Current state of acne treatment: Highlighting lasers, photodynamic therapy, and chemical peels

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Abstract

Acne vulgaris continues to be a challenge to dermatologists and primary care physicians alike. The available treatments reflect the complex and multifactorial contributors to acne pathogenesis, with topical retinoids as first-line therapy for mild acne, topical retinoids in combination with anti-microbials for moderate acne, and isotretinoin for severe nodular acne. Unfortunately, these conventional therapies may not be effective against refractory acne, can lead to antibiotic resistance, and is associated with adverse effects. With the rise of new technologies and in-office procedures, light and laser therapy, photodynamic therapy, chemical peels, and comedo extraction are growing in popularity as adjunctive treatments and may offer alternatives to those who desire better efficacy, quicker onset of action, improved safety profile, reduced risk of antibiotic resistance, and non-systemic administration. Whereas adjunctive therapies are generally well-tolerated, the number of randomized controlled trials are few and limited by small sample sizes. Furthermore, results demonstrating efficacy of certain light therapies are mixed and studies involving photodynamic therapy and chemical peels have yet to standardize and optimize application, formulation, and exposure times. Nevertheless, adjunctive therapies, particularly blue light and photodynamic therapy, show promise as these treatments also target factors of acne pathogenesis and may potentially complement current conventional therapy.

I. Introduction

Acne vulgaris is one of the most common disorders for which patients seek dermatologic care [1]. Although acne affects the majority of the adolescent population [2], it remains prevalent in adults, with up to 40-50 percent of men and women in their 20s and 10-20 percent in their 40s reporting acne [3], accounting for at least 5-6 million visits to physicians a year [4]. The disease burden of acne ranges from facial scarring to social, psychological, and emotional distress[5] as well as self-perception of poor health [6]. Current therapies against acne are targeted toward the multiple factors contributing to acne pathogenesis. Whereas retinoids and anti-microbials, available in topical and oral formulation, remain the cornerstone of conventional acne therapy, novel adjunctive treatments such as photodynamic therapy, laser therapy, chemical peels, and comedo extraction are on the rise, as patients and clinicians seek to circumvent antibiotic resistance, reduce adverse effects, and employ new technologies in acne care [7, 8]. This review summarizes findings from adjunctive therapy trials with an emphasis on efficacy and safety compared to the current standard of care.

II. Acne Pathogenesis

Current understanding of acne pathogenesis continues to evolve. Contributors to acne development include sebum secretion, abnormal desquamation of follicles, bacterial growth, and associated inflammation [9]. Recent molecular and clinical studies have advanced knowledge in areas such as sebocyte biology [10,11, 12, 13], the role of androgens [14, 15, 16], hyperkeratinization [17, 18, 19], dietary factors [20, 21, 22], and the effect of cytokines and toll-like receptors [23, 24, 25], leading to the identification of potential new targets for acne therapy. Management, therefore, is a multifactorial approach directed at each of the contributors to acne pathogenesis.

III. Acne Therapy

In 2003, the Global Alliance to Improve Outcomes in Acne published consensus recommendations for acne treatment based on clinical trials, clinical experience, and expert opinion[28] with an update published in 2009 [29]. The mechanism and rationale behind acne therapy, whether systemic or topical, is targeted directly at the factors of acne pathogenesis.

A. Retinoids

1. Topical retinoid therapy. Retinoid therapy is considered to be the cornerstone of most acne regimens. Indeed, the Global Alliance recommends topical retinoids as part of first-line therapy for most mild to moderate acne as well as for maintenance therapy. Retinoids influence cellular differentiation and proliferation as well as normalize abnormal follicular desquamation [30]. Their effect on keratinization is reflected by the inhibition of microcomedone formation [31, 32]. Furthermore, retinoids have been shown to reduce inflammation through a number of pathways, including downregulating toll-like receptors [24], cytokines [25], and nitric oxide [33]. However, topical retinoids are irritating to the skin with the most common adverse effects being dryness, erythema, stinging, and pruritis [34].

2. Isotretinoin therapy. Oral isotretinoin is generally reserved for severe, recalcitrant, nodular acne that is unresponsive to topical therapy. Its advantage over topical retinoids is the fact that it significantly decreases sebum production [35] and thus *P. Acnes* growth [36, 37] in addition to reversing hyperkeratinization and reducing inflammation. Although effective against severe acne [38], isotretinoin is associated with significant adverse effects, including cheilitis, dry skin and mucous membranes [39], epistaxis, increased risk of cutaneous *Staphylococcus aures* infections [40], myalgias, hyperlipidemia [41], and pseudotumor cerebri. Associations with inflammatory bowel disease are controversial [42, 43] as are associations with depression and suicide [44]. Isotretinoin is also teratogenic and is contraindicated in pregnancy.

B. Antimicrobials

1. Topical therapy. Antimicrobial treatment reduces the colonization of *P. Acnes* and its subsequent pro-inflammatory effects on comedogenesis. Current topical antibiotics include clindamycin and erythromycin as well as the anti-microbial agent benzoyl peroxide (BPO). Clindamycin and erythromycin are equally effective in the reduction of acne lesions [45]. However, concern over resistant forms *P. Acnes* has limited the use of antibiotics. BPO reduces the number of *P. Acnes* by suppressing growth without the risk of resistance selection and is often used in combination with topical antibiotics. The combination of BPO with clindamycin or erythromycin is more effective than monotherapy at reducing *P. Acnes* growth [46, 47] and decreases the risk of resistance [48, 49]. Like topical retinoids, topical antimicrobials can cause skin irritation, peeling, dryness, itching, erythema, and burning.

2. Systemic antibiotics. Compared to topical antimicrobials, oral antibiotics are more effective and have a faster onset of action. Unfortunately, the risk of antibiotic resistance is significant [50]. Furthermore, many patients are already colonized with resistant *P. Acnes* before starting any acne therapy, indicating that resistant strains are transmissible via human-to-human contact [51]. Adverse effects from systemic antibiotics have been well-documented and range from GI upset with erythromycin, photosensitivity with doxycycline, and benign intracranial hypertension with minocycline.Tetracyclines are also avoided in children under the age of 8 because of teeth discoloration and possible inhibition of bone growth [52].

C. Combination therapy

Given the multiple factors as well as the complex inter-relationship of these factors contributing to acne development, combination therapy targeted towards simultaneous processes has been increasingly favored in practice and is now first-line therapy. The complementary mechanisms of action of antimicrobials and topical retinoids lead to greater efficacy at reducing the number of inflammatory and non-inflammatory lesions compared to monotherapy [53, 54, 55, 56]. Furthermore, patients on combination therapy show faster signs of improvement [57, 58, 59]. The quicker onset of action is believed to lead to greater patient adherence and to reduce the amount of antibiotic exposure and risk of *P. Acnes* resistance.

IV. Adjunctive therapy

Compared to conventional therapy, adjunctive therapy encompasses new technologies and office procedures such as light and laser therapy, photodynamic therapy, chemical peels, and comedone extraction. The demand for adjunctive therapy arises from the desire for more effective and quicker therapy. Alternatives to refractory acne, aversion to prescription medications,

adverse effects to conventional therapy, and poor adherence to conventional therapy also drive interest in adjunctive therapy [7, 60]. Studies evaluating the efficacy of these adjunctive therapies are currently limited but growing in number. Recent studies evaluating the efficacy of laser therapy, photodynamic therapy, chemical peels, and combination adjunctive therapy will be reviewed below.

A. Light and laser therapy

Light and laser therapies that have been used to treat acne include intense pulsed light (IPL), pulsed dye lasers (PDL), potassium titanyl phosphate (KTP) lasers, and broad-spectrum continuous-wave visible light (blue and red) (**Table 1**). Light therapy is based on the observation that *P. Acnes* is capable of synthesizing chromophores such as porphyrins [61]. HPLC analysis has shown that the main porphyrin produced is coproporphyrin [62, 63]. An *in vitro* study demonstrated that blue light activation of porphyrin led to structural membrane damage in *P. Acnes*, suggesting cell death. Culture growths were indeed decreased 24 hours after one illumination with intense blue light at 407-420 nm. Growth was reduced 4-5 orders of magnitude further with 2nd and 3rd illuminations of light [62].

Whereas blue light has been shown to photoinactivate *P. Acnes*, it does not penetrate skin very far. On the other hand, red light, which is less effective at exciting porphyrins, can reach deeper sebaceous glands [7] and may have an anti-inflammatory effect by inducing cytokine-release from macrophages [64]. The combination of blue-red light therapy was shown to be more effective at reducing the number of inflammatory lesions than benzoyl peroxide monotherapy and blue light monotherapy. However, there was no statistical difference among the three treatments at reducing the number of comedones [65]. This may reflect the fact that blue light is more effective at porphyrin activation whereas red light penetrates deeper into the skin and can mediate inflammation through the stimulation of cytokine release, leading to differential effects on inflammatory lesions but not comedones. Indeed, the authors propose that the mechanisms of blue and red light work synergistically to induce a response.

In contrast to single color light therapy, intense pulsed light (IPL) devices employ polychromatic light. IPL devices were introduced commercially in 1994 and are comprised of flashlamps and computer-controlled capacitor banks, which generate pulsed polychromatic light. Subsequent treatment is guided by user determined parameters such as wavelength ranges through the use of filters, fluence, pulse duration, and pulse intervals [66]. Along with emitting wavelengths such as blue and red that can photoactivate porphyrins and target *P. Acnes* growth, the broad spectrum delivery by IPL devices is believed to lead to photothermolysis, where the absorption of light by endogenous chromophores in the skin create enough heat and energy to target the blood vessels that supply sebaceous glands in order to reduce sebum production. Current studies using IPL as an anti-acne therapy have led to mixed results. Although some studies have shown a short-term improvement in both

inflammatory and non-inflammatory acne lesions using IPL alone [67], others have shown that IPL alone and IPL with photodynamic therapy significantly reduced the number of non-inflammatory, but not inflammatory lesions [68]. Furthermore, in comparisons with other light sources, IPL was less effective at reducing acne lesions than pulsed dye lasers but more effective than blue-red combination light-emitting diodes [69]. With the controversial reports of efficacy with IPL and the adverse effects of pain, swelling, erythema, blistering, and crusting [66], it is unclear what role IPL will have in the future of acne therapy.

Lasers are also employed in acne therapy. Compared to light therapy, lasers have the ability to concentrate coherent light on a smaller area of tissue. Potassium titanyl phosphate (KTP) 532 nm green light pulsed laser therapy is believed to penetrate deeper than blue light and activate porphyrins to target *P. Acnes*. KTP has been shown to have short-term effects on improving acne severity with minimal side effects [70], although randomized controlled trials are scarce. Similarly, the effects of pulsed dye laser (PDL) at 585 nm yellow light on reducing acne lesions are controversial. Whereas PDL significantly reduced total lesions and inflammatory lesions compared to sham treatment in one study [71], a split-face trial showed no differences between PDL treatment and non-treatment [72]. Furthermore, PDL in combination with topical acne therapy was no better than topical therapy alone [73]. One reason for the equivocal results by PDL may be the fact that 585 nm is a wavelength that is more strongly absorbed by oxygenated hemoglobin than by endogenous *P. Acnes* porphyrins. Indeed, PDL therapy has been shown to be effective against vascular lesions such as port-wine stains [74]. This underscores the importance of acne therapy targeting factors of acne pathogenesis.

B. Photodynamic therapy

Photodynamic therapy (PDT) refers to the use of aminolevulinic acid (ALA), methyl-aminolevulinic acid (MAL), or other photosensitizing agents to enhance the effect of subsequent light or laser therapy (**Table 2**). Topical ALA is taken up by epithelial cells and converted into protoporphyrin IX, accumulating both in epithelium and pilosebaceous units [75]. Illumination after ALA treatment leads to photoactivation of protoporphyrin IX and subsequent cell damage. ALA also induces porphyrin production by *P. Acnes*. *P. Acnes* cultures grown in the presence of ALA led to a 5-fold decrease in culture viability after 3 illuminations of high intensity blue light [62]. A study by Hongcharu, et al showed that 20 percent ALA followed by red light therapy was shown to reduce inflammatory acne lesions on the back with sustained reduction for 20 weeks after multiple treatments. Histologically, sebaceous glands appeared 45 percent smaller with glandular destruction or atrophy. Furthermore, ALA-PDT decreased *P. Acnes* fluorescence, a marker for bacterial colonization, as well as sebum secretion at 20 weeks after therapy [76]. However, other studies have shown that although ALA-PDT with red light reduced the number of inflammatory acne lesions, the treatment had no effect on *P. Acnes* colonization or sebum excretion [77], suggesting that other mechanisms targeting acne pathogenesis may be involved. The differences in these two studies can potentially be attributed to the small study numbers in both studies, the different number of

total treatments received by subjects, and the higher fluence used in the study by Hongcharu. In these studies, ALA-PDT is associated with erythema, edema, pain, burning, exfoliation, and hyperpigmentation, which may limit its use in practice.

ALA therapy in combination with different sources of light has also been studied, including pulsed dye laser therapy [78], KTP laser [79], blue light [80], intense pulsed light [81], and even pre-treatment with radiant infrared light [82]. Direct comparisons of ALA-PDT with IPL, IPL and radiofreqency (RF) energy, and blue light in 22 patients showed the greatest mean reduction of lesions with ALA and IPL and the least amount of improvement with blue light. However, these differences were not statistically significant [83], suggesting that although studies with photodynamic therapy are promising, they are limited in study size. Given previous improvements with ALA-PDT with red light, comparisons between ALA-PDT with IPL and with red light would be of interest.

To address the phototoxic effects of ALA, different formulations have been developed to decrease the concentration delivered to the skin. A 0.5 percent ALA liposomal spray has been shown to effectively localize into sebaceous glands, thereby reducing skin exposure to ALA by 40-fold and resulting in fewer side effects. Although the reduction of acne lesions using 0.5 percent ALA liposomal spray in this randomized single blind study was comparable to rates of reduction reported in other studies using 20 percent ALA moisturizing cream, patients in this study were also treated with topical peeling agents [84], making conclusions about the comparative efficacy of 0.5 percent ALA unclear. Other attempts to decrease ALA-associated side effects include reducing application time. In a split-face study with 20 patients, patients were randomized to receive either ALA incubation times of 30 minutes or 3 hours. Whereas both incubation times of ALA led to improvements in inflammatory acne lesions, the longer incubation time was more effective at reducing the number of lesions and reducing sebum secretion, although these differences did not reach statistical significance compared to the shorter incubation time at the end of the 12 week study. Interestingly, there was no difference in the number of adverse effects between the 2 incubation times [85] and suggests that shorter incubation times may be both acceptable and more convenient.

As an alternative to ALA, methyl-aminolevulinic acid (MAL) is a lipophilic derivative of ALA that may have better penetration [86] and selectivity in skin lesions [87]. MAL-PDT has also been shown to be effective at reducing inflammatory lesions [88, 89]. However, like ALA, MAL can lead to adverse effects including pain, erythema, skin swelling, and exfoliation. Direct comparisons between ALA-PDT and MAL-PDT in a 15 patient split-face trial showed no significant differences in the efficacy of the photosensitizers at reducing inflammatory lesions. All patients also reported pain, edema, and inflammation, with the majority of patients experiencing greater severity of side effects on the ALA-PDT side. The authors postulate that the ALA-PDT may lead to more severe adverse events because of its homogeneous penetration compared to the more localized concentration of MAL within skin lesions [90]. It is possible that shorter incubation times with ALA may reduce adverse side effects without compromising efficacy. Further studies directly comparing both

photosensitizers would be beneficial in addition to further optimization of ALA or MAL application to maximize efficacy and minimize toxicity.

C. Chemical peels

Chemical peels are typically used for facial resurfacing in which removal of the epidermis promotes re-epithelization and skin rejuvenation. Chemical peels are grouped by their depth of penetration and subsequent destruction. For acne treatment, medium-depth chemical peels that remove the epidermis and part of the papillary dermis have been used for patients with acne scars. The most common chemicals used include alpha-hydroxy acids such as glycolic acid and beta-hydroxy acids such as salicylic acids (**Table 3**).

Glycolic acid reduces hyperkeratinization by decreasing cohesion of corneocytes at low concentrations and promoting desquamation and epidermolysis at higher concentrations [**91**, **92**]. Studies suggest that glycolic acid chemical peels are effective at improving mild, moderate, and severe nodular acne [**93**]. Women with comedogenic acne reported faster and more marked improvement with 70 percent glycolic acid chemical peels after an average of 3 sessions. Women with papulo-pustular acne reported improvement after an average of 6 sessions, whereas women with nodular-cystic acne reported moderate improvement after 8-10 sessions [**93**]. However, randomized controlled trials and standardized protocols with glycolic acid are limited. A randomized controlled trial comparing 70 percent glycolic acid and Jessner's solution, a superficial peeling agent, in a blinded split-face trial showed clinical improvement in the severity of acne with no significant differences between the 2 agents. However, glycolic acid was better tolerated with associated erythema and exfoliation resolving faster than exfoliation seen with the Jessner's solution [**94**]. Although clinical improvement was reported by Leeds scoring, it would also be interesting to report reductions in inflammatory versus non-inflammatory lesions. Mechanistically, glycolic acid peels may have greater effects on non-inflammatory lesions than inflammatory ones.

Salicyclic acid is a lipophilic agent that also decreases corneocyte cohesion and promotes desquamation, particularly of the lipophilic upper layers of the stratum corneum [**95**]. The lipophilicity of salicyclic acid is thought to confer better penetration into sebaceous glands. Its effects on the arachidonic acid pathway may also have anti-inflammatory effects. Whereas low concentrations of salicylic acid are found in daily acne cleansers, concentrations up to 20 and 30 percent can be used for superficial peels. Similar to studies with glycolic acid, salicyclic acid chemical peels have been reported to reduce the number of inflammatory and non-inflammatory acne lesions with erythema, dryness, exfoliation, and burning as the most common side effects [**96**]. Thirty percent glycolic acid peels and 30 percent salicylic acid peels were directly compared in a 12-week double-blind, split-face randomized controlled trial. Both treatments were equally effective at reducing acne lesions within 2 weeks after the first treatment with sustained reductions up to 1 month after the last treatment. However, only the salicylic acid peel had sustained improvement at 2 months post final treatment. Furthermore, the glycolic acid peel led to a greater degree

of exfoliation although the number of adverse events from the two peels was equal [97]. Given that salicyclic acid has a theoretical advantage by its anti-inflammatory properties, it would have been useful to evaluate whether differences between glycolic acid and salicyclic acid peels can be seen by the number of inflammatory versus non-inflammatory lesions.

D. Comdeo Extraction

Acne surgery is one of the older adjunctive therapies to medical treatment. The physical removal of comedones, either by mechanical extraction or light cautery, provides immediate improvement. Mechanical extraction of the keratin plug with gentle pressure around an open comedo or with an incision of a closed comedo prior to extraction is routinely performed in office visits. Although studies are limited, light cautery under local anesthesia for macrocomedones has been shown to be helpful without future scarring and is also easily performed in the office [98, 99]. However, refilling, incomplete extraction, and tissue damage are potential risks [8].

V. Conclusions

Acne continues to remain a challenge to practicing clinicians and dermatologists. As the pathogenesis of acne lesions is complex, so is the myriad of available treatments. The driving forces behind the development of alternative therapies come from the need for better efficacy for refractory acne, the rise of antibiotic resistance, systemic side effects, and consumer preference. Although alternative therapies may not see widespread use as single therapies, there may be a role for light and laser therapy, PDT, chemical peels, and comedo extraction in combination with standard medical therapy. The update from the Global Alliance to Improve Outcomes in Acne Group has recognized the growth in adjunctive therapy for acne treatment [29]. They conclude that more robust evidence supporting the use of light and photodynamic therapy need to be done, although existing studies show promise for the efficacy of blue light as well as PDT.

There remains potential in the study of adjunctive therapies against acne. In studies to date, there appears to be a trade-off among adverse effects, efficacy, and depth of penetration of these adjunctive agents. However, comparative analysis is difficult because of the lack of standardization in study design. Therefore, optimization and standardization of the parameters of light therapy, PDT, and chemical peels application should be addressed in future work before true efficacy can be determined. In addition, larger study numbers would provide more robust analysis as these novel treatments progress from pilot and open-label studies on to randomized controlled trials. Greater support for adjunctive therapy would also benefit from scientific evidence demonstrating mechanism of action against acne pathogenesis, such as the quantification of sebum levels and *P. Acnes* colonization, following inflammatory markers, and even histological analysis. Furthermore, discussions regarding cost, convenience, accessibility, and regulation [100] will become issues for clinicians

and consumers as these devices and agents gain popularity and will likely be the dominant considerations if efficacies from these new treatments are comparable.

Whereas retinoids and anti-microbials remain standard therapy in the treatment of acne, there exists a role for adjunctive therapy in practice and research as new technology develops and acne pathogenesis is better understood. However, the extent and use of adjunctive therapies will depend on larger bodies of evidence before it becomes more widely incorporated into practice. As acne remains one of the commonly seen dermatological conditions in practice [**101**], development of acne treatments will no doubt continue to be an active and changing field for today's clinicians.

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