Review

Acne vulgaris - current issues

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Not so long ago acne vulgaris was considered another "sore spot" of adolescence than a disease with any degree of morbidity. It was a nuisance not only to the adolescent but also to the physician who had little to offer to control acne, and also little awareness of the physical and mental morbidity it caused to the sufferer and a vague understanding of its aetiopathogenesis. Today it is considered a common skin disorder that could cause a considerable degree of morbidity both physically and psychologically. We have a better understanding of its multiple aeitological factors which in turn has given the opportunity to develop different treatment strategies more or less tailor-made to the individual patient.

Magnitude of the problem

Acne affects 85% of teenage boys and 80% of teenage girls in the U.K. and approximately 3.3 million patients consult their G.P. on account of acne annually with about 50,000 being referred for Dermatological opinion[1]. In The U.S.A. 80% to 90% of all adolescents have acne and 30% of them require medical treatment[2]. Acne is the commonest skin disorder treated by dermatologists in the U.S.A.[3].

In the past 20 years there has been a shift in the peak incidence of acne from mid-teens to late teens and early twenties[1]. Acne, therefore, has its impact on a population in their early working life and the stressful period of undergraduate life and at a time when facial cosmetics is of paramount importance to impress the opposite sex. A person with acne is more likely to be unemployed than a matched "non-acne" person[4]. It disables a person cosmetically. Cosmetic integrity of the facial skin is desired by all and is specially so in this particular age group. Physical discomfort from pain and tenderness of inflammed acne compounds the mental agony. Shame and embarassment is shared by majority of acne sufferers which profoundly affects their interpersonal relationships. A cross-sectional and longitudinal questionnaire study carried out recently in the U.S.A. shows that acne significantly affects the quality of life of the sufferer, and that the older the patient, more affected were they by their acne[5]. In a present-day dermatology practice, acne, therefore, assumes the place of an important skin disorder that warrants early and adequate treatment to avoid physical and psychological scarring in this particularly vulnerable age group.

It has also been shown that there is reduced levels of linoleic acid[9] and that there is infact an inverse relationship between sebum production and the levels of lenoleic acid production in the sebum[10]. This in turn is considered to a) increase follicular hyperkeratosis, b) increase proliferation of follicular microflora, c) increase penetration of pro-imflammatory products through follicular wall. An overtly vigorous immune response to P.acnes is considered to be the fundamental problem in patients with inflammatory acne[11]. This paper also records that although duct rupture is a feature of acne inflammation, many of the early inflammatory lesions are not infact associated with ductal rupture.

There is a well recognised group of patients who continue to suffer from acne past their adolescence and the early twenties beyond the age of 25 years. They are known as the persistent acne sufferers. Those who develop acne for the first time after the age of 25 years are called the late onset acne sufferers[6]. Severe acne has been observed to be familial.

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In a large study of identical twins, 97-9% of twin pairs were found to be affected by acne. 50% of patients with post-adolescent acne reported having at least one first degree family relative with acne[6]. Severity of acne in the East is said to be less than in the West, and Japanese are said to have a much lower incidence of acne. In the temperate climates acne is well known to improve in the summer with a worsening in late autum and in winter.

A few unanswered questions in the aetiology of acne are; i) why acne usually clear in late adolescence and early twenties, and what is responsible for this, ii) the exact role of androgen metabolism, iii) the role of the bacterial flora, and iv) how localised deficiency of essential fatty acids alter the micro-enviroment of the pilosebaceous unit. The relative significance of each of these is not clear. It is clear, however, that the increased sebum production in a pilosebaceous unit showing follicular obstruction leads to the dilatation of the follicle and eventually to leakage of its contents into the surrounding dermis. The ensuing release of the pro-inflammatry follicular contents into the dermis trigger a series of events responsible for inflammatory acne.

Therapeutic options

There is no single best method of treating a patient with acne. Each patient warrants individual assessment and evaluation taking into consideration the type of clinical lesions seen, the age.

Aeitology: different concepts

Acne is multifactional in aetiology. The retention of the hyperproliferating ductal keratinocytes, seborrhoea, colonisation of the pilosebaceous duct by Propionibacterium acnes and dermal inflammation are some of the more important contributory factors. There is controversy as to which is the primary triggering factor. Increased sebum production does not occur until puberty, and except for acne neonatorum, acne does not occur until puberty. Increased sebum production alone without follicular hyperkeratinization does not lead to formation of acne. This is well illustrated in patients with Parkinson's disease, who have increased amounts of sebum production, but do not have an increased incidence of acne. Though androgens is a pre-requisite to the initiation of seborrhoea, all pilosebaceous follicles are not prone to acne. At the molecular level it is now considered that the acne prone follicle shows an end-organ hyper-responsiveness to circulating normal levels of androgens. Also, seborrhoea often persists even after complete resolution of acne. Comedones represent one of the earliest features of acne. Comedone results from retention of the hyperproliferating ductal keratinocytes. However, the cause of ductal hyperproliferation is still not clear and is thought to be androgen mediated. Though plasma testosterone is not elvated in males with acne it is known that acne does not develop in males castrated before puberty, and also in oophorectomized women. The administration of testosterone could provoke acne lesions in eunuchs. 37% of female patients with post-adolescent acne had at least one symptom of hyperandrogenecity[6]. Women with treatment resistant acne was shown to have increased circulating androgens and a high incidence of clinical markers of hyperandrogenism such as hirsutism, menstrual irregularity, and/or amenorrhoea[7]. However a comparative study carried out by the Leeds group later showed that the clinical markers of hyperandrogenism do not correlate with response to conventional acne treatment[8]. They concluded that it is possible for the women with treatment resistent acne to have greater "biochemical hyperandrogenism" than those who respond to convential treatment.

Retention hyperkeratosis of the pilosebaceous follicle encourage the growth of bacteria within the occluded follicle, the commonest organism being the gram-positive, anaerobic diphtheroid, P.acnes, which normally inhabit the follicles. These bacteria hydrolyze sebaceous gland triglyerides to free fatty acids. P.acnes generate a variety of pro-inflammatory agents such as lipases, proteases, hyaluroindases, and chemotactic factors. These in turn set up the inflammatory cascade involving additional factors including leucotrienes, etc. leading to complement activation[5], distribution, duration, the sex, response to past and present treatment, and tendency to scarring and pigmentary changes. In assessing response to treatment it is vital to bear in mind that it could take an

average of 6 to 8 weeks to observe an appreciable improvement with whichever form of treatment protocol employed. In fact, stressing this important fact to your patient right at the onset will get you better patient compliance.

The object of treatment is to correct the altered pattern of follicular retention hyperkeratosis, inhibition of sebaceous gland activity, inhibition of extracellular pro-inflammatory products by reducing the population of follicular P.acnes, and reduction of the inflammatory response.

Benzoyl peroxide in different strenghts and formulations have been in use for several decades, and act primarily as antibacterial agents. They also unplug the blocked follicles. Azelaic acid is another antibacterial agent available in a cream base. It is also claimed to have a) an anti-inflammatory effect with b) the added advantage of its action on follicular hyperkeratosis and c) depigmentary effect on post-inflammatory hyperpigmentation. Its major advantage over benzoyl peroxide is the low irritancy. In a comparative study carried out with these two topical agents, there was no significant difference between the two[12]. Nicotinamide gel was introduced in 1995 as a topical anti-inflammatory agent. The anti-inflammatory action is thought to result from its effect on a variety of inflammatory mediators and cells, inhibition of neutrophil chemotaxis, and suppression of lymphocyte transformation. Like antibiotics, it is effective against inflammatory acne, but does not promote antibiotic resistence. There have been no reports of local irritancy, contact sensitivity or photo-allergy. Topical nicotinamide gel has been found to be equally effective as topical 1% clindamycin, and there was no evidence of irritancy[13].

The new retinoid, adapalene, is a derivative of naphthoic acid. It is available in an aqueous gel containing 0.1% adapalene. The moisturizing capacity has been enhanced by the addition of 4% propylene glycol. It is claimed to regulate terminal differentiation of keratinocytes through its high affinity to nuclear RARγ receptors with a low affinity to RAAα receptors. Adapalene, in contrast to tretinoin, does not bind to cytosolic retinoic acid binding protein (CRABP). The selective affinity to RARα and lack of binding to CRABP is thought to be the basis for its chemical efficacy together with the less frequent side effects.

Topical antibiotics available in the form of liquids, gels, and saturated pads, include erythromycin, clindamycin, and tetracycline. All have been found to be equally effective but none of them have been found to be more effective than benzoyl peroxide[14]. Erythromycin is also available in combination with zinc and with benzoyl peroxide. These combined preparations are more effective than the individual ingrediants used alone. Clindamycin is known to cause pseudomembranous colitis as a rare complication, and topical tetracyclines may stain the skin yellow. Topical erythromycin used alone or in combination with zinc or benzoyl peroxide could be combined to give synergistic advantage when used with systemic erythromycin orally. This is particulary useful in managing inflammatory acne of moderate severity failing to respond to topical therapy alone. Once the desired improvement is achieved the oral therapy could be stopped while maintaining the improvement with the topical therapy.

Topical tretinoin and isotretinoin act primarily on altered follicular keratinization. They are benefical in non-inflammatory comedonal acne and to some degree in inflammatory acne, specially in combination with oral antibiotics. A new arrival in the scene is a combination of isotretinoin and erythromycin in a topical gel formulation. The only drawback is the initial irritancy like with all the previous tretinoins, and isotretinoins, which wear off after a short period, and a degree of photosensitization amongst a few of the users. The bonus to be gained, like from its predecessors, is effacement of superficial scars and hyperpigmentation, together with prevention of photodamage to the facial skin.

With the knowledge that the pilosebaceous unit is androgen dependent, a number of studies have been carried out to determine the efficacy of topical anti-androgens in treating acne vulgaris. In 1969, topical cyproterone acetate in dimethyl sulphoxide was found to bring about no improvement[15]. In 1976, another group car-

ried out a similar study using cyproterone acetate in cetamacrogol cream BPC and that too was ineffective[16]. This lack of efficacy was considered to be due to the lack of a suitable vehicle for the steroid. The new non-steroidal topical anti-androgen, inocoterone, produced only moderate clinical improvement of acne[17]. Flutamide is the only truly pure non-steroidal anti-androgen available commercially today and is given orally for prostatic cancer. Following a successful outcome with the use of topical flutamide in treating hirsutism of the face in women, a pilot study was conducted to evaluate its efficacy in the topical treatment of acne vulgaris. 2.5% solution of flutamide was found to be effective in controlling acne[18]. Placebo controlled, randomised study carried out recently in female patients showed that topically applied cyproterone acetate, with liposomes to improve transdermal penetration of the anti-androgen showed a significant therapeutic improvement in acne after 3 months of treatment[19]. The results were comparable to the improvement seen with oral cyproterone acetate in combination with ethinyl oestradiol.

Systemic treatments include a) antibiotics oxytetracycline, minocycline, doxycycline, erythromycin, and trimethoprim, b) anti-androgens with ethinyl oestradiol for the female patient, and c) isotretinoin. Although all these antibiotics are equally effective in the management of mild to modarate inflammatory acne, there is wide variation in the outcome among different patients. During the past few years there has been an increasing resistance of P.acnes to antibiotics[20]. The resistance is most marked against erythromycin and clindamycin and to a lesser extent to tetracyclines, doxycycline, and trimethoprim.

Minocycline has been reported to cause rare but serious adverse reactions including hypersensitivity reaction syndrome, serum sickness like reaction, and drug induced lupus[21,22]. There are more reports of serious adverse effects from minocycline use than from the use of other tetracycline antibiotics[23].

Oral isotretinoin has been successfully used for managing moderate and severe acne including nodulo-cystic acne since the initial observation made by Peck and co-workers in 1979 while treating lamellar icthyosis with isotretinoin[24]. Remission rate using 1.0 mg/kg per day is now known to be much longer than with the use of 0.5 mg/kg of isotretinoin[25]. Use of isotretinoin has been found not only to be quite safe, but also to be more cost-effective than 1st line treatments in the long run, as the patients improve relatively quickly often achieving a complete cure, requiring much less in the way of the other forms of treatment[26]. Though originally prescribed only for the management of severe acne, indications for its use now also include those showing a partial response to 1st line treatments, and those with a predominantly facial distribution[27]. late onset and the persistant ance sufferers also warrant isotretinoin therapy.

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