Topical, Biological and Clinical Challenges in the Management of Patients with Acne Vulgaris

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ABSTRACT: Acne vulgaris is one of the most common chronic inflammatory skin disorders among adolescents and young adults. It is associated with substantial morbidity and, rarely, with mortality. The exact worldwide incidence and prevalence are currently unknown. Current challenges involve improving understanding of the underlying pathophysiology of acne vulgaris and developing a practical treatment consensus. Expert panel discussions were held in 2013 and 2014 among a group of scientists and clinicians from the Omani and United Arab Emirate Dermatology Societies to ascertain the current optimal management of acne vulgaris, identify clinically relevant end-points and construct suitable methodology for future clinical trial designs. This article reviews the discussions of these sessions and recent literature on this topic.

Keywords: Acne Vulgaris; Molecular Biology; Diagnosis; Therapeutics; Benzoyl Peroxide; Retinoids; Isotretinoin; Antibiotics.

Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit among adolescents and young adults.1 It is associated with substantial morbidity and sometimes mortality due to associated disorders.2 The term acne was introduced by the Greek philosopher Celsus in the second century C.E. to describe the presence of pustules/papules on the skin, although the ancient Roman physician Pliny had previously used the word varus to describe similar pustules.3 The condition is part of a heterogeneous group of skin disorders, the precise aetiology of which is unknown; however, several potential aggravating factors have been identified.4 The main feature is a chronic process leading to excessive sebum production (seborrhoea), altered keratinisation and bacterial colonisation by Propionibacterium acnes within the pilosebaceous units or hair follicles.4 The natural history is that of a non-inflammatory process, resulting in open and closed comedones and widespread inflammatory lesions including papules, pustules [Figure 1], nodules, cysts and scarring.1 These lesions can evolve rapidly in some patients and are likely androgen-induced.2

The current challenge in treating acne vulgaris is improving the understanding of its precise underlying cellular and molecular biology, identifying any potential candidate trigger factors and developing treatment guidelines within a regional and demographic context. The latter concept is of particular interest in view of several recent reports suggestive of diverse causal factors, such as seasonal variations, unique dietary and ethnic factors and comorbidities.5,6 Other factors which need to be addressed include the precise methods and timing of treatment and which strategies

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yield optimal long- and short-term clinical outcomes. Little, if any, high-quality evidence exists to support the effectiveness and safety of many existing therapies, particularly topical therapies. Evidently, new research is urgently required to better understand the biology and treatment of acne. Recent efforts have also identified potential genetic and molecular abnormalities; concepts of how best to integrate such advances into treatment algorithms will also therefore need to be addressed.7,8 In addition, new research is needed to assess the comparative therapeutic effectiveness and safety of the many available medications for acne treatment, determine the best preventive strategies and investigate the natural history, subtypes and triggers of this condition.

This review seeks to clarify some of these challenges and the natural history of treatment in order to help improve clinical outcomes for patients with acne vulgaris. An international panel of scientific and clinical experts was formed under the aegis of the United Arab Emirates (UAE) and Omani Dermatology Societies to review current knowledge regarding the biology and diagnosis of acne vulgaris and novel therapeutic approaches. An independent panel convened on 11 October 2013 in Dubai, UAE, 12 October 2013 in Muscat, Oman, and on 16 September 2014 in Dubai. This review reflects the results of these discussions as well as information collected from literatures searches on the MEDLINE, Google Scholar and Cochrane Library databases using the terms acne and acne vulgaris.

Epidemiology

The precise worldwide incidence and prevalence of acne vulgaris is currently unknown; this is unusual given that it is considered a common disease globally. Hospital-based dermatology registries in the USA suggest that approximately 40–50 million people and 80% of adolescents and young adults are affected by this condition.9 In the UK, recent estimates suggest that acne accounts for more than 3.5 million annual visits to general practitioners.10 A Kuwaiti study assessing over 3,700 patients with skin disorders indicated that approximately 75% of the study cohort had non-infectious disorders compared to 25% with infection-related skin ailments; the researchers found that acne was the second most common skin disorder (9.41%) after atopic dermatitis (11.07%).11 A Saudi Arabian study revealed similar findings in a cohort of 3,051 patients with skin disorders.12 Further research from Saudi Arabia confirmed that acne vulgaris was a common dermatological condition, accounting for 20–30% of all skin disorders.13 In the UAE, acne vulgaris anecdotally comprises 30% of all chronic skin conditions; other research has indicated that this condition is the cause of 9% of all dermatology outpatient visits.14–16

Acne vulgaris appears to affect more pubescent boys than girls; in contrast, when the disorder affects adults, more women than men appear to be affected.4 A Western study among Arab Americans reported a peak incidence of acne vulgaris occurring...
in adolescents at puberty. An Iranian community-based study involving individuals aged 12–20 years old reported an overall acne prevalence of 93.2%; the prevalence was higher in females, with a female-to-male ratio of 1:0.4. The researchers speculated that this ratio perhaps reflected gender-based perceptions of overall body image, with females more likely to seek dermatological assessment than adolescent boys. Acne can have profound psychosocial effects as well as result in permanent skin scarring; these can act as a motivation for acne patients to seek medical attention. A recent Syrian study found that the prevalence of acne increased with body mass index.

Pathophysiology

The precise pathogenesis of acne vulgaris has remained enigmatic, although overproduction of sebum, altered keratinisation and bacterial colonisation by P. acnes within the pilosebaceous units are generally agreed upon as causal factors. The significant role of androgens is also recognised. The Gram-positive bacterium P. acnes, which is part of the normal skin microbiome, is present in the pilosebaceous units and uses lipid-rich sebum as a nutrient source; its growth is therefore increased in the presence of acne-associated excessive sebum production. Lipid-rich sebum is hydrophobic in nature and it facilitates lubrication and protection of the skin while P. acnes hydrolyses triglycerides in the sebum, causing the release of free fatty acids which increase the chance of bacterial adherence. The potential association of Demodex mites and acne vulgaris has been speculated upon, but definitive evidence remains elusive.

INFLAMMATORY FACTORS

Agak et al. suggested that P. acnes plays an important role in eliciting an inflammatory response by activating inflammasomes, which in turn results in the production of interleukin (IL)-1β and other inflammatory cytokines. P. acnes was a potent inducer of T helper (Th) 17 and Th1; however, it did not induce Th2 responses in human peripheral blood mononuclear cells. In addition, P. acnes was found to stimulate the expression of key Th17-related genes, including IL-17A, retinoid-related orphan receptor (ROR) α, ROR C, IL-17A receptor and IL-17C receptor, as well as trigger IL-17 secretion from cluster differentiation (CD) 4+ cells, but not from CD8+ T cells. Agak et al. also noted that the combination of IL-1β, IL-6 and transforming growth factor-β neutralising antibodies completely inhibited P. acnes-induced IL-17 production. This is of considerable interest since IL-17-expressing cells were present in skin biopsies from patients with acne vulgaris but not in healthy controls. Furthermore, it was observed that all-trans-retinoic acid and 1,25-dihydroxyvitamin D3 inhibits P. acnes-induced Th17 differentiation. Collectively, these observations support the notion of using both retinoids and 1,25-dihydroxyvitamin D3 in inhibiting the above inflammatory cascades. Kistowska et al. also confirmed the idea that P. acnes activates inflammasomes, resulting in the production of IL-1β. The investigators were able to decipher the underlying mechanisms which contribute to the inflammatory lesions in acne by demonstrating that IL-1β messenger ribonucleic acid and the active processed form of IL-1β are abundant in these lesions in a murine model. They hypothesised that P. acnes activates the monocyte-macrophage nucleotide-binding domain leucine-rich repeat family pyrin domain-containing-3 (NLRP3) inflammasome and activates a cascade reaction involving IL-1β processing, lysosomal destabilisation, reactive oxygen species and cellular potassium efflux. If confirmed independently, the NLRP3 inflammasome and IL-1β appear to be candidate therapeutic targets for acne treatment.

GENOMIC LANDSCAPE

A recent genomic analysis of over 1,000 Chinese patients with severe acne vulgaris revealed two new genetic factors that could potentially play a role in the pathogenesis of this condition. The study found that two genetic loci—11p11.2 (for the damage-specific DNA binding protein 2 gene) and 1q24.2 (for the selectin L gene)—were involved in androgen metabolism, inflammation processes and scar formation. Yaykasli et al. recently demonstrated the importance of extracellular matrix remodelling, which is regulated by matrix metalloproteinases and tissue inhibitors of metalloproteins (TIMP), in the pathogenesis of acne vulgaris. The investigators analysed polymorphisms in 85 patients with acne vulgaris and noted that the TIMP-2 (-418 G>C) genotype was twice as prevalent in the study cohort in comparison to normal controls.

FUTURE RESEARCH

Recently, there has been interest expressed in other molecular abnormalities, such as Toll-like receptor 2 (TLR2) activation and comedogenesis. Selway et al. observed the expression of TLR2 in basal and infundibular keratinocytes and sebaceous glands and determined that TLR2 activation led to the release of IL-1α from primary human keratinocytes. In addition, Selway et al. suggested that the release of IL-1α from infundibular keratinocytes in response to P. acnes-
mediated TLR2 activation could be the initiating steps in comedogenesis and acne formation. Additionally, IL-1α may cause sebaceous hypercornification, a feature of acne.

Increased fibroblast growth factor receptor-2 (FGFR2) signalling has been proposed in the pathogenesis of acne and related disorders, following initial observations in patients with Apert syndrome and acneiform nevus with a gain-of-function mutation in the FGFR2 gene. Furthermore, several studies have provided in vitro evidence of many anti-acne agents, including benzoyl peroxide (BPO), anti-androgens and retinoids, attenuating FGFR2 signal transduction in murine models. Collectively, these inflammatory, genetic and molecular findings are of considerable interest and may pave the way to the identification of candidate pathways and targets for acne vulgaris treatment (e.g. NLRP3 inflammasomes and IL-1β) in future clinical trials.

Clinical Features

Most acne patients present with localised lesions on the face, neck [Figure 2] and truncal areas. However, acne vulgaris can affect all areas of the body except the palms of the hands and soles of the feet, as these regions do not have sebaceous glands. Even ocular areas can be involved; the meibomian glands (also known as tarsal glands) are sebaceous and produce the lipid layer of tears. Additionally, with severe acne vulgaris, in particular the nodulocystic type, pilosebaceous units on the eyelids may sometimes produce ocular symptoms. A range of diverse factors have been found to clinically impact acne vulgaris, including stress levels, diet and even seasonal variation; these factors might be affected by prevailing regional geographical and cultural elements and therefore merit further study and validation. Additionally, there appears to be some causal evidence supporting a link between acne and hyperglycaemic diets, certain dairy products and refined sugars.

There is little doubt that acne vulgaris results in significant morbidity, in particular with regards to its impact on quality of life (QOL). However, this condition can also result in mortality by affecting self-esteem and increasing the risk of suicide, particularly in cases of severe acne. Severe acne appears to be more prevalent in older age and among females, Caucasians and those with a higher socioeconomic status. Studies from Iran and Saudi Arabia have confirmed the symptom burden associated with severe acne vulgaris. Research has demonstrated an association between severe acne and several other conditions, ranging from sinopulmonary to gastrointestinal and psychological comorbidities; the latter includes depression, insomnia and attention deficit and hyperactivity disorders. Scarring is a serious complication of acne vulgaris and occurs commonly despite the high availability of acne treatment options. The scars occur due to skin damage during the healing process. Acne scars are often atrophic and are sometimes accompanied by hyperpigmentation; they can therefore have considerable psychological impact, often affecting QOL. These observations indicate the importance...
of multidisciplinary assessment for acne patients, preferably by a team which includes dermatologists, psychologists and psychiatrists.

**Clinical Management**

In the absence of well-defined aetiological factors, the principle objective for optimal clinical management of acne vulgaris is to identify potential precipitating and/or aggravating factors and to prevent significant associated morbidities. Additionally, it is important to prevent new acneiform lesions and associated scarring and hyperpigmentation [Figure 3]. Most experts advocate the use of a stepwise treatment algorithm in accordance with the severity of the disorder, typically combining non-pharmacological and pharmacological agents concomitantly with counselling and support. Topical agents, including BPO, retinoids, azelaic acid and antibiotics are used to control mild to moderate acne. Systemic therapy, such as oral antibiotics and oral retinoids, tend to be reserved for patients with severe acne; they are often combined with BPO or topical retinoids such as adapalene and tretinoin. Although there are a lack of randomised trials comparing topical versus oral treatments, several consensus-based recommendations and treatment algorithms are available. Figure 4 depicts a potential treatment flowchart for adult patients with mild, moderate or severe acne.

**TOPICAL THERAPIES**

For topical therapy, most specialists tend to use BPO or adapalene, a third-generation topical retinoid, or a combination of the two for the treatment of mild to moderate acne. First introduced in 1934 for the treatment of papulopustular acne, BPO appears to have diverse mechanisms of action, including antibacterial mechanisms by virtue of its oxidative effect and sebostatic and comedolytic properties. BPO is effective, rapid and substantially reduces P. acnes colonies while also reducing the risk of resistance when used in combination with topical antibiotics. Adapalene has been in clinical use for over two decades; research has confirmed its efficacy.
and safety, both as a monotherapy and when combined with topical antibiotics.36 Both tretinoin and adapalene are anti-inflammatory agents; however, adapalene works by inhibiting keratinocyte differentiation and comedone formation. Topical antibiotics are known to inhibit \( P. \) acnes and reduce inflammation.4 Azelaic acid appears to have antimicrobial and anti-inflammatory properties.37 In addition, it can cause hypopigmentation which might help patients to counteract any side-effects, and dapsone. There is some evidence supporting the use of combinations of topical treatments with different mechanisms of action.37–39

Both BPO and adapalene are available in a variety of strengths. Although the efficacy is generally similar, higher concentrations are often associated with increased side-effects, such as skin peeling and irritation.40 A fixed-dose combination of 0.1% adapalene and 2.5% BPO is also available.36 In addition to topical BPO and adapalene, the treatment guidelines of the American Academy of Dermatology (AAD) also recommend topical antibacterials, such as erythromycin and clindamycin.41 Evidence from several randomised studies supports the use of a combination of topical antibacterial and BPO therapy.37–39 In a double-blind controlled study involving 378 patients, Dréno et al. demonstrated the clinical benefit of combining adapalene or BPO with lymecycline in comparison to treatment with BPO and a placebo.39 A Turkish clinical trial among young adults with mild to moderate facial \( \text{acne vulgaris} \) found that combination 5% BPO lotion was significantly more effective in the reduction of inflammatory lesions compared with 1% nadifloxacin cream alone.38 Furthermore, it has been shown that combination therapy is also more effective in preventing relapse compared to monotherapy.39 Currently, most specialists advocate the use of 0.02–0.05% topical retinoids on all affected areas for mild to moderate forms of \( \text{acne}. \)

**ORAL THERAPIES**

Oral retinoids, in particular isotretinoin, reduce the size of the sebaceous glands and reduce sebum production which helps to normalise follicular epithelial desquamation; topical retinoids also appear to have these characteristics, although to a lesser degree.4 According to the current AAD guidelines, both topical and oral formulations have a strong evidence-based recommendation (category 1A).41 In general, most patients appear to achieve longer-term positive responses with both formulations.40 Oral retinoids are generally reserved for more severe forms of \( \text{acne} \) or for patients who are resistant/refractory to conventional therapy, regardless of severity. While side-effects—including skin irritation and peeling—are common, these effects are usually mild and easily managed.45 Retinoids are rarely associated with other potentially serious adverse side-effects, such as psychiatric issues and, in particular, depressive illnesses.44–45 The association between psychiatric issues and retinoids is challenging to address since such side-effects are often already present among patients with \( \text{acne vulgaris} \), especially those with moderate or severe forms.30–32 A study from the UAE found that oral isotretinoin was effective in improving psychiatric comorbidities and body image among adolescents and young adults with severe \( \text{acne} \).45 Another study noted that certain patients undergoing oral isotretinoin therapy sometimes demonstrated abnormalities in liver function tests and serum lipids, especially low-density lipoproteins and triglycerides; however, this was generally reversible upon discontinuation of the therapy.45

Oral antibiotics, such as tetracyclines, erythromycin and clindamycin, are often utilised as part of a combination regimen for patients with severe \( \text{acne} \), particularly in the presence of inflammatory lesions.36–40 Antimicrobials should be discontinued once the inflammatory lesions abate and other treatments, such as topical agents, should be used as maintenance therapy thereafter. While antibiotics are generally well-tolerated, they are occasionally associated with severe adverse events.40 There appears to be no important difference in the efficacy of the choice or dose of antibiotics; the decision is often based on patient preference, cost and side-effect profile.44,45 However, there is considerable concern regarding antibiotic resistance; as such, their use for extended periods should be avoided.40–50 Concomitant BPO use helps to reduce the risk of resistance, possibly by eliminating resistant bacteria.44,45

**HORMONAL AND OPTICAL THERAPIES**

Combined oral oestrogen and progesterone hormonal therapy is sometimes used as an adjunctive therapy for women with moderate to severe \( \text{acne} \) who also need oral contraception.4 Oestrogen helps to suppress sebaceous gland activity in addition to suppressing androgen synthesis; in contrast, progesterone, if used alone, can worsen \( \text{acne} \).4 Optical treatments, particularly fractionated laser and photodynamic therapies, and selective photothermolysis can be useful in improving post-\( \text{acne} \) scarring; however, formal comparative studies have not yet been conducted.51,52
CHALLENGES IN MANAGEMENT

Additional challenges in management include determining the definitive timing of topical acne treatments and optimal management of post-acne scarring and hyperpigmentation as well as maintaining patient adherence to treatment.50 The time taken between the initiation of topical therapy and clinically-relevant improvement is an important factor. In a systematic review on acne treatment, Jacobs et al. noted that different concentrations of BPO and adapalene did not seem to influence the time taken for resolution of inflammatory lesions; however, both agents produced earlier responses when compared to retinoids, particularly isotretinoin.46 In addition, combined clindamycin and BPO produced faster responses in comparison to adapalene alone.54 It is therefore necessary for clinicians to offer longer-term management plans in order to be sure that the treatments are successful in resolving the acne.

The management of acne in pregnant women is challenging largely due to the potential teratogenicity associated with retinoids, which considerably limits treatment options for patients with moderate to severe acne.50,56 Women of childbearing age with acne should therefore be counselled and offered effective contraception before beginning treatment. Most specialists tend to use non-retinoid topical agents and add azelaic acid in an effort to improve efficacy and, more specifically, to help reduce the post-acne-associated hyperpigmentation.

Conclusion

Acne vulgaris is a chronic inflammatory disorder which occurs worldwide. Various effective and well-tolerated options are available for the management of acne vulgaris, although none are optimal. For the management of mild to moderate acne, evidence-based guidelines advocate topical therapies, in particular BPO or adapalene, sometimes combined with antibiotics. Patients with severe acne can benefit from oral tretinoin; however, the drug is associated with potentially challenging side-effects. It is important for clinicians to recognise acne as a potentially serious medical condition and offer prompt management, appropriate counselling and support when indicated. The importance of a longer-term multi-disciplinary management plan in order to evoke a response to treatment should be emphasised. In addition, new clinical research is needed to assess the comparative effectiveness and safety of the many treatments available and the impact of patient compliance. Further research regarding the natural history, subtypes and triggers of acne is also required.

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CONFLICT OF INTEREST

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