ACNE: A CLINICAL UPDATE

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Acne is by far the most common cutaneous disorder with a high prevalence in children, adolescents and adults. Approximately 80% of patients with acne developed their first skin lesions by age 11. Although acne usually resolves by age 30, in some patients, acne persists far into adulthood. Active physical findings of acne, as well as post-inflammatory hyperpigmentation (PIH) and scarring, can have a profound psychosocial impact. Current therapies target noninflammatory and inflammatory acne lesions, decrease PIH and scarring, and minimize the risk of developing antibiotic resistance.

THE ETIOLOGY OF ACNE

Although the pathogenesis of acne is not completely understood, several factors are thought to play a role in the development of inflammatory/noninflammatory lesions. The etiology of acne involves follicular hyperkeratinization, sebaceous gland activity and the proliferation of Propionibacterium acnes. Of course, the anaerobic bacterium is not only increased in the skin, but it is also responsible for the inflammatory and immune hypersensitivity events. The hyperproliferation of the ductal keratinocytes leads to occlusion or plugging of the follicle, and the onset of the primary precursor lesion of acne, which is the microcomedo (See Figure 1). Contributory factors associated with an increase in P. acnes and follicular hyperkeratinization (See Figure 2) include increased androgen production, increased interleukin-1 (IL-1) activity and linoleic acid deficiency. In patients with acne, there is increased sebaceous gland activity, which is driven by androgens. It would be prudent to test the free testosterone levels, dehydroepiandrosterone sulfate (DHEAS) and dihydrotestosterone (DHT) in patients refractory to conventional therapy or with severe disease when there are additional signs of hyperandrogenism. However, there is a large segment of the patient population with normal androgen levels. It has been proposed that their sebaceous glands are increasingly sensitive to normal levels of androgens. Normal androgen levels and sebaceous activity are sufficient to cause acne in many patients.

P. ACNES

P. acnes is a common, normal constituent of the continuous flora, relatively slow growing, aerotolerant anaerobic Gram-positive bacterium, most notably recognized for its role in acne vulgaris. Evidence supports a major role for this anaerobic diphtheroid in the pathogenesis of inflammatory acne. P. acnes can activate chemotactic factors and pro-inflammatory mediators, including lipases, proteases and hyaluronidases, leading to the development of inflammatory acne or inflammation. Activation of the compliment pathway and stimulation of cytokine release by macrophages through toll-like receptors (TLRs) also drives inflammatory disease.

TLRs

Toll-like receptors are a family of proteins that serve as the body’s first line of defense against infection. TLRs, a critical component of the innate immune system, recognize molecular patterns associated with bacterial pathogens and mediate immune responses to microbial ligands. These receptors have been identified on keratinocytes, dendritic cells, monocytes and granulocytes. The structure of the TLRs contains an extracellular and intracellular domain. The extracellular domain contains the pattern recognition receptors that bind conserved molecular structures from the many microbial pathogens, such as lipids. The intracellular domain is homologous to the IL-1 receptor and shares common signaling components with the transcription nuclear factor κB (NF-κB) pathway.
PSYCHOLOGICAL IMPACT OF ACNE

It is important not to underestimate the psychological impact of acne. Gupta and Gupta\(^1\) looked at the psychological impact of acne and psoriasis, using the Carroll Rating Scale for Depression to determine the prevalence of depression and suicidal ideation among patients with dermatologic conditions. A score greater than 10 is consistent with clinical depression. They found that in patients with non-cystic facial acne (\(n=72\)), a large percentage scored in the range of depression (mean score, 11.2), which was similar to patients with psoriasis (\(n=138\); mean score, 13.4). Findings suggest that even mild-to-moderate facial acne can be associated with significant depression and suicidal ideation. This underscores the importance of recognizing depression as a psychiatric comorbidity and the emotional impact of acne on patients should not be taken lightly.

TREATMENT OF ACNE

There is a confusing array of treatment options. However, by targeting the various factors that trigger acne, the clinician can design a systematic treatment regimen. Topical agents include benzoyl peroxide, retinoids (eg, tretinoin, adapalene and tazarotene) and antibiotics. Systemic acne therapy includes oral antibiotics (eg, erythromycin, tetracycline, doxycycline and minocycline), hormonal agents (eg, oral contraceptives and spironolactone) and isotretinoin. Combination topical agents have been shown to be more effective than using single agents alone.

What Is New?

Research has brought several new developments to the acne forefront, and studies appear favorable. Adapalene is now available in a stronger 0.3% strength, clindamycin has been paired with 0.025% tretinoin in a combination product, and benzoyl peroxide has been shown to minimize antimicrobial resistance in \(P.\) acnes, with or without the addition of topical antibiotics.

Adapalene 0.3% gel. Adapalene 0.3% gel was recently FDA-approved. Thiboutot et al\(^3\) performed a multi-centered (653 subjects ≥12 years old in 33 centers), double-blind, randomized (2:2:1) trial in which they compared the efficacy of 0.3% adapalene gel with 0.1% adapalene gel versus vehicle for 12 weeks. The primary endpoint was clearing — either total clearing or almost total clearing. The results indicated that almost 25% of patients in the 0.3% adapalene group were rated as clear or almost clear. About 17% of patients in the 0.1% adapalene group were rated as clear or almost clear. This compares to 10% of the vehicle control. This particular study had a diverse group of individuals (approximately 70% white, 10% black, 12% Hispanic and 4% Asian).

When evaluating the adverse events (ie, erythema, scaling, dryness, stinging and burning) of the 0.3% versus the 0.1% adapalene, there were more adverse events in the 0.3% adapalene group (approximately 22%) compared to approximately 12% in the 0.1% adapalene group. Adapalene gel 0.3% was associated with a significantly greater treatment success rate and reduction in total and inflammatory lesion count from baseline than adapalene 0.1% or vehicle gel. Although the study indicates increased efficacy with 0.3% adapalene gel compared to the 0.1% version, adverse events are also increased with the 0.3% adapalene gel. However, the authors confirmed that all of the therapies were well tolerated.

**Clindamycin 1%/tretinoin 0.025% versus each agent alone.** James Leyden, M.D., et al\(^4\) evaluated two randomized, double-blind controlled trials (\(n=2,219\)), looking at the efficacy and safety of a combination of clindamycin 1% concentration with tretinoin 0.025% concentration, compared to each ingredient alone, as well as a placebo for 12 weeks. They found that the combination of clindamycin 1%/tretinoin 0.025% in one product out-performed both clindamycin 1% or tretinoin 0.025% alone or vehicle control. Adverse events reported included dryness, desquamation, burning, erythema, pruritis, sunburn and irritation (combination: 19%, clindamycin 1%: 5%, tretinoin 0.025%: 17%, vehicle: 5%).

**Clindamycin 1.2%/tretinoin 0.025% versus each agent alone.** A combination of three trials (Study 1: \(n=1,252\); Study 2: \(n=1,268\); Study 3: \(n=2,010\)) reported by Schlessinger and Plott\(^5\) compared clindamycin 1.2% and tretinoin 0.025% combination therapy versus each alone versus vehicle. Inclusion criteria were 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions, and two or fewer nodules. Primary endpoints were Evaluator’s Global Severity Scale of “clear” or “almost clear” or at least two grades of improvement, and the percent improvement in two of three lesion counts (inflammatory, noninflammatory and total) from baseline to week 12. Similar to the previous study, the percent of patients who achieved the primary efficacy endpoint of clear or almost clear was superior with the combination product at 25% compared to 19% in the clindamycin 1.2% group, 17% in the tretinoin
0.025% group and 10% in the vehicle group. Adverse events included itching, burning and stinging (combination: 27%, clindamycin 1.2%; 22%, tretinoin 0.025%; 27%, vehicle: 22%).

In summary, several different trials have demonstrated the combination of clindamycin coupled with tretinoin was effective or more efficacious than both monotherapies in achieving either clear or almost clear status. This combination has shown a significant ability to reduce inflammatory, noninflammatory and total lesion counts in acne vulgaris.

6% benzoyl peroxide in antibiotic-resistant P. acnes. A major concern in the treatment of acne is antibiotic resistance. Leyden performed a study in which he evaluated resistant P. acnes strains and treated those patients with a 6% benzoyl peroxide wash. There were 30 patients enrolled with P. acnes strains resistant to erythromycin, tetracycline, doxycycline or minocycline. These patients washed daily for 3 weeks. They were supervised and subsequent counts were obtained. Total P. acnes and individual antibiotic-resistant strain counts were obtained at baseline and after weeks 1, 2 and 3.

After week 1 of therapy with 6% benzoyl peroxide wash, a significant reduction of the total resistant P. acnes strains was found. After week 3, there was a greater than 2 logarithm reduction in total P. acnes (ie, in all antibiotic-resistant strains). Results suggest that daily washing with 6% benzoyl peroxide wash reduces antibiotic-sensitive and antibiotic-resistant strains of P. acnes after week 1 of therapy, which is helpful information concerning the use of benzoyl peroxide in treating patients with acne. Combination products containing benzoyl peroxide and the topical antibiotics have been shown to both prevent the development of antibiotic resistance in patients with acne and confer significant clinical improvement to patients who have already developed antibiotic resistance.16

Tazarotene versus tazarotene plus clindamycin 1%/benzoyl peroxide 5%. Tanghe et al17 evaluated a multi-centered, randomized, double-blinded parallel-group trial with 121 patients with moderate-to-severe acne. They compared the adjunctive use of clindamycin 1%/benzoyl peroxide 5% gel or vehicle gel every morning in combination with tazarotene cream 0.1% every evening in patients with moderate-to-severe inflammatory acne. Patients were treated for 12 weeks. Primary endpoints included comedo and inflammatory lesion counts. Secondary endpoints included adverse events. They concluded the combination of using clindamycin 1% and benzoyl peroxide 5% gel in the morning and tazarotene cream 0.1% at night resulted in significantly greater reduction in comedo count versus tazarotene monotherapy (mean reduction, 70% vs 60%). Among patients with a baseline papule and pustule count greater than 25, a significantly greater reduction in inflammatory lesion count was noted (mean reduction, 63% vs 52%) with the combination. A lower incidence of peeling (10% vs 18% and dryness 8% vs 12%) was a favorable benefit of the coupled agents.

SKIN OF COLOR: ACNE AND HYPERPIGMENTATION

According to several practice surveys, acne vulgaris and particularly PIH come out in the top 10 diagnoses of practice surveys involving patients with skin of color.18,19 With skin of color patients, early and aggressive management is essential to prevent PIH and scarring. Frequently, these patients present with the chief complaint of dark marks or blemishes. It is the PIH that truly concerns them because those pigmented macules can last for months, whereas an acne lesion typically resolves within 1 week or so (See Figure 3).20 It is important to balance aggressive efficacy with non-irritating topical therapy that does not inflame uninvolved skin.

Treatment of Hyperpigmentation and Acne in Patients of Color

When treating patients with skin of color, therapy should target acne as well as PIH. An additional depigmenting agent may be necessary. Maintenance therapy to prevent the formation of new comedones leading to acne and PIH, coupled with sunscreens, should be emphasized in the treatment of patients with skin of color. In addition, clinicians should advise these patients to avoid the sun and use sun protection.

In a 12-week, multicentered (41 centers), investigator-blind, randomized, prospective, community-based trial (n=353), Kircik et al compared the efficacy and tolerability of the combination of 1% clindamycin/5% benzoyl peroxide gel (C-BPO) coupled with tretinoin microsphere (RAM) 0.04%, RAM 0.1% or adapalene gel 0.1% in a subset of patients of color with moderate-to-severe acne.21 In addition to assessing improvement of the acne, PIH was evaluated in the skin of color population. C-BPO was used in the morning, and a different retinoid was used at night (ie, RAM 0.04%, RAM 1% or adapalene gel 0.1%). Approximately 50% of the patients enrolled were Caucasian and 50% were patients with skin of color.21,22

Hyperpigmentation was assessed using a 6-point scale with 0 being absent and 5 being very severe. The overall population

FIGURE 3. PIH on a Patient with Skin of Color

started out with slight hyperpigmentation at baseline. After 4, 8 and 12 weeks of therapy with RAM 0.04%, adapalene gel 0.1% or RAM 0.1%, a decrease in the severity of the hyperpigmentation with all three retinoids for the overall population was noted. Looking at the skin of color cohort, including Asians, Hispanics and African-Americans, total hyperpigmentation was rated at slight-to-mild (1.75). Although there was efficacy with the RAM 0.1% and a suggestion with the adapalene gel 0.1%, the mean change from baseline (p=0.0045) of the total skin of color cohort in regard to hyperpigmentation indicated that the RAM 0.04% performed best. The author suggests that the combination of C-BPO and a topical retinoid would be beneficial for acne and PIH, no matter the retinoid. 

The African-American subset of patients started out with mild-to-moderate (2.35) hyperpigmentation at baseline. After 4, 8 and 12 weeks, a subtle trend toward improvement of PIH was noticed with the RAM 0.04% and adapalene gel 0.1%. There was a trend toward more rapid and greater resolution of PIH in the combination C-BPO + adapalene gel 0.1% treated African-American patients. In the Hispanic population, the mean baseline severity was slight-to-mild (1.6), and after treatment, the mean change was quite significant in the RAM 0.04% group with some improvement in the adapalene gel 0.1% group. Finally, the Asian cohort’s baseline hyperpigmentation was slight (1.17), but improvement was indeed noticed as the study progressed, particularly with the RAM 0.04%. There was a trend toward more rapid and greater resolution with the combination C-BPO and the adapalene gel 0.1% and the RAM 0.04% in the Asian cohort. However, all three retinoids in combination with C-BPO can help reduce hyperpigmentation, while clearing acne in patients of color.

Tazarotene 0.1% Cream

Grimes and Callender evaluated tazarotene 0.1% cream for PIH and acne vulgaris in darker skin in a multi-centered (two centers), double-blind, randomized, vehicle-controlled study (n=74). Subjects had mild-to-moderate facial acne and acne-induced PIH with noticeable pigmented lesions. Tazarotene 0.1% cream versus vehicle was used once daily for up to 18 weeks and was effective in reducing PIH. Compared to vehicle, tazarotene resulted in significantly greater global improvement for PIH and acne, reductions in overall disease severity for PIH and acne, reductions in pigmenitary intensity of hyperpigmented lesions and reductions in area of hyperpigmented lesions.

CONCLUSIONS

Acne and the sequelae can deeply impact individuals physically and emotionally. Several new acne therapies have been shown to be safe and efficacious, while minimizing the resistance of P. acnes and PIH. Concomitant treatment of PIH is crucial for skin of color patients with acne. The mechanism of action is still unknown for hyperpigmentation. An additional depigmenting agent may still be required for optimum results. All topical retinoids have shown efficacy at decreasing epidermal pigmentation while minimizing follicular hyperkeratinization. Furthermore, using retinoids in combination with C-BPO has been shown to reduce antibiotic resistance and hyperpigmentation in patients with acne. Remember that reinforcing education on daily sun protection is essential, even to those patients with skin of color.

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