Current Issues in the Treatment of Acne Vulgaris

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abstract

Acne vulgaris is an extraordinarily common skin condition in adolescents. The mainstays of acne treatment have remained largely unchanged over recent years. In the context of increasing antibiotic resistance worldwide, there is a global movement away from antibiotic monotherapy toward their more restrictive use. Classically reserved for nodulocystic acne, isotretinoin has become the drug of choice by dermatologists for moderate to severe acne. Given the virtually ubiquitous nature of acne in teenagers, there remains an appreciable need for novel therapies. In this article, we will cover the currently used acne treatments, evaluate the issues and data supporting their use, explore the issues of compliance and the mental health implications of acne care, and recommend directions for the field of acne management in adolescents in the years ahead.

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PSYCHOSOCIAL IMPACT OF ACNE VULGARIS

Acne vulgaris affects 85% of adolescents, often starts in preadolescence, and persists into adulthood.[1] It is associated with a profound negative impact on mental health, including increased prevalence of mood disorders, psychiatric hospitalizations, school absenteeism, unemployment, and suicidality.[2,3] The estimated financial burden of acne in the United States is $3 000 000 000 per year.[1] A 2019 study of 87 053 155 admissions from the 2002–2012 US National Inpatient Sample (which includes adolescents) revealed more primary hospital admissions for a mental health disorder in patients with coexistent acne compared with those without acne (adjusted odds ratio = 13.02). This includes primary admission for depression, schizophrenia, and disorders related to alcohol use, development, impulse control, anxiety, adjustment, personality, substance use, and attention-deficit/hyperactivity disorder.[2] In addition, the presence of ≥1 mental health disorders is more common in patients with acne versus those without acne (43.7% vs 20.0%, respectively).[2] Acne and resulting postinflammatory hyperpigmentation negatively impact self-perception, social interactions, and quality-of-life scores in adolescents.[4] Acne negatively impacts self-esteem and self-identity in adolescents.[5] It has been associated with higher rates of unemployment and has a detrimental impact on social, emotional, and psychological function compared with asthma and epilepsy.[3] Treatment has been shown to improve quality of life.[3]

TREATMENT COMPLIANCE

Despite the negative impacts of acne vulgaris, treatment compliance is poor because of numerous factors.[6] Adolescents discontinue treatment, in part, because of early improvement, perception of worsening acne, and side effects, especially with topical treatments,[7] suggesting that anticipatory guidance and mitigation of side effects may improve compliance. Treatment with oral isotretinoin and satisfaction with treatment have been linked with increased acne treatment compliance in adolescents,[7] which suggests that treatment simplification (often monotherapy), patient selection, and increased acne severity associated with isotretinoin use may contribute to increased compliance. Conversely, prescription of multiple treatments, topical retinoids, and recommendation of treatment with over-the-counter products have been associated with primary noncompliance in adolescents with acne,[8] a challenge given that current acne guidelines include topical retinoids as a mainstay of treatment and recommend against monotherapy with the currently available medications.[9] In addition, cost has been identified as a barrier to treatment in adult patients,[10] although its effect on parents of adolescents is less clear. Authors of only one study assessed an interventional method aimed at improving adolescent compliance with acne treatment.[11] A randomized control study (N = 40 patients) of an automated text message reminder system did not yield increased compliance with topical acne treatment in adolescents (33.9% in reminder group versus 36.5% in control group) after 12 weeks.[11]

TREATMENT MODALITIES

A multimodal approach with a combination of products is recommended to address the various steps in acne pathogenesis.[9] Topical and oral antibiotic monotherapy is not recommended given worldwide increases in bacterial resistance. Topical benzoyl peroxide is a broad-spectrum bactericidal agent to which bacterial resistance has not been reported.[9,12–15] Its critical role in helping prevent antimicrobial resistance will be discussed below.

Topical Retinoids

Topical retinoids is a diverse group of vitamin A derivatives that modulate gene expression. The US Food and Drug Administration (FDA)–approved topical retinoids for the treatment of acne vulgaris, including adapalene, tretinoin, and tazarotene, prevent comedone formation by regulating keratinocyte proliferation and differentiation; they also have antiinflammatory effects.[17] Topical retinoids are the preferred treatment and maintenance therapy for all acne, decreasing both comedonal and inflammatory acne lesion counts.[18] They also help prevent and reduce the appearance of atrophic scars[19] and dyspigmentation.[12] Because of common and limiting side effects of dryness, irritation, redness, and peeling, retinoid-naive patients are typically started on low concentrations of topical adapalene or tretinoin and escalated stepwise to higher concentrations or to tazarotene as needed and tolerated. However, there remains a paucity of comprehensive comparative non–industry-sponsored randomized controlled head-to-head studies of the various topical retinoid formulations.[9] Therefore, the clinical teaching that tazarotene is the most effective and most poorly tolerated retinoid whereas adapalene is the least effective and best-tolerated retinoid is not well grounded in generalizable evidence and is an area for further study. In a 2019 review of 54 trials, adapalene was demonstrated to have a favorable tolerability profile[20] and therefore may be the preferred treatment of retinoid-naive or sensitive eczema-prone skin. Adapalene 0.1% gel has been available over the counter since April 2016.[21]

Topical and Oral Antibiotics and Benzoyl Peroxide

Topical antibiotics can be used in the first-line treatment of acne vulgaris and have additional antiinflammatory effects[12] but should not be used as monotherapy because of the rapid development of high rates of antibiotic resistance after weeks to months.[9,12,22] High rates of resistance of *Cutibacterium acnes*, formerly known as *Propionibacterium acnes*, to erythromycin and clindamycin have been reported globally.[13,15,23] Increased resistance correlates with decreased efficacy for acne treatment.[24] Resistance may persist after treatment is discontinued, and resistant *C acnes* strains have been found in untreated contacts.[15] Furthermore, high rates of resistance of colonizer *Staphylococcus aureus* to erythromycin and clindamycin (44% and 40%, respectively) in patients with acne have been reported.[25] This is of special concern given the potential for serious infections caused by multidrug-resistant *S aureus* strains. Studies reveal reduced rates of resistance of *C acnes* and *Staphylococcus epidermidis* with concomitant benzoyl peroxide use,[16,22] likely because of its nonselective bactericidal activity. Hence, current guidelines recommend use of topical antibiotics in combination with benzoyl peroxide either as a rinse-off or leave-on product.[9,12]

Oral antibiotics are indicated for the treatment of moderate to severe inflammatory acne or inflammatory acne recalcitrant to topical therapy alone.[9,12] They should be used in combination with topical retinoids and/or benzoyl peroxide; monotherapy is not recommended.[9,12] Therapy should be temporary, as a bridge to other oral therapies or to topical medications alone.[9,12] Long-term treatment (>3–6 months) should be avoided to limit the development of antibiotic resistance.[9,12,13] The tetracyclines, namely doxycycline and minocycline, have antiinflammatory properties and are considered first-line oral antibiotic therapy per US guidelines.[9] Rates of *S aureus* resistance to tetracyclines (<10%) in patients with acne who are treated with antibiotics are far lower than those to clindamycin and erythromycin.[25] Sarecycline, a novel tetracycline with narrow-spectrum activity, was FDA approved in October 2018 for the treatment of moderate to severe inflammatory acne in patients 9 years of age and older.[26] Oral macrolides, such as azithromycin, may be used for patients in whom tetracyclines are contraindicated, although use of erythromycin should be restricted because of high rates of resistance. Treatment with other classes of antibiotics used in acne, including trimethoprim and sulfamethoxazole, trimethoprim, penicillin, and cephalosporins, is discouraged because of limited supporting evidence, unless tetracyclines and macrolides are contraindicated.[9] If repeat treatment with oral antibiotics is needed, some recommend avoiding class switching unless otherwise justified to reduce the risk of antibacterial resistance.[13,27] It is reasonable to try an alternate class of antibiotics if a patient fails first-line therapy.

Hormone-Based Therapies and Considerations

There are currently 4 combination oral contraceptives (COCs) approved by the FDA for the treatment of moderate acne in postmenarcheal girls: ethinyl estradiol and norgestimate (for those 15 years of age and older); ethinyl estradiol, norethindrone acetate, and ferrous fumarate (for those 15 years of age and older); ethinyl estradiol and drospirenone (for those 14 years of age and older); and ethinyl estradiol, drospirenone, and levomefolate (for those 14 years of age and older). The benefit of treating acne likely arises from the net antiandrogenic effect of COCs, ultimately leading to decreased size and function of sebaceous glands.[28] COCs decrease both inflammatory and comedonal lesion counts.[29] Familiarity with World Health Organization recommendations for COC eligibility is important for their safe use.[9]

In general, when discussing contraceptive options with patients, it is important to consider the acnegenic effects of unopposed progesterone-based contraceptives, including injections of medroxyprogesterone and the etonogestrel implant, particularly in patients with a personal or family history of moderate to severe acne. The levonorgestrel intrauterine device may exacerbate inflammatory acne, as suggested by 2018 survey data[30] and a 2016 retrospective study.[31]

The potassium-sparing diuretic spironolactone is used in girls with moderate to severe hormonal acne for its antiandrogenic effects and is generally well tolerated at low doses (50–200 mg daily). It is not an FDA-approved acne treatment, although it is commonly used by dermatologists, albeit with varying comfort levels and practice patterns. A 2015 retrospective study of healthy patients with acne 18 to 45 years of age, compared with controls, revealed no risk of hyperkalemia, suggesting that screening for hyperkalemia is not necessary in young, healthy patients who are not on potassium-elevating medications.[32] Furthermore, despite a black-box warning to avoid off-label use given oncogenicity in animal studies, large retrospective cohort studies have revealed no increased risk of breast or gynecologic cancers.[33,34]

Isotretinoin

The systemic retinoid oral isotretinoin is generally safe and well

tolerated, despite certain societally ingrained negative connotations. It is FDA approved for the treatment of severe recalcitrant acne vulgaris and is also recommended for moderate acne that is treatment resistant, leads to scarring, or causes significant psychosocial distress.[9] A 2017 meta-analysis revealed no increased risk of depression while on isotretinoin and an improvement in depressive symptoms after treatment,[35] although rare cases of mood exacerbation have been reported in patients who are clinically unstable. The literature also supports a lack of association between inflammatory bowel disease and isotretinoin use.[9] However, authors of a 2018 Cochrane review did not find sufficient high-quality evidence to draw conclusions regarding the safety and efficacy of isotretinoin.[36]

Although it is generally considered safe, isotretinoin has clear embryotoxic and teratogenic properties. Therefore, its use is monitored by the FDA via the Risk Evaluation and Mitigation Strategy, termed iPLEDGE, which dichotomizes patients as (1) boys and girls who cannot become pregnant and (2) girls who can become pregnant. iPLEDGE requires that girls who can become pregnant use either abstinence or, for sexually active patients, 2 accepted methods of birth control. However, proper counseling on highly effective contraceptive methods (subdermal implant or intrauterine contraception), compared with COCs, among dermatologists prescribing isotretinoin is lacking.[37] A brief fact sheet for reviewing the various contraceptive methods has been shown to increase knowledge of these methods,[38] and a handout is now included in iPLEDGE information packets.

A 2019 retrospective analysis of pregnancy reports from the FDA Adverse Event Reporting System (the first study on iPLEDGE outcomes using national data) revealed an absolute decrease in pregnancy-related outcomes (spontaneous abortion, therapeutic abortion, pregnancy while using contraception, and isotretinoin-related fetal defects) after the implementation of iPLEDGE in 2006.[39] However, the authors were unable to directly link these trends to the implementation of iPLEDGE. The absolute number of these events did not plateau until 2011, without clear explanation. Furthermore, the actual rate of fetal exposure could not be calculated for most years because data on the annual number of isotretinoin prescriptions were not available. Evidence reveals that iPLEDGE has decreased the number of prescriptions to girls of childbearing potential.[40] Therefore, further research on the effect of isotretinoin in reducing pregnancy rates, not just reducing absolute pregnancy-related events, is needed.

iPLEDGE is under increasing scrutiny for its categorization of patients who are gender binary based on sex assigned at birth rather than classification based on pregnancy potential alone. Acne is highly prevalent in transgender male patients on testosterone therapy, in which isotretinoin is often indicated, but unfortunately, these limitations of iPLEDGE complicate and inhibit its use.[41] The American Medical Association and the American Academy of Dermatology have both released statements calling for gender neutrality in drug-monitoring programs and have recommended categorization on reproductive potential rather than gender.[42,43]

Diet and Acne

There is increasing evidence regarding the role of diet in acne. High glycemic index diets, dairy consumption (especially skim milk), and whey protein consumption have been implicated.[9,44] Dietary modifications and natural treatments will likely play an increasing role in acne treatment as further evidence accrues.

THE ROLE OF NONDERMATOLOGY PROVIDERS AND FUTURE DIRECTIONS

Knowledge of physician comfort with acne treatment and management, especially with isotretinoin, is minimal. One small survey study of 20 general physicians in New South Wales revealed divergent management plans, lack of available written resources for patients, and desire for further dermatology input in acne management.[45] Many participants preferred to defer isotretinoin to dermatologists because of discomfort with its side effect profile. Data reveal that use of an algorithmic approach to acne treatment among pediatricians could reduce referrals to dermatology, patient cost, wait times, and no-show rates[46] and therefore could be useful to standardize and implement broadly. We recommend additional studies to evaluate comfort and desire among pediatricians to manage acne and prescribe isotretinoin in the context of iPLEDGE in the United States. Conversely, we also recommend consideration of the role of pediatricians in helping to guide contraceptive management in patients requiring treatment with isotretinoin. Additional input from the field of psychiatry is needed to help create guidelines for isotretinoin screening and referral because data suggest that dermatologists may be prone to overrefer to psychiatry.[47] The Patient Health Questionnaire–2 and the Patient Health Questionnaire–9 have been suggested as tools for dermatologists to screen for depression before and after isotretinoin initiation.[48] In general, additional high-quality randomized controlled trials and other analytical studies are needed for definitive conclusions regarding safety and comparative efficacy of various acne treatments.

ABBREVIATIONS

COC: combination oral contraceptive
FDA: US Food and Drug Administration

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