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Review of the Therapeutic Advance of Acne Treatment

Noha Saleh Gholais[1], Chunrui Shi[2*]

[1]The First Clinical Medical College, Lanzhou University, Lanzhou, China
[2]Department of Dermatology, The First Hospital of Lanzhou University, Lanzhou, China
Email: *shichr@lzu.edu.cn

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Abstract

Acne vulgaris is among the most frequent chronic skin disorders in adolescents, characterized by inflammation of the pilosebaceous unit. The psychological distress due to the disfiguring is the main problem that affects the quality of life for patients suffering from acne. Drugs for the treatment of acne are one of the main contents of drug research on common skin diseases. Acne treatment has remained relatively unaltered over the last years. Still, in conjunction with the increase of bacterial resistance to antibiotics throughout the world, there is a global trend away from antibiotic monotherapy treatment. This review discussed the currently used treatment options and evaluated the issues and evidence supporting their usage for patients with acne, including drug therapy with topical, oral, hormonal therapy, and so on. Drug therapy is the most common method in the clinic. Due to the multifactorial etiology of acne vulgaris, most drugs cannot meet the treatment requirements. Therefore, the screening and development of excellent drugs are one of the key targets for treating acne in the future.

Keywords

Acne, Therapeutic Advance, Oral, Topical Therapy

1. Introduction

Acne vulgaris is a chronic inflammatory disease that affects the hair follicle and sebaceous glands. Acne vulgaris mostly appears in adolescence under the effect of dehydroepiandrosterone (DHEA) and may persist through the early thirties. Propionibacterium acnes which was recently renamed Cutibacterium acnes is the main organism involved in the pathogenicity of acne vulgaris. Acne vulgaris is common in adolescents and ranks number eight in the list of the most pre-

valent diseases worldwide. It can present with inflammatory lesions like comedones or non-inflammatory lesions, and is mainly found on the face and also occur on the shoulder, trunk, and back [1] [2] [3] [4] [5]. There are four key elements in acne pathogenesis, follicle colonization with Propionibacterium acnes (P. acnes), hyper-keratinization, alteration of amount and quality of sebum, and inflammatory reaction [6]. Acne's negative emotional and psychological impact is generally significant and persistent, including depression and anxiety [7]. Acne is more common in males. It is estimated that around 20% of the population may have severe acne, which will result in scarring. Acne can also occur in newborns, although the majority of cases cure spontaneously [5]. There are a variety of factors that might contribute to acne exacerbation, for instance, the use of medicines such as steroids, excessive exposure to sunlight, endocrine problems such as Polycystic ovarian syndrome (PCOS), pregnancy, and genetic variables that influence the quantity of branched fatty acids in sebum are all factors that might contribute to acne [8]. Acne occurs due to the sebaceous gland hypersensitivity to an average circulating level of androgen hormone, aggravated by Cutibacterium acnes and inflammation. During puberty and under the influence of androgens, the production of sebum increases as 5-alpha reductase converts testosterone into the more active form dihydrotestosterone (DHT), which binds to specific receptors in the sebaceous glands, causing an increase in sebum production and hyperproliferation of the sebaceous epidermis (follicular epidermis hyperproliferation), resulting in sebum retention. Distended follicles with sebum break and release pro-inflammatory mediators into the dermis, causing inflammation. P. acnes, Staphylococcus epidermis, and Malassezia furfur are the most common bacteria that induce inflammation and follicular epidermis hyperproliferation in the skin [9] [10]. Acne vulgaris is clinically diagnosed. However, women of reproductive age should be asked whether they have a history of hirsutism or dysmenorrhea. If the test results are positive, then testosterone, LH, FSH, and Dehydroepiandrosterone (DHEA) levels should be tested [11]. The cornerstone of acne management has remained substantially unaltered over the last decade but in conjunction with increasing bacterial resistance to antibiotics throughout the world. Topical and oral antibiotic monotherapy is being phased out in favor of more limited usage across the world [12]. It's important to remember that acute therapy and long-term maintenance medication in the same patient with acne vulgaris might have a little resemblance, especially if the acne is moderate to severe. The purpose of acute therapy is to improve the patient's condition as quickly as possible; this usually necessitates a combination of drugs, including oral antibiotics, with other medicine. For patients with mild to moderate acne, topical medications are considered as main treatments [13].

The most common acne vulgaris treatment is as follows.

2. Topical Therapy

Topical medicines are generally regarded as safer than oral medicines for preg-

nant or breastfeeding women. Some topical drugs don't even have a pregnancy category since systemic absorption is often viewed as insignificant unless the medication is used frequently or for a long period of time [14].

2.1. Benzoyl Peroxide (BP)

Benzoyl peroxide (BP) is a strong antibacterial medicine that has been found to destroy Propionibacterium acnes by releasing free radicals and possesses minor comedolytic, keratolytic, and anti-inflammatory properties. It can be used as first-line therapy for acne vulgaris [15]. Although it is effective as a monotherapy, it is frequently used combined with topical retinoids, which have been found to improve the efficacy of Benzoyl peroxide [16] [17] [18]. Irritation is the most common side effect of benzoyl peroxide; however, tolerance can be enhanced by adding excipients such as urea and glycerin, as well as the emollient dimethicone to the base. Formulation variables, such as micronization of the Benzoyl peroxide and the addition of emollients, might influence efficacy and tolerability; therefore, concentration alone cannot be used to determine equivalency [19]. Benzoyl peroxide has not been linked to the development of resistant P. acnes strains, unlike other antibacterial drugs used to treat acne [20].

2.2. Topical Antibiotics

In addition to their antibacterial properties, topical antibiotics, such as erythromycin and clindamycin, are known to have indirect anti-inflammatory effects on the skin [21]. Using topical clindamycin as a monotherapy resulted in a significant rise in resistant strains as early as two months; however, using topical clindamycin in combination with Benzoyl peroxide 5% did not result in a significant increase in the resistance strain [22]. Topical erythromycin is less effective than clindamycin in treating acne because of P. acnes resistance to the antibiotic [21] [23] [24] [25] [26].

2.3. Retinoids

Topical retinoids are derivatives of vitamin A with anti-inflammatory effects that help to prevent microcomedo formation by correcting follicular hyperkeratinization. They've been demonstrated to help other topical and oral regimens work better [27]. Adapalene, tazarotene, and tretinoin are the three active medicines now available. All have been shown effective and safe in randomized, double-blind, placebo-controlled studies [28] [29] [30] [31].

Cutaneous irritation is the most frequent adverse effect of topical retinoids, which includes stinging/burning, itching, redness, and skin peeling. Despite continued use, the irritation usually reaches a peak and then fades after 1 to 2 weeks. Reduced adverse effects can be achieved by lowering the concentration, switching to a cream or lotion formulation, reducing the frequency of use, and applying moisturizers simultaneously [27]. Daily sunscreen use is recommended in the patient using the topical retinoids due to the desquamation of the outer lay-

ers of the skin (stratum corneum), which causes increased sun sensitivity [11]. In general, increasing the retinoid concentration improves effectiveness but decreases tolerability [28].

Pregnant women should avoid using any topical retinoids since they are teratogens much the same as oral retinoids. When used for acne, all three topical retinoids (Adapalene, tazarotene, and tretinoin) exhibited minimal systemic absorption, and there have been no reports of retinoid embryopathy associated with the use of these medications during unexpected pregnancies [32] [33].

One clinical study shows that tazarotene is the most effective and least tolerated among retinoids, whereas adapalene is the least effective and best-tolerated retinoid, although it is being investigated since the evidence does not support it. According to a 2019 review of 54 trials, adapalene has a great tolerability profile and may thus be the best treatment for retinoid-naive or sensitive eczema-prone skin [34]. The United States Food and Drug Administration (FDA) authorized adapalene 0.1% gel in April 2016, and it has been accessible over the counter (OTC) since then [35].

2.4. Azelaic Acid

The characteristics of azelaic acid 20% cream may contribute to its moderate therapeutic effectiveness in acne. It has a slight lightening impact on acne-induced hyperpigmentation and serves as a comedolytic, antibacterial, and anti-inflammatory [36] [37]. Azelaic acid 15% foam, which has been approved by the Food and Drug Administration (FDA) for treating rosacea, was recently tested in a short, open-label pilot study. According to the results, it has been shown to be effective in reducing the number of lesions while still being tolerable in most cases. Additionally, it has been shown to be useful in treating truncal acne [38] [39]. Azelaic acid has been found to be safe during pregnancy, according to studies. It is one of the few available medications besides metronidazole and clindamycin, which may be the most helpful treatment option in that patient population [40].

2.5. Dapsone

It is a topical sulfone. For acne, dapsone gel has been shown to be effective in the treatment of mild to moderate acne. In order to evaluate its effectiveness, a large number of clinical studies have been conducted and show that Inflammatory acne lesions are the most responding to dapsone, and most people notice a difference within the first month after starting the regimen. When it comes to non-inflammatory lesions (comedonal lesions), they are less receptive to treatment, and improvement is often noticed after 2 - 3 months of treatment. And it may be more useful in females than in adolescents and males, according to some research. Its antimicrobial mechanism is well understood; it is also considered to work as an anti-inflammatory; in comparison to its antibacterial activities, the anti-inflammatory activities of dapsone are less well known than their antimi-

crobial counterparts [41] [42] [43] [44]. Dapsone gel 7.5% is offered as a once-daily or twice-daily if it's a 5% treatment [45]. The gel form of dapsone is generally well tolerated. Baseline testing for Glucose-6-phosphate dehydrogenase (G6PD) is unnecessary even in people with a known G6PD deficiency because systemic absorption is minimal. In comparison to the 5.0% twice-daily formulation, pharmacokinetic investigations on the 7.5% every-day dosage show fewer side effects and less systemic exposure [46].

2.6. Other Topical Agents

In individuals with acne, the following topical treatments do not have sufficient evidence to support their usage. Nevertheless, clinical practice has shown that they are effective: sodium sulfacetamide [47] [48]. sulfur, resorcinol [49], aluminum chloride [50], topical zinc [51], and niacinamide [52].

3. Oral Medications

3.1. Oral Antibiotics

When treating moderate to severe inflammatory acne and also inflammatory acne that has failed to respond to topical treatment, oral antibiotics are often recommended. It is not recommended to use the oral antibiotic alone; instead, it should be used in conjunction with topical retinoids and/or benzoyl peroxide. In order to avoid the development of antibiotic resistance, long-term therapy (more than 3 to 6 months) should be avoided. Instead, it should be used as a bridge to other oral or topical therapies to prevent the development of this resistance [12] [53] [54].

3.1.1. Tetracycline Class

The first line oral antibiotics of tetracyclines class are the doxycycline, and minocycline, which are mainly characterized by their anti-inflammatory properties [12]. Tetracyclines are very helpful for inflammatory acne due to their antibacterial and anti-inflammatory properties; this is notably true for antibiotics belonging to the tetracycline class, which inhibit matrix metalloproteinase activity, cytokine production, and chemotaxis in particular [55] [56]. Tetracyclines are recommended first-line oral treatment for acne because of their anti-inflammatory properties, low cost, simplicity of administration, and favorable safety profile. Minocycline hydrochloride extended-release pills, taken daily at a dose of 1 mg/kg, had equivalent effectiveness to higher dosages and much fewer vestibular side effects than other minocycline preparations [57].

3.1.2. Macrolides

Several writers propose reducing the use of erythromycin due to global antibiotic resistance. The strong performance of azithromycin has been investigated in a number of dosage regimens in open-label studies, with the most prevalent being pulse dosing of three to four doses per month. Gastrointestinal disturbances are the most prevalent adverse effect of macrolides [12] [58].

3.1.3. Other Oral Antibiotics

Treatment with other oral antibiotic groups used to treat acne, such as trimethoprim-sulfamethoxazole, cephalosporins, trimethoprim, and penicillin, are unsatisfactory due to a lack of evidence except in cases when tetracyclines and macrolides are contraindicated [12]. To decrease the development of antibacterial resistance, several experts advocate avoiding class change when extended therapy with oral antibiotics is required unless otherwise warranted. Still, if a patient's first-line antibiotic fails, it's reasonable to try an antibiotic from a different class [54] [59].

3.2. Isotretinoin

Although some societally ingrained unfavorable connotations, Oral isotretinoin is typically considered to be safe and well-tolerated. In addition to the treatment of severe recalcitrant acne vulgaris, it is also authorized by the Food and Drug Administration (FDA) for the treatment of moderate acne that is resistant to treatment, acne results in scarring or causes significant psychological distress. In 2017, a meta-analysis concluded that using isotretinoin did not raise the risk of depression. And that isotretinoin therapy reduced depressive symptoms. However, in clinically unstable individuals, rare occurrences of mood aggravation have been observed [60]. The evidence also suggests that there is no relationship between isotretinoin usage and inflammatory bowel illness [12]. However, the authors of a Cochrane study published in 2018 concluded that there was insufficient high-quality data to establish that isotretinoin is safe and effective [61]. Isotretinoin has obvious embryotoxic and teratogenic characteristics, regardless of the fact that it is commonly thought to be safe. As a result, the United States Food and Drug Administration (FDA) monitors its usage using the iPLEDGE Risk Evaluation and Mitigation Strategy based on whether or not they are able to get pregnant; patients are divided into two groups. Girls who are potentially pregnant must utilize abstinence or sexually active patients, two widely approved birth control methods, according to the iPLEDGE. In comparison to combined oral contraceptive (COC), doctors prescribing isotretinoin do not provide enough advice on extremely effective contraceptive options (subdermal implant or intrauterine contraception) [62].

4. Hormonal Treatment

Hormonal treatment is used to reverse androgen's effects on the sebaceous gland. Oral contraceptives, glucocorticoids, and gonadotropin-releasing hormone (GnRH) agonists are working as anti-androgens or can be used to suppress endogenous androgen synthesis by the adrenal glands or ovary.

4.1. Oral Contraceptives

Oral contraceptives can help with acne in four main ways. First, they restrict LH production, thereby decreasing gonadal androgen production. Second, they stimulate the production of sex hormone-binding globulin, which decrease the

amount of free testosterone in the body. Third, by inhibiting the action of the 5-alpha reductase enzyme, they prevent testosterone from being converted into the more potent Dihydrotestosterone (DHT). Finally, the anti-androgen effect of progestins can inhibit androgen receptors on keratinocytes and sebocytes. The third-generation progestins, such as gestodene (which isn't accessible in the US), desogestrel, and norgestimate, have the least intrinsic androgenic action [63].

4.2. Glucocorticoids Gonadotropin-Releasing Hormone (GnRH) Agonists

Systemic glucocorticoids in high doses may be beneficial in treating acne vulgaris because of their anti-inflammatory properties. In fact, they are normally reserved for the most seriously affected individuals, and they are frequently used in conjunction with isotretinoin to prevent any possible flare-ups from the start of treatment. Furthermore, due to the numerous possible side effects and recurrences following therapy, these medications are usually only administered for a short time. Steroid acne can occur as a result of long-term usage of glucocorticoids. Glucocorticoids are also indicated in small dosages in female patients with increased serum Dehydroepiandrosterone (DHEAS) linked with an 11- or 21-hydroxylase insufficiency, as well as in other persons who have revealed androgen excess. To suppress adrenal production of androgen, low-dose prednisone or dexamethasone can be taken orally at bedtime [64].

4.3. Gonadotropin-Releasing Hormone Agonists

GnRH agonists work by disrupting the cyclic release of gonadotropins from the pituitary gland. Women's ovarian steroidogenesis is suppressed as a result of this. These medications are used to treat ovarian hyperandrogenism. Using GnRH agonists to treat acne and hirsutism in women with or without endocrine issues has been demonstrated to be effective [65].

5. Others

Metformin: In a review of the literature, researchers found some evidence that patients with acne who took metformin with other topical or topical and oral antibiotics had a greater reduction in total lesion counts and inflammatory lesions from baseline compared to their control counterparts, with less adverse effects (e.g., diarrhea and flatulence) [66].

Dairy: A 2017 longitudinal research discovered correlations between high consumption of full-fat diet and acne, as well as high intake of total dairy [67].

A meta-analysis of 14 studies discovered a relationship for total dairy, skimmed milk, and full-fat milk, with each additional serving increasing the risk of acne by 83%, 26%, and 13%, respectively; they also discovered a nonlinear dose-response relationship for total dairy, whole fat-milk, low-fat milk, and skimmed milk, with each additional serving increasing the risk of acne by 83%, 26%, and 13%, respectively. According to a newly published study, there is a link between consuming skim or low-fat milk on a daily basis and the development of acne. In

other words, persons who consumed a lot of skimmed or low-fat milk were more likely to suffer from acne.

Surprisingly, researchers discovered that this was not the case for persons who consumed full-fat milk [68].

6. Conclusion

Acne vulgaris is among the most frequent chronic skin disorders. Acne has been studied in terms of the illness itself as well as present and potential acne treatment solutions. Acne therapy focuses on the four pathogenic elements that cause this disease. We reviewed in this work many choices for acne therapy, such as topical as the first-line therapies, and for more severe cases, the systemic and hormonal therapies are more effective. However, we must be aware of the increasing hazard of P. acnes becoming resistant to currently available antibiotics. As a result, more study in this sector will always be necessary, and new therapeutic options will be required.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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