Editorial

What's new in the management of acne?

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Acne vulgaris is the most common skin disease of adolescents and young adults with reported prevalence being nearly 80%.[1] Its predominance in this psychologically labile age group coupled with its potentially lifelong sequelae makes it a matter of huge financial and psychosocial concern.

Excessive sebum production, ductal hypercornification, changes in the microbial flora, as well as inflammatory and immunological host reactions have long been considered to be the four pillars of acne pathogenesis. Ongoing research has seen the changing importance of one factor over the other from time to time.

Propionibacterium acnes biofilms, composed of a glycocalyx polymer, serves as a biological glue between keratinocytes promoting comedogenesis.[2] It also acts as a protective physical barrier, limiting effective anti-microbial concentrations within the biofilm microenvironment. It further promotes antibiotic resistance of the colonies by stimulating the production of certain proteins.[3]

Molecular research has demonstrated the lipogenic role of the peroxisome proliferator-activated receptor (PPAR) subfamily in sebocytes. Drugs like fibrates (PPAR-α agonist) and thiazolidinediones (PPAR-γ agonist) have shown a direct increase in sebum production.[4] But the recent evidence of the anti-apoptotic effect of the PPAR-γ agonist, rosiglitazone on SZ-95 sebocytes *in vitro*, (thereby inhibiting the final step in holocrine secretion of sebum),[5] prompts us towards the consideration of PPAR ligands as future options in acne management.

Research on the hormonal influence on acne has revealed the importance of insulin-like growth factor 1 (IGF-1) as the final mediator of other hormones (like androgens, growth hormone and insulin), with its levels directly correlating with the production of sebum and acne.[6] IGF-1 polymorphism has recently been shown to predispose Turkish individuals to acne.[7] The acnegenic effect of glycemic foods and dairy products, which are thought to increase IGF-1, is another area of interest.

The current standard treatment approach of acne vulgaris is targeted towards the type of the lesions and severity of acne.[8] There is no ideal treatment for acne, although a suitable regimen targeted at reducing the number of lesions and preventing the permanent sequelae, can be made out for most patients.

In view of the wide range of products flooding the market and limited good-quality evidence on their comparative efficacy and safety, clinicians need to be constantly updated about the latest progress in this field to improve upon acne treatment. This limited review summarizes the important recent developments in the management of acne.

WHAT'S NEW IN TOPICAL THERAPY?

Topical antibiotics, benzoyl peroxide (BPO) and retinoids have been the cornerstone of topical treatment of acne. Recent developments in topical treatment encompass newer formulations and combinations of conventional treatments as well as emerging topical therapies.

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SYNERGISTIC TOPICAL COMBINATIONS

Fixed dose combination products as well as topical combination regimens (with a quicker onset of action and synergistic effect), lead to greater patient adherence, reduction in the amount of antibiotic exposure and the risk of antibiotic resistance in *P. acnes*.

BPO has been combined with antibiotics (essentially clindamycin and more recently, nadifloxacin),[9] retinoids (only with adapalene), and with salicylic acid (SA). BPO 2.5% or 5%/clindamycin combination has demonstrated superior efficacy than either agent as monotherapy in treating inflammatory lesions.[10,11] This combination has also been compared with the previously established clindamycin 1.2%- tretinoin 0.025% gel. According to a randomized, investigator-blinded trial, the clindamycin-BPO combination group not only showed faster reduction in inflammatory and total lesion counts compared with the clindamycin-tretinoin combination group, but also showed reductions in clindamycin-resistant *P. acnes* colonization.[12]

The best approach to limit the emerging antibiotic resistance in *P. acnes* is to combine BPO with topical retinoid as neither the retinoid nor the BPO creates selective pressure for resistance. BPO has been uniquely combined with adapalene 0.1%, among the retinoids, in a fixed dose combination product. It targets three of the four main pathophysiologic factors in acne (ductal hypercornification, *P. acnes* proliferation, and inflammation).[13] Moreover, topical retinoids may affect skin permeability enhancing the penetration of topical antibiotic. An open-label study has demonstrated the *in vivo* effectiveness of adapalene 0.1%/BPO 2.5% gel in inhibiting both antibiotic-sensitive and resistant strains of *P. acnes* on the facial skin.[14]

Further, adapalene 0.1%/BPO 2.5% gel does not significantly differ from clindamycin 1%/BPO 5% gel in terms of efficacy.[15] It is generally well tolerated in the long term, while in the short term, higher irritation potential was observed as compared to clindamycin 1.2%/BPO 2.5% gel in a split face study.[16] Individual's skin type has not shown any significant correlation with the susceptibility to irritation from treatment with the adapalene-BPO gel, according to a sponsored meta-analysis.[17]

Topical SA alone is only moderately effective in acne. However, in a recent meta-analysis, 5% BPO used in combination with SA has shown better efficacy than even BPO/clindamycin gel in reducing both inflammatory and non-inflammatory lesions in the early weeks of therapy. The magnitude of benefit in the later weeks was questionable.[18] Its exfoliant ability has been utilized in conjunction with the BPO/clindamycin gel. However, higher frequency of mild to moderate transient dryness was observed as the only limiting factor in this combination regimen.[19]

Azelaic acid 5% has been combined with clindamycin 2%,[20] and also with erythromycin[21] with better efficacy and tolerability than monotherapy.

Owing to the recent interest in topical dapsone 5% gel, it has also been evaluated in combination with adapalene 0.1% as well as BPO 4% and has been reported to be safe and well tolerated.[22]

NEWER FORMULATIONS

Formulation technology has focused on novel systems for drug delivery, including microsponge/spheres, liposomes, nanoemulsions and aerosol foams. Microsphere formulations of topical tretinoin and BPO, currently in the market, have demonstrated good efficacy and tolerability. Microsphere encapsulation eliminates the rapid delivery of high concentrations of active drug to the application site, while it facilitates controlled release of potentially irritating drugs. It makes tretinoin photostable in the presence of fluorescent light or ultraviolet radiation. The encapsulation also enables the use of convenient topical combination regimens with a strong oxidizing agent such as BPO, leading to improved treatment outcomes and minimal irritation.[23] In a randomized controlled trial, tretinoin 0.04% microsphere gel has been found to be effective as a maintenance therapy in the prevention of recurrent acne after 6 months of isotretinoin.[24]

A micronized formulation of tretinoin (0.05%) gel has also been developed that enables more efficient penetration into the skin layers because of its optimal particle size. It enables the use of lower concentration of tretinoin with better cutaneous tolerability than tretinoin gel microsphere (0.1%) without compromising its efficacy.[25,26]

Retinoic acid loaded, solid, lipid nanoparticles represent another interesting formulation to increase it's tolerability without reducing efficacy.[27] The nano-emulsion gel formulation of adapalene/clindamycin combination appears to be more efficacious and better tolerated than the conventional formulation in Indian acne patients.[28]

The latest entry to the newer formulations list is micronized BPO particles in an emollient foam vehicle which offers significant clinical and bioavailability advantages. It enhances follicular penetration and skin moisturization. In addition to its use for facial acne vulgaris, cleanser formulations of BPO are now commonly used for truncal acne due to the ease of use on a large body-surface area and to avoid bleaching of fabric. The BPO 5.3% foam formulation has demonstrated good efficacy when used either as a "leave-on" or as short-contact therapy for 5 minutes.[29] More recently, it has been found that short contact therapy for 2 minutes with BPO 9.8% emollient foam used once daily provided a reduction in *P. acnes* colonization comparable to "leave-on" therapy using BPO 5.3% emollient foam.[30]

EMERGING TOPICAL THERAPIES

Recent research in acne pathogenesis has unveiled some newer microbiological targets; thus, the need to explore the potential of alternative treatments for acne.

Topical dapsone 5% gel offers documented efficacy for the reduction of inflammatory lesions in mild-to-moderate acne, especially in patients exhibiting intolerance to conventional anti-acne agents.[31,32]

Amongst topical retinoids, retinol has better tolerability compared with tretinoin, but it is only used in cosmeceuticals due to its low biologic activity. A combination product using retinol with hexamidine di-isothionate, known to have anti-bacterial activity, and rose extract, known to possess anti-inflammatory activity has been proposed to be an effective alternative in the treatment of mild-to-moderate acne.[33]

The *P. acnes* biofilm model as mentioned earlier, explains the mechanism of anti-microbial resistance in acne. Coenye *et al*.,[34] identified five herbs with potent anti-biofilm activity against *P. acnes* out of which, extracts from *Epimedium brevicornum* and *Polygonum cuspidatum*, as well as their active compounds (icariin and resveratrol, respectively) showed marked anti-biofilm and anti-inflammatory properties. In another vehicle-controlled, pilot study, resveratrol, a natural phytoalexin produced by grapes and other plants was formulated into a carboxymethylcellulose-based gel and has shown good efficacy.[35]

Taurine bromamine, the product of taurine and hypobromous acid, was introduced as a novel topical treatment for acne when its anti-inflammatory and bactericidal activity against *P. acnes* was confirmed in a double blind trial. It showed comparable efficacy as clindamycin.[36] Data suggests that it can be used in antibiotic resistant acne. However, no recent trials have been undertaken to substantiate the results.

Another agent of interest has been sodium L-ascorbyl-2-phosphate (APS), which is a stable vitamin C derivative, known for its anti-inflammatory and anti-oxidant effects. In a randomized double blind, vehicle controlled trial, APS 5% lotion has been shown to be effective and well tolerated.[37]

Results from a Japanese experimental study suggest that chlorhexidine gluconate ointment, a frequently used antiseptic, has both therapeutic as well as preventive role in the comedone formation presumably owing to its anti-bacterial activity and dissolving action of its base on free fatty acids.[38]

A small observational study demonstrated that 20% sodium sulfacetamide, when used in combination with 50% sulphur foam, decreases acne, rosacea, and seborrheic dermatitis lesions without adverse effects.[39]

COMPLEMENTARY AND ALTERNATIVE MEDICATIONS

The use of complementary and alternative medications in dermatological conditions, especially acne is common place despite the absence of any evidence based data on their efficacy. A recent systematic review of the botanical products for acne found poor quality evidence for most of the products, except few studies supporting the use of topical tea-tree oil 5% gel and gluconolactone (obtained from *Saccharomyces bulderi*) in mild to moderate disease, with the latter comparable with BPO 5%.[40] There is no controlled trial evaluating the efficacy of homeopathic remedies in acne.[41]

ORAL ISOTRETINOIN

Oral isotretinoin continues to be the mainstay of therapy for severe acne, because of its efficacy, ability to target all the four pathophysiologic factors, high rates of permanent remission and prevention of permanent scarring in acne. However, there remains ambiguity regarding the best dosage, including desired cumulative dose of isotretinoin. The current recommended dose of 0.5-1.0 mg/kg/day for 4-8 months (average cumulative dose of 120-150 mg/kg), quite often encounters relapse cases in clinical practice that require further medical management. Higher dosages have led to less favorable safety/tolerability profiles. Recently, data presented by Cyrulnik *et al*,[42] challenges this paradigm. They observed 100% disease free rates with no side-effects or laboratory abnormalities on prescribing isotretinoin at 1.5 mg/kg/day or greater for an average duration of 5-6 months in severe nodulocystic acne. However, larger prospective multicentre trials need to be undertaken to substantiate the claims of this study, which appears unlikely considering the day-to-day experience in Indian patients with low-dose and even standard dose regimens.

Isotretinoin should be considered early in the management of mild to moderate acne, with lower-dose isotretinoin (0.25-0.5 mg/kg/day for 24 weeks) offering a good balance between efficacy and dose-related side-effects.[43,44] Isotretinoin 20 mg in an alternate day regimen seems to be an effective and safe treatment option in mild to moderate cases, according to an Indian study.[45] However, intermittent regimens with 0.5-0.7 mg/kg/day of isotretinoin for a week, every 4 weeks, did not achieve good patient satisfaction and remission.[43] A combination of low-dose isotretinoin and oral azithromycin pulse was found to be effective in severe acne, with a reasonably acceptable adverse-effect profile and low post-treatment relapse rates.[46] Presently, there is no sufficient evidence for routine determination of cumulative dose of isotretinoin necessary to obtain optimal treatment response and low relapse rates in clinical practice.

A large retrospective cohort study from Sweden,[47] has thrown light on the potential link between depression/suicide and isotretinoin. They found an increased risk of attempted suicide up to a maximum of 6 months after discontinuation of isotretinoin. However, it depicted a rising trend before initiation of isotretinoin also. Those with a history of suicide attempts before treatment made fewer new attempts after being started on isotretinoin. Supported by other studies, it is now recommended that patients with severe acne with a history of attempted suicide should not be denied isotretinoin. Suicidal ideation and social impairment in acne patients largely reflects the burden of substantial acne rather than being associated with therapy.[48,49]

As an addition to its side effect profile, there have been occasional reports of elevated serum creatine phosphokinase levels with or without muscle-related symptoms in isotretinoin-treated patients. This has largely been interpreted as a benign phenomenon, but a fatal generalised rhabdomyolysis in a young male has been recently reported.[50] Association of isotretinoin with inflammatory bowel disease is a subject of controversy with no study yet demonstrating a causal association.[51]

ORAL ANTIBIOTICS

The major concern with the use of oral antibiotic therapy in acne is its indirect link with the development of antibiotic resistance in non *P. acnes* bacteria in community. Prescribers can alter their practice to minimize future risks by limiting the therapy to the shortest possible period, combining antibiotic monotherapy with BPO or retinoids to make use of their useful synergistic properties, and avoiding the simultaneous use of topical and systemic antimicrobials.[52]

Minocycline is an effective treatment for moderate to moderately-severe inflammatory acne vulgaris, but there is still no evidence to recommend it as the first line agent. This is primarily because of an uncertain safety profile and lack of advantages over other tetracyclines (i.e., first-generation cyclines, doxycycline and lymecycline).[53] Data also does not support the fact that the more expensive extended-release preparation is safer than standard minocycline preparations.[54]

Lymecycline is another member in the tetracycline family, with similar efficacy as minocycline, but with slightly less side effects and much better cost effectiveness. A multicentre, randomized, double-blind controlled study demonstrated the clinical benefit of combining oral lymecycline 300 mg with adapalene 0·1%- BPO 2·5% fixed-dose gel as compared to the oral antibiotic alone in moderate to severe acne vulgaris.[15]

HORMONAL THERAPY

Hormonal therapy is regarded as an excellent choice for women with acne who need oral contraception. Only few head to head comparative trials have been done comparing combined oral contraceptives (COC's) with other acne treatments.[55] COC's work well in acne with estrogen suppressing sebaceous gland activity and decreasing the formation of ovarian and adrenal androgens. Progestogen-only contraceptives tend to flare acne and should be avoided in women who have no contraindications to oestrogen-containing preparations.[56]

In a recent review, the combinations of ethinyl estradiol with cyproterone acetate, desogestrel or drospirenone have shown the strongest anti-acne activity and should be continued for a 6-12 month period. Low dose prednisolone is only to be administered in non-classic congenital adrenal hyperplasia and dopamine agonists in hyperprolactinemia. Estrogens as monotherapy, spironolactone, flutamide, gonadotrophin-releasing hormone agonists and inhibitors of peripheral androgen metabolism are not recommended.[57]

CHEMICAL PEELING

Glycolic acid peel is known to be effective in treating comedones. Recent data from an *in vitro* study demonstrated its moderate growth inhibitory and bactericidal effects on *P. acnes* and this explains its use in inflammatory acne also.[58] As per the European Academy of Dermatology and Venereology recommendations, the use of chemical peels; mainly glycolic acid and SA, in acne is well supported, as all trials have shown generally favorable results despite differences in assessments, treatment regimens, and patient populations. Notably, no comparative studies of peeling agents against conventional acne medications have been performed.[58,59]

ROLE OF LIGHT THERAPY AND PHOTODYNAMIC THERAPY

Light based treatments and photodynamic therapy (PDT) using topical precursors of porphyrins are off-label alternative treatments for acne vulgaris. Their therapeutic role is based on the endogenous production of porphyrins by *P. acnes* which serve as reactants for photochemical reactions. This leads to the production of free radicals which have direct inflammatory and damaging effects over sebaceous glands, *P. acnes* and also its glycocalyx coat, as observed recently. Overall, the results from trials of light alone have been disappointing in the past, but the red-blue light was observed to be more effective than topical 5% BPO cream in the short term.[60]

Owing to the low amount of endogenous porphyrins, topical photosensitizing agents such as aminolevulinic acid (ALA) or methyl aminolaevulinate (MAL) are required to augment the effect of subsequent light therapy. Earlier trials have shown some benefit of PDT for non-inflammatory acne, whereas no better results were obtained for inflammatory lesions as compared to topical adapalene 0.1% gel.[60] But in a recent split face trial, low dose ALA has been shown to be a safe and effective option with red light for the treatment of moderate to severe acne.[61] MAL-PDT has shown a quicker onset of action with better response than red light alone and may induce a reduction in the size of the sebaceous glands and thus long-term acne remission.[62] PDT with intralesional ALA has also been used as an adjunct to other light treatments like intense pulsed light (IPL) with minimal and tolerable side effects and less recurrence rates.[63]

There is no standardization on PDT methodology and parameters. Its use has been limited by complexity of the PDT procedure and the adverse effects like pain, redness and hyperpigmentation following the intense phototoxic reaction observed in the days following treatment. Although several forms of light therapies show reasonably good short term effects,[64] longer-term outcomes and comparisons with conventional acne therapies are needed.

LASER THERAPY FOR ACNE SCARS

Compared with light therapy, lasers have the advantage to concentrate coherent light on a smaller area of tissue. Lasers for acne scars that have been explored include 532-nm potassium titanyl phosphate laser, 585-nm and 595-nm pulsed dye laser, infrared and fractional lasers. Fractional resurfacing lasers may best be classified into two categories: non-ablative fractional lasers (NAFL) and ablative fractional lasers (AFL).

The microthermal zone (MTZ) area coverage in newer NAFL systems may range from 5% to 48%, with higher levels resulting in greater thermal injury and subsequent collagen remodeling.[65] It has been shown that the use of higher energy settings and multiple laser passes leads to improved clinical results, while use of

increased densities results in increased post-treatment erythema, edema, and hyperpigmentation.[66]

Similar to NAFLs, AFLs work by achieving collagen contraction and neocollagenesis. Split-face studies have found equal or slightly greater clinical improvement scores with the AFL than with the NAFL, only at the cost of higher chances of post procedural erythema and hyperpigmentation.[67] The ideal patient for fractional laser skin resurfacing undeniably belongs to skin prototypes I, II, or III, hence its use in Indian skin tones (IV-VI) must be dealt with caution keeping the risk of post inflammatory hyperpigmentation in mind.[68]

The 1450-nm diode laser is an infrared laser and has now become a common modality for laser treatment of acne in view of its ability to heat the sebaceous glands, thereby reducing seborrhea and improving inflammatory acne. It has been assessed in a randomized, split face, blinded trial and found to improve acne on the non-treated side as well, thus suggesting a possibility of a systemic effect of the laser.[69]

Recent innovation in non-ablative resurfacing is combined fractional laser with bipolar radiofrequency (RF) in a single hand piece followed by fractional RF. It causes reductions in peri-follicular inflammation and sebaceous gland areas. This novel device has been shown to be safe and effective for both superficial and deep acne scars with modest improvement and lower post-inflammatory hyperpigmentation risk comparable to other resurfacing techniques.[70,71]

The future application of these devices in acne will likely include combination therapy and exploration of more precisely targeted chromophores.

OTHER MINIMALLY INVASIVE APPROACHES FOR ACNE SCARRING

Non-laser options for acne scar reduction include peels, subcision, fillers, dermabrasion, and surgical excision, although all deserve cautious administration in our Indian skin types.

Out of all, subcision employing a different and basic mechanism for correcting depressed acne scars, has been a constant modality for combination with other techniques. Hyaluronic acid fillers have been used in combination with subcision, injecting the product beneath the subcised skin to maintain optimized wound healing.[72] A recent study reported success by combining subcision with a skin suctioning treatment.[73]

It is currently recommended that patients should wait for at least 6 months after completion of isotretinoin therapy before undergoing resurfacing with dermabrasion.[74] Despite this recommendation, there are recent reports of patients undergoing dermabrasion during treatment with oral isotretinoin therapy, without any hypertrophic scar formation.[75] This certainly needs further validation to constitute a recommendation.

Another upcoming technique is the soft tissue augmentation techniques for treating superficial atrophic scars, such as rolling scars. The recent development of non-collagen fillers like hyaluronic acid, calcium hydroxyapatite and poly-L-lactic acid, have largely replaced injectable collagens. Calcium hydroxyapatite is a semi-permanent dermal filler comprised of microspheres in a hydrogel vehicle, that imparts it the unique ability to be molded, which avoids contour irregularities.[72]

WHAT'S NEW IN ROLE OF DIET?

Apart from earlier reports of association with high glycemic load diets, acne vulgaris has also been linked to increased milk consumption, more with skim milk than whole milk.[76] Silverberg,[77] found moderate to severe acne flares precipitated by whey protein supplementation in teenagers leading to the hypotheses that whey protein might be the "acnegenic" fraction of dairy products. The role of omega-3 fatty acids, anti-oxidants, zinc, vitamin A, and dietary fiber in acne vulgaris remain to be conclusively proven.

PROMISING THERAPIES

Over the past years, natural anti-microbial peptides including epinecidin and granulysin and omiganan pentahydrochloride have attracted considerable interest as a new anti-microbial agent because of their selective targets (microbial membranes) and the low frequency in selecting resistant strains. The anti-inflammatory effects combined with potent anti-microbial activities and O_2-production-inhibition activities of cathelicidin also justify its anti-acne potential.[78]

CONCLUSION

The large number of available products and product combinations, and the scarcity of comparative trials, has led to disparate guidelines. Chronicity of the condition, adverse effects, poor adherence to conventional therapy and the constant need to minimize the risk of permanent scarring drives the treating physician to be well versed with the latest developments in the field of acne management.

Sebaceous gland activity and seborrhea driven by hormonal influence appear to be prime mover in acne pathogenesis. Only isotretinoin and anti-androgens among the medical options have demonstrated efficacy on seborrhea. The limited options in this aspect, particularly for patients who do not tolerate either of the agents and non-suitability of anti-androgens in the male patients indicate that we need more anti-seborrhoea options.

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