REVISITING ACNE VULGARIS

Firas Al-Niaimi discusses the pathogenesis and therapy options for acne vulgaris, focusing on the available topical and systemic therapies

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ABSTRACT
Acne vulgaris is a common inflammatory disease of the pilosebaceous unit affecting millions of people worldwide. Its pathogenesis is multifactorial and a number of therapies are available, which include topical, systemic, chemical peels, and light-based devices. This article revisits all aspects of the disease, including relatively recent advances in pathogenesis and therapy.

ACNE VULGARIS IS A CHRONIC inflammatory disease of the pilosebaceous unit affecting almost all adolescents to some degree. Understanding of the underlying pathophysiology, the range of treatments and their side-effects will help the attending physician to use the most appropriate therapy. There are a number of diseases that could resemble acne vulgaris, such as gram negative folliculitis, rosacea fulminans, mechanical acne, tar acne, chloracne, and congenital adrenal hyperplasia. These will not be discussed in this article. The use of chemical peels and lasers in acne will be discussed in a future article.

Pathogenesis

The pathogenesis of acne vulgaris is multifactorial and can be considered to result from four aetiological factors[1]:

- Hyperseborrhoea (patients with acne and seborrhoea have a significantly greater number of lobules per gland compared with unaffected individuals)
- Hyperkeratinisation of follicular ducts (consequently follicular pore plugging, clinically manifest as comedones)
- Bacterial colonisation and proliferation with *Propionibacterium acnes*
- Inflammation induced by upregulated pro-inflammatory mediators.

The disease results from interplay between these four factors.

Acne produces chemotactic factors and promotes the synthesis of tumour necrosis factor (TNF)-α and interleukin (IL)-1β. Cytokine induction by *P. acnes* occurs through Toll-like receptor (TLR)-2 activation via activation of nuclear factor (NF)-κB and activator protein 1 (AP-1) transcription factor. Activation of AP-1 induces matrix metalloproteinase (MMP) genes, which degrade the dermal matrix, leading to scarring[2]. It is becoming more apparent that acne vulgaris is a complex disease that involves both the innate and adaptive immune systems.

The up-regulation of IL-1α contributes to the development of comedones independent of the colonisation with *P. acnes*. A relative linoleic acid deficiency has also been described. Sebaceous lipids are

Table 1 Mechanism of action of topical and systemic acne therapies

	Reduced sebum production	Comedolytic	Anti-microbial	Anti-inflammatory
Topical therapies				
Benzoyl peroxide		+	+	
Retinoids		+	+	+
Antibiotics			+	+
Systemic therapies				
Combined oral contraceptive	+	+		
Antibiotics			+	+
Isotretinoin	+	+	+	+

regulated by peroxisome proliferator-activated receptors (PPARs), which act to regulate epidermal growth and differentiation, as well as lipid metabolism. Sebocyte activity is also regulated by a number of mediators such as neuropeptidases, α-melanocyte stimulating hormone, insulin-like growth factor (IGF)-1R, corticotrophin releasing hormone (CRH)-R1, dipeptidyl peptidase-IV (DPP4), and aminopeptidase N[2,3].

Treatment is directed towards one or more of these underlying causes and will be explored in greater detail in this article, as outlined in *Table 1*.

Risk factors

It is clear that acne is multifactorial, with both genetic and environmental factors playing their part. Recent molecular genetics studies have implicated genes involved in the innate immune response, steroid hormone metabolism and associated receptors in the pathogenesis of acne; however, our understanding of the interaction of mechanistic pathways remains incomplete. The issue of genetics has never been doubted; there is a high concordance among identical twins and a tendency towards severe acne in the presence of a positive family history. It is probable that a number of genes are involved in predisposing an individual to acne. These include the genes that encode for cytochrome P450-1A1 and steroid-21-hydroxylase. There is no conclusive evidence that acne is associated with poor hygiene, lack of exercise, sunlight, factors often cited by patients as possible causes of their acne. Some drugs can elicit acneiform eruptions, which typically lack comedones[4,5].

Clinical presentation and assessment

Clinical findings can be divided into inflammatory and non-inflammatory lesions. The microcomedo is considered to be the earliest subclinical lesion, although recent findings have challenged, this as will be explained later. Non-inflammatory lesions encompass both open (blackheads) and closed comedones (whiteheads). Mid-facial distribution of comedones in childhood is often indicative of poor prognosis. Most patients have a mixture of inflammatory as well as non-inflammatory lesions.

Inflammatory lesions could be subdivided into superficial and deep lesions. Superficial inflammatory lesions include papules and pustules (5mm or less in diameter). Inflammatory macules represent regressing lesions that may persist for many weeks and contribute to the inflammatory appearance. Deep inflammatory lesions include nodules and cysts. Nodules are larger than 5mm in diameter (large nodules if greater than 1cm) and are often painful.

Assessment of patients with acne should include the disease duration, subjective severity, effect on quality of life, previous treatments, duration of treatment, how topical treatments were applied (all over the face, as it should be, or just on active lesions), their effectiveness, and side-effects. Exploring patients' expectations of therapy is an important part of the consultation. To guide treatment options, all patients should be asked about previous psychiatric morbidity, current medications being taken, and females about plans for family and current contraceptive measures being used as some treatments for acne can interfere with the aforementioned issues. Objective measurement of severity is aided by use of standardised scales, such as the Leeds Acne Grading Scale[6].

Failure of initial therapy

Patient concordance with prescribed therapy is a significant determinant of success. Apparent failure of a treatment modality often reflects poor concordance with prescribed therapy, with either incorrect application of topical treatments, insufficient duration of use or premature termination owing to side-effects. Other apparent reasons for treatment failure include *P. acnes* antibiotic resistance and incorrect diagnoses (e.g. rosacea or acne variants). Treatment plans must be agreed with the patient, anticipated side-effects and the need for a number of months of treatment explained. As disease activity may fluctuate, a few courses of treatment may be required.

The optimal strategy for the treatment of acne vulgaris should include an induction phase followed by a maintenance phase, often supported by adjunctive treatments and/or cosmeceuticals. More often than not, maintenance therapy is not initiated and in the author's opinion this is vital to long-term success to reduce the

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risk of recurrence. The use of adjuvant skincare is integral to the management of acne. Treatment should incorporate an appropriate daily skincare regimen to cleanse, soothe and moisturise the skin[7,8].

Poor prognostic factors for acne include family history, persistent or late-onset disease, hyperseborrhoea, androgenic triggers, truncal acne, and relapse following isotretinoin.

Topical therapies

Topical therapies are the mainstay of treatment of mild-to-moderate acne. Patients should be advised of how to use their therapy, gradually building up from low to higher concentrations using increasing durations of application, from a few hours initially to overnight, to up to twice daily in some cases.

Topical benzoyl peroxide has both keratolytic and antimicrobial properties through its bactericidal effects and by inhibiting the release of reactive oxygen species (ROS). It can therefore be applied to inflammatory and non-inflammatory lesions. Unlike antibiotics, use of concurrent benzoyl peroxide reduces the risk of development of antibiotic-resistant strains of *P. acnes*, making it a useful adjunct to other agents. Tolerance is limited by local irritation, which causes a dose-dependent dermatitis and bleaching of both skin and clothes. Lower dose formulations and the choice of vehicle can lead to better tolerability[9].

For predominantly non-inflammatory (comedonal) acne, topical retinoids (adapalene, isotretinoin, tretinoin) are of particular use[1,9]. Retinoids are vitamin A agonists, the mechanisms of action of which include: keratolytic, anti-inflammatory activity, anti-proliferative effect, inhibition of the release of ROS, down-regulation of the innate immune response, and inhibition of the dermal matrix degradation. These actions make retinoids valuable in the treatment of any form of acne vulgaris. Side-effects include dryness of the skin and local irritation. Clinical trials on the microcomedo, the natural precursor of comedones, have shown that retinoids significantly reduce microcomedo counts. Topical (and systemic) retinoids are contraindicated in pregnancy owing to their teratogenicity (see below).

Predominantly inflammatory acne warrants the use of topical antibiotics (such as clindamycin, erythromycin) to reduce *P. acnes* colonisation of the pilosebaceous unit and the ensuing inflammation. Effectiveness of such agents is improved and the chance of bacterial resistance is decreased by concurrent use of benzoyl peroxide or retinoids. Where retinoids cannot be tolerated, salicylic acid and azelaic acid can provide additional keratolytic action.

Newer fixed-dose combination therapies, combining two of the above classes of agent, allow more rapid resolution and greater efficacy than a single agent by aiming to treat the maximum number of underlying aetiological factors. It also leads to greater patient adherence to therapy. A topical retinoid in combination with an antimicrobial agent (either benzoyl peroxide or topical antibiotic) are usually used as the first-line therapy for most patients with acne.

Dapsone is a sulfone antibiotic with both anti-inflammatory and anti-bacterial effects, and a topical formulation has recently been introduced (not available in the UK) that has shown good efficacy in clinical trials.

Combined oral contraceptive

The role of androgens in acne vulgaris has been well-established. Androgen receptors on keratinocytes and sebocytes mediate hyperkeratinisation and play a role in sebaceous gland development. Dihydrotestosterone (DHT) and dehdroepiandrosterone sulphate (DHEAS) are the most commonly implicated androgens in acne. The use of combined oral contraceptives in acne has been shown to be effective in multiple systemic reviews and currently form part of acne management of the adult-type female acne[10].

In females, a useful initial adjunct, where there are no contraindications, is the introduction of a combined (oestrogen-containing) oral contraceptive pill. By increasing the levels of sex hormone-binding globulin, such agents reduce both total androgen and free testosterone plasma concentrations, and can be useful in the presence or absence of hyperandrogenic states, such as polycystic ovarian syndrome (PCOS). The contraceptive pill may be combined with anti-androgen drugs, such as spironolactone or flutamide for greater efficacy. The effects are also the result of blocking of the androgen receptors on the sebaceous glands. It should be noted that progesterone-only contraceptive agents can exacerbate acne, owing to non-selective agonism of both progesterone and androgen receptors. Comprehensive endocrinological assessment is not

Key points

- Acne vulgaris is a common inflammatory dermatosis of multifactorial aetiology, typically first affecting patients during adolescence
- There is increasing evidence for a possible link between acne and diet
- Topical and systemic treatments are targeted at one or more of the underlying causes: hyperseborrhoea, comedogenesis, *P. acnes* colonisation and inflammation
- Recognition of predominantly 'inflammatory' or 'non-inflammatory' lesions will aid initial selection of treatment
- Patient understanding of therapies, their correct application, need for prolonged duration of treatment, and therefore concordance, often dictates success of treatment modalities
- *P. acnes* antibiotic resistance is a burgeoning problem that can be abrogated through concomitant use of benzoyl peroxide
- Isotretinoin is highly effective against acne vulgaris; caution must be taken in its use owing to its side-effect profile, most notably teratogenicity
- There are a range of techniques used to reduce scarring following inflammatory acne, none of which are perfect. Prevention is better than cure
- The role of biofilms in acne has been increasingly recognised

necessary for the majority of female patients with acne. However, this may be indicated where there are clinical features of hyperandrogenism, such as recalcitrant acne, infrequent menses, hirsutism, infertility, acanthosis nigricans, or truncal obesity. Indications for hormonal therapy in females with acne include proven ovarian or adrenal hyperandrogenism, recalcitrant acne, acne not responding to or relapsing following isotretinoin therapy, PCOS, the presence of alopecia, and marked hyperseborrhoea[10,11].

Systemic antibiotics

In moderate-to-severe acne, and in cases of back, shoulder and chest involvement, and where topical therapies have failed, a course of systemic antibiotics should be considered. Antibiotics have both antimicrobial and anti-inflammatory effects: agents commonly used include tetracyclines (tetracycline, oxytetracycline, lymecycline, doxycycline, minocycline), macrolides (erythromycin, clarithromycin), and trimethoprim. In addition to the anti-inflammatory effects of tetracyclines, they act through inhibition of MMPs, inhibition of neutrophil chemotaxis, down-regulation of pro-inflammatory cytokines, antioxidant properties, and inhibition of cell proliferation and angiogenesis[1,3].

Current evidence shows comparable efficacy of doxycycline, lymecycline, minocycline, and tetracycline against inflammatory lesions[3]. As there remains little conclusive evidence as to the superiority of any one antibiotic over others, choice of antibiotic is governed by patient preference, side-effect profile, likelihood of concordance and cost. Response to regular use of an oral antibiotic should be gauged at least 8 weeks after instigation, before considering switching to an alternative agent. Typical treatment duration is 3–6 months, but longer durations are justified in selected cases. The burgeoning problem of increasing community antibiotic resistance may be avoided by concurrent use of topical benzoyl peroxide with systemic antibiotics and avoidance of concomitant topical antibiotic application, in addition to avoidance of antibiotic switching when an antibiotic has previously been efficacious.

Isotretinoin

In cases of severe acne, and where two or more protracted courses of systemic antibiotics together with other therapies have failed to control the disease, systemic isotretinoin can be considered by a dermatologist. It should also be considered in cases of severe cystic acne, acne fulminans, and where there is evidence of scarring. Isotretinoin, a retinoid, is hugely effective in the treatment of acne, being the only therapy to effectively target all four aforementioned underlying mechanisms. In addition, it has effects on MMPs, normalising their expression pattern and that of their inhibitors; a vital mechanism in arresting the scarring process largely attributed to the action of MMPs. Its use is limited by side-effects, for which the patient must be counselled and documented consent obtained prior to commencement of treatment, which requires regular monitoring throughout the course of treatment[12].

Foremost among these is teratogenicity, with babies born to mothers who have taken isotretinoin at any time during their pregnancy being at high risk of craniofacial, nervous system and cardiovascular abnormalities. The British Association of Dermatologists' Guidelines recommend that all women of child-bearing potential should be counselled of this risk and receive the patient information leaflet of the brand they are due to take. Two methods of contraception are advised 1 month prior to initiation, throughout treatment and 1 month after cessation of isotretinoin therapy[13].

Dosage usually starts at 0.5mg/kg body weight and is increased as tolerated to 1mg/kg body weight. The cumulative dose aimed for is 120–150mg/kg body weight, typically over a 20-week time span. Following such a course of systemic isotretinoin, 40% of patients feel that their acne has fully resolved, 40% require less intensive treatment, and 20% may require a further course of isotretinoin. In cases of severe inflammation, a short course of oral steroids can be considered concurrently with isotretinoin.

What's new?

Our understanding of diseases evolves with time as new evidence emerges and old notions are challenged. This has similarly been the case in acne vulgaris with some interesting developments published over the last few years.

The traditional view of acne lesion progression from the microcomedone to either a clinically visible comodone or an inflammatory lesion has been challenged by emerging evidence, which has shown the presence of subclinical inflammation preceding the microcomedone formation. Immunohistochemical studies identified significant inflammation around clinically-normal follicles of uninvolved skin from acne patients prior to follicular hyperkeratinisation. These included CD4 T-cells, up-regulation of IL-1, and integrin expression. Another study demonstrated the presence of inflammatory cell infiltrates in acne scarring in the absence of visible clinical inflammatory lesions. *P. acnes* has been shown to promote inflammation in its non-viable state through up-regulation of TLR-2. These studies highlighted the persistence of inflammation throughout the acne life cycle, a finding that could have implications on early and continuous treatment of the inflammatory component. There is increasing evidence showing up-regulation of multiple genes associated with inflammation and tissue modelling, which include MMPs 1 and 3, IL-1 and IL-8, β-defensin 4, L-selectin, tenascin C, and CD163 antigen[14].

Increasing evidence has shown that the sebaceous gland is modulated by neuropeptides and acts as an independent neuroendocrine organ. Both the expression of melanocortins (MCs) and corticotrophin-releasing hormone (CRH) play a functional role in sebaceous gland activity with the CRH-pathway likely to explain the role of stress (leads to an increase in CRH levels) in acne.

The role of diet in the pathogenesis of acne has always

been controversial. Some recent studies have demonstrated a possible link with certain food items that could play a role in acne, particularly through the mediation of IGF. High-glycaemic index diet has been shown to stimulate the IGF-1 receptors leading to sebogenesis and follicular hyperkeratinisation. IGF-1 has also been shown to stimulate adrenal and gonadal androgen synthesis, androgen receptor signal transduction, and lipogenesis. Interestingly chocolate and skimmed milk (the latter possibly partly owing to the presence of a precursor of 5α-DHT in milk called 5α-pregnanedione in addition to an increase in IGF-1) have also been shown to worsen acne, while the consumption of fish was associated with a protective effect. A possible role of dietary effect may be the result of an increase in androgen levels, an observation particularly with whey-containing protein supplements that have mild androgenic effects. The roles of omega-3 fatty acids and zinc have yet to be proven.

The role of the innate immune system in acne was clearly demonstrated through the up-regulation of TLR-2 by *P. acnes*. TLRs are pattern recognition receptors that elicit an innate immune response through activation of the transcription factors, NF-κB and AP-1. Both modulate intracellular signalling cascades leading to up-regulation pro-inflammatory cytokines (particularly TNF-α, IL-1 and -8, and MMP). Topical retinoids have been shown to down-regulate TLRs, a mechanism that explains its high efficacy in the treatment of acne vulgaris. *P. acnes* has also been shown to elicit cellular responses via the protease-activated receptor-1 (PAR-2) with down-stream signalling, which mediates inflammation[14,15]. These studies have elaborated on the role of protease signalling in acne triggered by *P. acnes*.

The concept of biofilms in dermatology has gained a lot of attention recently, with our improved understanding of its role in skin diseases and management. Biofilms are diverse communities of microorganisms embedded within a self-produced matrix of extracellular polymeric substance, which are firmly attached to biotic or abiotic surfaces. They act as protective barriers against antimicrobial agents. With the relative recent elucidation of the *P. acnes* strain KPA171202, genome sequencing has demonstrated the presence of genes involved in the production of EPS and QS molecules; structures that are vital in the formation of the glycocalyx 'adhesive glue' of the *P. acnes* biofilms. This 'adhesive glue' serves to adhere the keratinocytes to the infundibular epithelium and the *P. acnes* to the sebaceous glands leading to comedogenesis and relative poor response to antimicrobial therapy[16].

The future?

Medicine evolves and is ever-changing with new evidence emerging and old accepted theories challenged. Acne remains a challenge, but we have seen a great amount of advances over the last few years. Dermatologists and scientists are continuing to work on a better understanding of the pathogenesis and treatment. The area of biofilms is interesting with possible future therapies targeting the glycocalyx structures allowing for better response to therapy. The role of PPAR receptors on sebogenesis is also of interest and we may not be far from anti-PPAR therapies for acne. This would similarly be the case with anti-MCR or CRH receptor drugs.

Finally, the role of diet in acne is becoming a bit clearer, and in future this may lead to a change of attitude toward the advice we give to acne sufferers.

Conclusions

Acne vulgaris remains one of the most common dermatological pathologies, with high prevalence and profound psychosocial consequences. While recognised to have a familial propensity, its aetiology is multifactorial and remains largely unknown. Early recognition and active treatment avoids post-inflammatory scarring and hyperpigmentation, which remain difficult to treat. Evolving evidence is emerging on the role of diet and subclinical prelesional inflammation (occurring prior to or concurrent with follicular hyperkeratinisation), along with the role of *P. acnes* initiating an inflammatory response through TLR-2, all of which may have future implications on therapy. Further large randomised controlled trials comparing different topical and systemic agents are required to devise the optimal initial treatment algorithm, taking into account the burgeoning problem of antibiotic resistance.

Declaration of interest *none*

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