WHITE PAPER PRESENTED BY PREMIER RESEARCH

What's New in Acne

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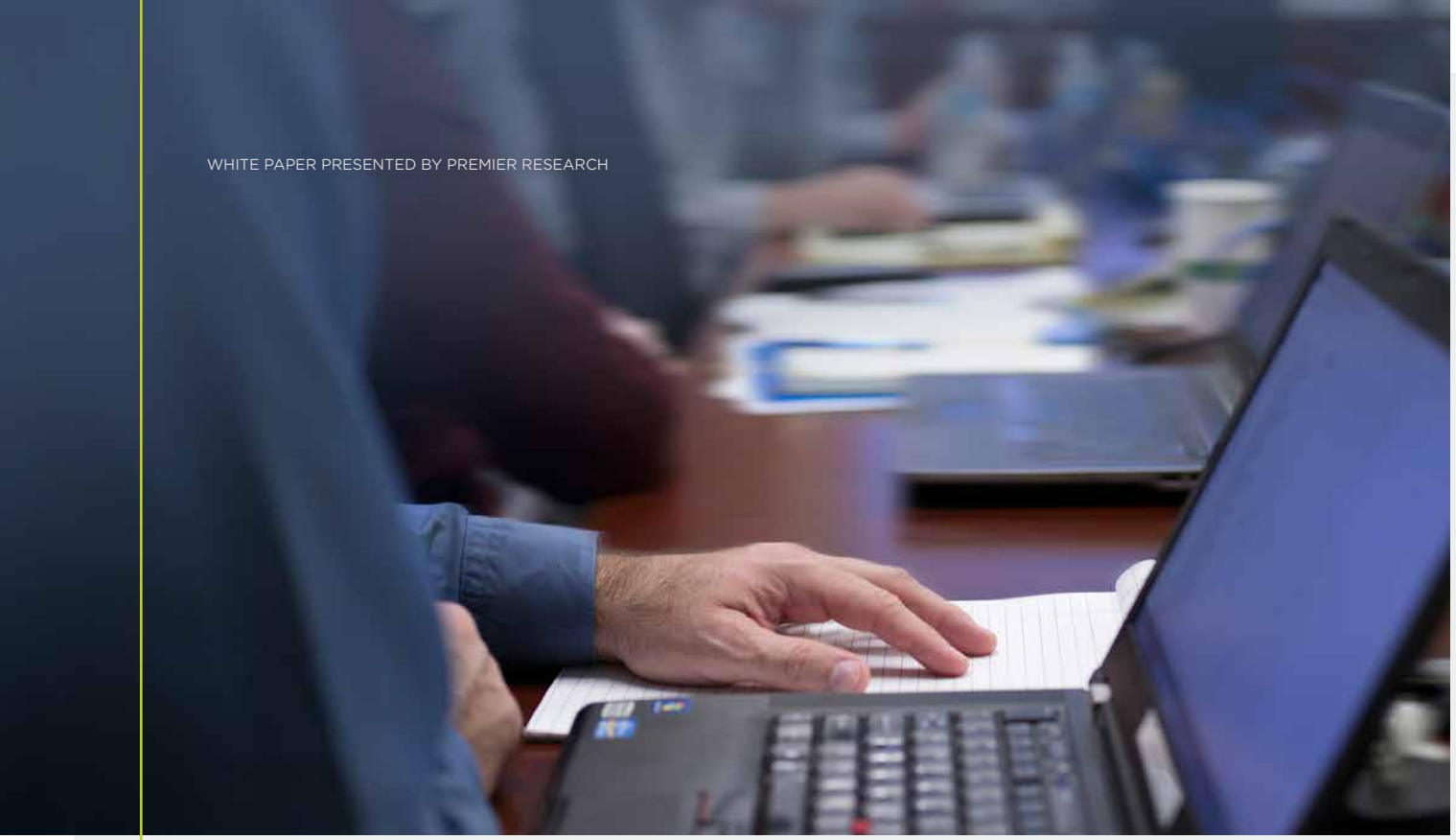
ABSTRACT

Acne is the most common skin condition in the U.S., affecting up to 50 million Americans annually. In this white paper, we explore the history and future of acne treatment, with a focus on emerging therapies that may help patients with moderate to severe acne gain and maintain control of their acne.

DERMATOLOGY



Introduction

Acne is a highly visible condition that can have a major impact on a patient's quality of life. The most common skin condition in the U.S., acne affects up to 50 million Americans each year and often causes significant physical and psychological morbidity, including permanent scarring, poor self-image, depression, and anxiety.[1,2] The annual costs associated with the treatment of acne exceed $3 billion, representing significant opportunity for sponsors of potential acne therapies.[3] In this white paper, we explore the history and future of acne treatment, with a focus on emerging therapies that may help patients with moderate to severe acne gain and maintain control of their acne.

Pathogenesis of acne

Acne is a complex skin disorder of the pilosebaceous unit that commonly occurs in adolescence and young adulthood. Clinically, acne is characterized by open and closed comedones, papules, pustules, and nodules affecting the face, neck, chest, back, and upper extremities. In moderate-to-severe cases, acne can cause significant scarring.

The major pathogenic factors involved in the development of acne are:[4]

+ Hyperkeratinization
+ Obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium
+ Stimulation of sebaceous gland secretion by androgens and retention of sebum, an oily substance that lubricates the skin, in the pilosebaceous ducts
+ Microbial colonization of pilosebaceous units by *Propionibacterium acnes (P. acnes)*, an anaerobic bacterium which promotes perifollicular inflammation

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Existing treatments

In February 2016, the American Academy of Dermatology (AAD) issued new guidelines of care for acne treatment. These evidence-based guidelines cover acne treatment recommendations for both adolescents and adults.[5]

Combining two or more treatments is very common practice by dermatologists and is often the best option for most patients.

Topical therapy. This includes topical retinoids, benzoyl peroxide (BP), and, less commonly, topical antibiotics.

Topical retinoids, which lack the teratogenicity of oral retinoids, are a mainstay of acne treatment. Topical retinoids are particularly effective in treating comedonal acne and represent the most common topical prescription treatment for acne.

BP has anti-microbial, anti-comedogenic, anti-keratolytic, and anti-inflammatory properties. It is used alone or in combination with other topical or oral medications.

In 2008, topical dapsone (brand name Aczone®) 5% gel was approved for treatment of adult female acne. Of note, topical dapsone 5% gel should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency (G-6-PD deficiency), as it may cause methemoglobinemia.[6]

In February 2016, topical dapsone 7.5% gel was approved for the treatment of acne in patients 12 years and older. In a 12-week, double-blind study, patients using dapsone 7.5% gel once a day demonstrated a greater than 50 percent reduction in inflammatory lesions and a greater than 40 percent reduction in noninflammatory lesions.[7] However, much of this effect was provided by the vehicle, which is typical in acne clinical studies.

Antibiotics. When oral antibiotics are used for the treatment of moderate to severe acne, the AAD guideline recommends that topical therapy with BP, a retinoid, or both be used at the same time. This is to reduce the likelihood of developing antimicrobial resistance, which has become an increasing problem. The tetracycline class of antibiotics, including minocycline and doxycycline, are the most commonly used oral antibiotics in acne. In addition to their antibacterial properties, they are also anti-inflammatory.[8]

Isotretinoin. Oral isotretinoin is the most effective drug for severe and nodulocystic acne. Isotretinoin inhibits sebaceous gland differentiation and sebum production. It is unique in that approximately 60 percent of patients given a five-month course are permanently cured of their acne, never requiring further treatment of any kind. Isotretinoin carries an extremely high risk of birth defects, so females must take care to prevent pregnancy while taking this drug. In addition, all patients who take isotretinoin and all physicians who prescribe it must enroll in the federal iPledge program, a computer-based risk management program designed to help eliminate fetal exposure to isotretinoin.

Some studies have suggested an association between oral isotretinoin and inflammatory bowel disease or depression, but the evidence is inconclusive. Nevertheless, patients should be made aware of these risks.

In 2013, a new formulation of isotretinoin, isotretinoin-lidose, was introduced to the market with the goal of reducing the bioavailability differences of isotretinoin during fed and fasted states. As it is less dependent on the presence of fat in the gut for absorption, isotretinoin-lidose has the advantage of providing high levels of absorption even when patients are in a fasting state, with no difference in safety or efficacy.[9] In an open-label, single-dose, four-treatment crossover study, isotretinoin-lidose was found to be bioequivalent to isotretinoin under fed conditions, but delivered twice as much isotretinoin and 4-oxo-isotretinoin when administered after an overnight fast.[10]

Hormonal therapies. Some female patients may see their acne improve with the use of certain oral contraceptives (e.g., Ortho Tri-Cyclen®, Estrostep®, Yaz®) which can be combined with other treatments. These oral contraceptives act to reduce sebum production. The use of oral contraceptive pills (OCPs), as well as the anti-androgen spironolactone, represents an opportunity to reduce the use of antibiotics, both oral and topical, in patients with acne. A Cochrane meta-analysis of randomized, controlled trials comparing the efficacy of antibiotics and OCPs in managing acne found that, while antibiotics may be superior at three months, OCPs are equivalent at six months in reducing acne lesions and may represent an alternative to antibiotics for long-term acne treatment.[11] However, OCPs that are effective in acne are estrogenic, and the potential for disease improvement must be balanced with the attendant risks (e.g., thromboembolism) of this approach.

The use of spironolactone in the treatment of acne has recently increased. In the past, the risk of hyperkalemia and the practice of potassium monitoring may have deterred physicians from prescribing this medication. However, a recent retrospective review in young, healthy women taking spironolactone found no increased risk of hyperkalemia versus the general population.[12] Nevertheless, patients on other medications that can increase potassium or who eat high amounts of potassium-containing foods should be educated and monitored.

Laser treatments or chemical peels. Although limited data has shown that these treatments may improve the signs and symptoms of acne, the AAD guidelines do not recommend such procedures for routine acne management.

New and emerging treatment options

More recently, there has been a shift toward inhibiting sebum, rather than killing *P. acnes* as a strategy for drug development in acne. Excessive sebum production is a key to the pathogenesis of acne, and the inhibition of sebum secretion predicts acne therapy outcome.[13]

Topical adapalene/benzoyl peroxide. Combining retinoids, antibiotics, or BP into a single topical product has become increasingly popular over the past decade. While topical treatments are not thought to have substantial efficacy in treating severe acne, recent research on patients with severe inflammatory acne suggests that once-daily use of a combination topical gel of adapalene 0.3% and benzoyl peroxide 2.5% (brand name Epiduo® Forte) may be an effective treatment option. In a 12-week, Phase III, multicenter, randomized, double-blind study, over 33 percent of patients treated with the combination topical gel achieved Investigator's Global Assessment (IGA) success (i.e., 'clear' or 'almost clear' skin) compared to only 11 percent of patients treated with vehicle. Treated patients also experienced a 68 percent reduction in inflammatory lesion count, compared to 37 percent with vehicle.[14]

Micronized BP/lipohydroxy acid (LHA). Unlike BP alone, the combination of BP 5.5% with LHA 0.04% (brand name Effaclar Duo) is able to penetrate the pilosebaceous unit. LHA is a derivative of salicylic acid which contains a long-chain fatty acid that makes the molecule lipophilic and more readily penetrable into intercellular spaces.

Data demonstrate the efficacy of BP 5.5%/LHA 0.04% as monotherapy and in conjunction with a topical prescription retinoid. A 10-day, unpublished trial of BP 5.5%/LHA 0.04% monotherapy showed significant mean reductions in papules and pustules, as well as open and closed comedones.[15] In another study, combination therapy with BP 5.5%/LHA 0.04% and tretinoin 0.025% was shown to be as effective as

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combination therapy with prescription BP 5%/clindamycin 1% gel and tretinoin 0.025% in reducing inflammatory and non-inflammatory acne lesions.[15]

Cortexolone 17 α-propionate. This is a topical anti-androgen. In a pilot study with male patients, cortexolone 17 α-propionate was shown to decrease acne lesions over both placebo and tretinoin 0.05% cream.[16] Cortexolone 17 α-propionate is now in Phase III clinical trials in the U.S. and Europe.

Topical minocycline. BPX-01 is an early-phase topical minocycline being studied for acne. Preclinical data show delivery of minocycline directly to the epidermis and pilosebaceous unit. Clinical trials of minocycline 4% foam (FMX 101) show greater than 70 percent reductions in both inflammatory and noninflammatory lesions at 12 weeks.[17] However, in recent Phase III studies, minocycline 4% foam did not meet its co-primary endpoints in one of the two trials conducted.

Acetyl coenzyme A carboxylase inhibitor. This prodrug of 5-tetradecyloxy-2-furoic-acid (TOFA) inhibits synthesis of sebum lipids in vitro and reduces sebaceous gland size in the hamster ear model. In an early phase study, this compound reduced lesion counts by 64 percent, as compared to 46 percent for the vehicle.[18] Topical TOFA is now in Phase III studies of acne as a sebosuppressive agent.

Melanocortin-1 and -5 receptor antagonists. The melanocortin-1 and -5 receptors (MC1R, MC5R) are expressed in the sebaceous glands. A dual MC1R and MC5R antagonist has been shown to inhibit sebocyte differentiation in vitro and to reduce sebum production in human skin transplanted onto immuno-deficient mice.[13] Thus far, melanocortin antagonists have not displayed clinical efficacy in the treatment of acne.

Nitric oxide in a nanotechnology vehicle. Nitric oxide-release nanoparticles have been shown to inhibit the *P. acnes*-stimulated inflammatory cascade with minimal toxicity to keratinocytes.[19] In a Phase II study, this compound was shown to decrease sebum, and Phase III studies were just completed.[18] The co-primary endpoints of lesion count reduction and IGA success were met in one Phase III acne trial, but not in the other.

Conclusion

The potential physical and emotional sequelae of acne are compelling reasons to implement early and efficient therapy. The ongoing evolution in acne therapy is driven by improved understanding of the pathogenesis of the disease and new therapeutic developments. New and emerging prescription topical and over-the-counter acne treatments offer new drug targets, sebosuppressive approaches, improved penetration of the active drug, and potentially better outcomes than traditional acne therapies.[20]

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Dr. Welgus has extensive experience in pharmaceutical R&D and in academia. He supported the development efforts of several companies through his own consultancy company and previously was Chief Medical Officer at Nycomed U.S. and Vice President and Head of Dermatology and Inflammation at Pfizer Global R&D in Ann Arbor, Michigan.

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