm Nd:YAG laser in the treatment of atrophic facial scars: a prospective clinical and histologic study. Dermatol Surg 2004;30:152-7.
214. Sadick NS, Schecter AK. A preliminary study of utilization of the 1320-nm Nd:YAG laser for the treatment of acne scarring. Dermatol Surg 2004;30:995-1000.
215. Bellew SG, Lee C, Weiss MA, Weiss RA. Improvement of atrophic acne scars with a 1,320 nm Nd:YAG laser: retrospective study. Dermatol Surg 2005;31:1218-22.
216. Chan HH, Lam LK, Wong DS, Kono T, Trendell-Smith N. Use of 1,320 nm Nd:YAG laser for wrinkle reduction and the

treatment of atrophic acne scarring in Asians. Lasers Surg Med 2004;34:98-103.
217. Carniol PJ, Vynatheya J, Carniol E. Evaluation of acne scar treatment with a 1450-nm midinfrared laser and 30% trichloroacetic acid peels. Arch Facial Plast Surg 2005;7:251-5.
218. Alster TS, McMeekin TO. Improvement of facial acne scars by the 585 nm flashlamp-pumped pulsed dye laser. J Am Acad Dermatol 1996;35:79-81.
219. Alster TS. Improvement of erythematous and hypertrophic scars by the 585-nm flashlamp-pumped pulsed dye laser. Ann Plast Surg 1994;32:186-90.
220. Dierickx C, Goldman MP, Fitzpatrick RE. Laser treatment of erythematous/hypertrophic and pigmented scars in 26 patients. Plast Reconstr Surg 1995;95:84-92.
221. Alster TS, Tanzi EL, Lazarus M. The use of fractional laser photothermolysis for the treatment of atrophic scars. Dermatol Surg 2007;33:295-9.
222. Glaich AS, Rahman Z, Goldberg LH, Friedman PM. Fractional resurfacing for the treatment of hypopigmented scars: a pilot study. Dermatol Surg 2007;33:289-94.
223. Batra RS. Surgical techniques for scar revision. Skin Therapy Lett 2005;10:4-7.
224. Alam M, Omura N, Kaminer MS. Subcision for acne scarring: technique and outcomes in 40 patients. Dermatol Surg 2005; 31:310-7.
225. Elson ML. The role of retinoids in wound healing. J Am Acad Dermatol 1998;39(Suppl):S79-81.
226. Mandy SH. Tretinoin in the preoperative and postoperative management of dermabrasion. J Am Acad Dermatol 1986;15:878-9.
227. Hevia O, Nemeth AJ, Taylor JR. Tretinoin accelerates healing after trichloroacetic acid chemical peel. Arch Dermatol 1991; 127:678-82.
228. Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. Arch Facial Plast Surg 2006;8:362-8.
229. Asilian A, Darougheh A, Shariati F. New combination of triamcinolone, 5-fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. Dermatol Surg 2006; 32:907-15.
230. Pawin H, Chivot M, Beylot C, Faure M, Poli F, Revuz J, et al. Living with acne: a study of adolescents' personal experiences. Dermatology 2007;215:308-14.
231. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol 1998;134:454-8.
232. Krowchuk DP, Stancin T, Keskinen R, Walker R, Bass J, Anglin TM. The psychosocial effects of acne on adolescents. Pediatr Dermatol 1991;8:332-8.
233. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999;140:672-6.
234. Yazici K, Baz K, Yazici AE, Kokturk A, Tot S, Demirseren D, et al. Disease-specific quality of life is associated with anxiety and depression in patients with acne. J Eur Acad Dermatol Venereol 2004;18:435-9.
235. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA 2002;288:2868-79.
236. Lee IA, Maibach HI. Pharmionics in dermatology: a review of topical medication adherence. Am J Clin Dermatol 2006;7: 231-6.
237. Weiden PJ, Rao N. Teaching medication compliance to psychiatric residents: placing an orphan topic into a training curriculum. Acad Psychiatry 2005;29:203-10.
238. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
239. Renzi C, Picardi A, Abeni D, Agostini E, Baliva G, Pasquini P, et al. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. Arch Dermatol 2002;138:337-42.
240. Baldwin HE. Tricks for improving compliance with acne therapy. Dermatol Ther 2006;19:224-36.
241. Flanders PA, McNamara JR. Enhancing acne medication compliance: a comparison of strategies. Behav Res Ther 1985;23:225-7.
242. Zaghloul SS, Cunliffe WJ, Goodfield MJ. Objective assessment of compliance with treatments in acne. Br J Dermatol 2005; 152:1015-21.
243. McEvoy B, Nydegger R, Williams G. Factors related to patient compliance in the treatment of acne vulgaris. Int J Dermatol 2003;42:274-80.
244. Rasmussen JE, Smith SB. Patient concepts and misconceptions about acne. Arch Dermatol 1983;119:570-2.
245. Tan JK, Vasey K, Fung KY. Beliefs and perceptions of patients with acne. J Am Acad Dermatol 2001;44:439-45.
246. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989;261:3273-7.
247. Kellett N, West F, Finlay AY. Conjoint analysis: a novel, rigorous tool for determining patient preferences for topical antibiotic treatment for acne; randomized controlled trial. Br J Dermatol 2006;154:524-32.
248. Pawin H, Beylot C, Chivot M, Faure M, Poli F, Revuz J, Dréno B. Creation of a tool to assess adherence to treatments for acne. Dermatology 2009;218:26-32.
249. Balkrishnan R, Kulkarni AS, Cayce K, Feldman SR. Predictors of healthcare outcomes and costs related to medication use in patients with acne in the United States. Cutis 2006; 77:251-5.
250. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is this patient taking the treatment as prescribed? JAMA 1993;269:2779-81.
251. Lucero M, Bendeck S, Ramos-Ceballos F, Foster J, Chen SC. Language disparities between patients and dermatologists in describing acne lesions. Dermatol 2007;56:268-73.
252. Del Rosso JQ. A qualitative and quantitative assessment of the application and use of topical acne medication by patients. Cutis 2005;76:109-13.
253. Koo J. How do you foster medication adherence for better acne vulgaris management? Skinmed 2003;2:229-33.