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Modalities in Acne Vulgaris Treatment: Review Article

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ABSTRACT

Background: Acne Vulgaris is a complex illness linked to the pilosebaceous unit. Almost 85% of adolescents suffer from this disease, which results in a higher incidence of low self-esteem since it affects primarily the face. Inflammatory and non-inflammatory lesions are common in acne vulgaris. There are different lines of treatment that can be tailored to the patient's condition. New modalities emerge every day to combat the possible side effects of the traditional lines.
Objective: To determine the updated treatment modalities in acne vulgaris management.
Conclusion: Several modalities have been introduced to treat acne vulgaris including topical, systemic, light assisted, and novel topical agents like Triafortene and Nitric oxide gels.
Keywords: Acne vulgaris, Novel, Treatment.

INTRODUCTION

Acne Vulgaris is a complex illness of the pilosebaceous unit. It appears as comedones, papules, pustules, and less frequently as nodules and cysts [(1)].

Although it doesn't shorten the patients' life expectancy, it is thought to have a negative impact on their quality of life, much like diabetes and coronary heart disease do. Low self-esteem and increased incidence of social isolation, unemployment, and depression were seen in adolescents with acne compared to those who had not had acne [(2)].

The word acne is derived from " acme "; a Greek word meaning any pointed thing that comes out of the surface. The earliest documentation of the disease was in the Roman literature as "Akmas" meaning the prime of life in the roman language, referring to the most commonly affected pubertal age group [(1)].

Acne is mostly a self-limiting disease that usually resolves after adolescence however in some cases it can take many years and persist till adulthood [(2)].

This review aimed to determine the updated treatment modalities in acne vulgaris management.

Acne Vulgaris:

Acne presently affects 9.38 percent of the world's population [(3)]. It is estimated that almost 85% of teenagers will experience acne at some point in their lives. According to recent epidemiological research, developed countries face a greater danger than developing countries [(4)].

Course:

In most situations, acne is a self-limiting illness that goes away after puberty, but it can last for many years and even into adulthood in certain people [(5)].

Pathogenesis:

Hyperkeratinization of the follicular epithelium, excessive sebum, Cutibacterium acnes colonization, and finally inflammatory changes are the four main pathogenic events implicated in the pathogenesis of acne vulgaris [(6)].

Inflammatory changes:

Acne lesions are now known to be primarily driven by inflammatory changes mediated by the host's innate and adaptive immunity, and inflammation is required for the emergence of acne lesions and is not a coincidental occurrence [(7)].

Clinical presentation:

Acne's primary lesion is microcomedone. It makes up histological changes that aren't visible clinically. The follicle is damaged by sebum buildup, and so comedones are formed, which are closed lesions also known as "white heads," or open, also known as "black heads." The dark color is a result of sebum oxidation, which is why it is black. Papules, pustules, nodules, and cysts are inflammatory lesions. Papules are raised red spots on the skin, whereas pustules are the same but include a little amount of pus in the center. Nodules are large, hard lesions that are more than 5 cm in diameter and have become firmly indurated as a result of the inflammation [(8)]. Typically, the lesion is painless and itchless, however, itchiness or pain may accompany it in some situations [(9)].

There are two outcomes to acne: either it goes away on its own with no sequelae, or it leaves erythema, post-inflammatory hypo-or hyperpigmentation, or scarring which can be either atrophic or hypertrophic but more usually is atrophic [(10)].

Treatment:

General lifestyle changes such as reducing high glycemic diets, avoiding oil-based cleansers that clog pores, and using cleansers no more than twice daily are critical to the effectiveness of medical treatment [(11)]. Alkaline soap (9-10 PH) with various surfactants is recommended for acne patients as well [(12)].

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Topical Therapy:

1. Retinoids:

In acne treatment, retinoids, a class of vitamin A derivatives, are essential. To combat inflammation, they reduce Toll-like receptor expression on monocytes, while also reducing the production of microcomedones by inhibiting sebocyte hyperproliferation and differentiation. Lastly, they inhibit the manufacture of pro-inflammatory mediators such transcription factor activator protein, prostaglandins, and proinflammatory cytokines like Interleukin -6, Interleukin-12, Tumor necrosis factor α, and Interferon -γ [(13)].

Retinoids such as tretinoin, adapalene, and tazarotene are among the retinoids that can be used to treat acne. Several undesirable side effects such as photosensitivity, dryness, and exfoliation have been linked to the use of tretinoin. Adapalene is steadier and more tolerant than tretinoin in terms of adverse effects. While tazarotene falls under pregnancy category X, both tretinoin and adapalene are pregnancy category C [(14)].

2. Benzoyl peroxide (BP):

When used topically, it has antibacterial properties due to the generation of free nitric oxide, which is bactericidal yet it does not lead to antibiotic resistance. Retinoids should be taken in conjunction with this product [(15)]. It is safe to use during pregnancy. Bleaching and staining of clothing are two of the most typical undesirable side effects [(16)].

3. Topical antibiotics:

In the treatment of acne, the antibiotics erythromycin and clindamycin are the two most commonly prescribed options. They suppress protein synthesis by attaching to the 50s ribosome [(17)]. Erythema, itching, and exfoliation are the most common side effects. Topical clindamycin use has been linked to a very small number of occurrences of pseudomembranous colitis, so it is best to proceed with caution if the patient already has antibiotic-associated colitis [(18)]. Both medications fall under pregnancy category B, which means they can be taken in conjunction with benzoyl peroxide to treat acne while pregnant if necessary [(19)].

It is critical to use the correct topical therapeutic combinations to ensure the treatment's success. Combining retinoids and benzoyl peroxide is more effective than using them alone as monotherapy. This is the initial line of treatment for comedonal acne, but it is important to leave enough time between applications to avoid benzoyl peroxide inactivating the retinoids. The most common side effect is orange skin discoloration when benzoyl peroxide and dapsone are combined [(10)].

4. Azelaic acid (15% cream or 10% gel):

In addition to its anti-inflammatory and antibacterial properties, azelaic acid is a comedolytic. Additionally, it aids in the reduction of post-acne hyperpigmentation when used as an adjuvant. The most common side effects include stinging, dryness, exfoliation, hypopigmentation, and hypertrichosis, which normally go away after 8 weeks of continuous use because of the acidic qualities that can irritate sensory nerves. Even though it is pregnancy category B, there is no proof that it is safe to use on children just yet [(20)].

3. Topical dapsone (5% gel):

It is a synthetic sulphone antibacterial agent. When it comes to inflammatory lesions, it is important to keep this in mind as a good option for treatment, especially for women with darker skin. No need for testing G6PD deficiency even in high-risk populations, but a rare instance of hemolysis in a toddler taking trimethoprim antibiotics due to methemoglobinemia has been recorded [(21)].

6.Topical salicylic acid:

A beta-hydroxy acid called salicylic acid has been discovered to have keratolytic and anti-comedogenic effects. It has been given the green light to be utilized in the formulation of acne drugs, but it must be used in conjunction with other treatments regularly [(12)].

Intralesional corticosteroids:

Large nodules are treated with intralesional injections of corticosteroids, particularly triamcinolone acetonide. It has the advantage of flattening the lesion quickly, however adverse effects including atrophy or telangiectasia can occur. The dosage is typically 3 mg/ml [(22)].

Systemic therapy:

1. Systemic antibiotics:

Antibiotics from the tetracyclines family, such as tetracycline, doxycycline, and minocycline, are widely recommended to treat acne. In mild to moderate inflammatory acne, antibiotics are often the initial line of treatment. However, they are no longer utilized as monotherapy because of their systemic resistance adverse effect [(23)].

Additionally, tetracyclines have an anti-inflammatory impact because of the inhibition of chemotaxis and the reduction of proinflammatory cytokines, as well as matrix matelloproteinase activity [(24)].

In addition to their inability to be used during pregnancy and in children under 9 years, tetracycline most commonly reported side effects are photosensitivity and tooth discoloration [(25)].

Azithromycin use should be conserved only to pregnant women for the fear of bacterial resistance [(26)]. As a last resort, trimethoprim-sulphamethoxazole is used to treat patients when all other treatment options have failed [(27)].

2. Oral isotretinoin:

Isotretinoin, a systemic vitamin A derivative, is FDA approved for the treatment of severe recalcitrant acne or acne that was more likely to leave scars. It activates Forkhead box O1(Fox01) and FoxO3 proteins, which causes sebocyte death and suppresses sebogenesis. It also reduces the expression of Toll-like receptor (TLR)-2 on monocytes, which inhibits the release of cytokines [(28)].

The proper dose is between 0.5 and 1 mg/kg for a period of 16 to 30 weeks. The most common side effects are dryness of the skin, lips, and eyes, as well as an increase in blood triglycerides and cholesterol [29]. Isotretinoin has been linked in certain studies to inflammatory bowel illness, however, this has not yet been proven [30]. Depression is a serious side effect of isotretinoin, but acne is also linked to depression, particularly in adolescents. So, it is still up for debate, meanwhile, it is not recommended for use in patients who are depressed [31].

Hormonal Therapy:

Females exhibiting signs of hyperandrogenism, or flares before menstruation, or deep nodules on the face are candidates for hormone therapy. The majority of therapeutic options target suppression of androgen production or androgen receptor blockade [32].

1. Oral contraceptive pills (OCPs):

Oral contraceptive pills are authorized by the FDA as second-line medication in adolescent or adult females. There are three types of ethinyl estradiol available: ethinyl estradiol-norgestimate, ethinyl estradrospirenone, and norethindrone acetate [33]. Low-androgen progesterone was introduced to minimize the risk of malignancies linked to estrogen [34]. They are naturally antiandrogenic in their effects. Additionally, they raise the production of sex hormone-binding globulin (SHBG), which binds to free testosterone, lowering the total amount of testosterone in the body. In addition, they inhibit 5-α reductase activity, and ultimately, they inhibit androgen receptors [35].

Side effects include lower libido, increased risk of deep venous thrombus, pulmonary embolism, myocardial infarction, and estrogen-induced malignancies such as breast and endometrial malignancy [25].

2. Oral spironolactone:

It is indicated in females with hormonal acne when OCPs fail to manage it, especially in the setting of polycystic ovary syndrome, spironolactone is an off-label potassium-sparing diuretic given. It acts by of 5 alpha α activity and increases SHBG levels, so eventually, androgen levels drop [35].

3. Cyproterone acetate (CPA):

In cases of severe acne, this antiandrogen and progestin work wonders. Combining it with oral contraceptives maximizes its effectiveness. It works by inhibition of androstenedione synthesis from DHEA leading to a reduction in sebum production [25].

4. Metformin:

Acne associated with diabetes, insulin resistance, or polycystic ovary can all be improved with metformin, an anti-diabetic drug. It does this without causing hypoglycemia. It upregulates the P53 pathway, which in turn decreases the amount of insulin-induced mammalian target of rapamycin complex 1(mTORC1). Their use is based on the fact that acne's lesion development is mediated by mTORC1 **(29).** Women with PCO may take up to 2000 mg of this medication daily [19].

5. Corticosteroids:

Only severe cases of fulminant acne or acne-associated diseases warrant the use of low-dose short-term corticosteroids due to the potential for flare-ups from elevated androgens. It works by preventing the release of adrenal androgen [33].

Acne and light assisted therapy:

Light therapy works by generating oxygen-free radicals, suppressing the release of inflammatory cytokines, and shrinking the sebaceous glands' size and activity [28].

1. Photodynamic therapy (PDT):

Photodynamic therapy relies on the usage of a photosensitizing chemical that is applied topically before being exposed to the light source. It creates reactive oxygen species upon activation by light, which leads to destroying the cells it is applied to. Additionally, Cutibacterium acnes creates a rare porphyrin molecule capable of absorbing blue light (415 nm). This porphyrin molecule releases free radical molecules when it absorbs blue light, which leads to the killing of the bacteria itself [29].

2. Intense pulsed light (IPL) (400nm-1200nm):

Cutibacterium acnes' porphyrin degradation is activated by polychromatic high-intensity pulsed light. Endogenous chromophores absorb light in a way that damages the blood vessels that supply the gland, which in turn reduces sebaceous gland activity [31]. Tumor necrosis factor-alpha (TNF-α) is believed to be lowered by IPL while transforming growth factor-beta (TGF-β) is increased, which all in all has an anti-inflammatory effect [28].

3. Pulsed dye laser (PDL):

It is a type of laser used for the treatment of inflammatory acne. This Laser chromophore is oxyhemoglobin After absorbing the laser energy by the chromophore, it pushes dilated blood vessels to be selectively photothermolyzed, also targets cutaneous immune activation. When used to heal acne scars, it causes dermal remodeling. As an added benefit, it works by causing new collagen to be synthesized via the stimulation of transforming growth factor B (TGF-β) [30].

4. Ablative laser for scarring:

Post acne scars can be successfully treated with fractional CO2 laser resurfacing (10,600 nm wavelength). Water is the chromophore target for energy absorption. Microthermal zones (MTZ) are created which are coagulation and dermal remodeling zones bordered by ablated, vaporized tissue columns. Resurfacing with Er: YAG (Fractional Ablative Erbium: Yttrium–Aluminum Garnet) (2,940 nm) is possible. It has fewer adverse effects than CO2 laser resurfacing, and you have more control over how deep the laser penetrates. The second method of Er: YAG resurfacing procedure is known as dual-mode. Short-

pulsed Er: YAG lasers and Nd-YAG lasers produce the best outcomes for people with darker skin tones [30].

5. Non-ablative laser for scarring:

There is only a 40-50 % efficacy after numerous treatment sessions for non-ablative lasers such as the Nd-YAG at 1064 nm and the 1450 nm diode laser. This method is used for shallow boxcar scars [31].

Acne and peeling:

The possible role of peeling is to reduce inflammation, reduce lesion count, and enhance skin texture. In comedonal and papulopustular acne, superficial peels can be used as adjuvant treatment; however, they cannot be utilized on nodulocystic types of acne. Peels include 20-30% salicylic acid (SA), 70 % glycolic acid (GA), 40-60% pyruvic acid (PA), 20-25% mandelic acid (MA), Jessner's solution (JS), and 10% trichloroacetic acid (TCA) [31].

Chemical Reconstruction of Skin Scars (CROSS technique):

Focused treatment of high-concentration trichloroacetic acid has shown significant improvement in ice pick scars**.** When used on scars of all types, including severe boxcar scars, 70% TCA CROSS shows remarkable improvement. Dark-skinned persons with ice pick scars can benefit from TCA CROSS as an effective treatment option. It was discovered that CO2 pinpoint radiotherapy was better than TCA CROSS for the treatment of ice pick scars [30].

Physical methods:

Comedone extraction:

Cryotherapy: Large chronic nodules can be treated with two 15-30 second freeze-thaw cycles**.** Devices that use Selective Cryolysis came next. The sebaceous glands' output was shown to be reduced in just two weeks after being exposed to temperatures as low as -20 C for 20-minute cycles. Due to the possibility of concomitant hypopigmentation, this method use is still under conservation [28].

Subcision: It is a method in which a needle is repeatedly inserted under the skin in various directions. Fibrotic strands under the scar are severed and released as a mechanism for scar treatment. The best candidate type of scar is rolling acne scars, while when used in treating boxcar and ice pick scars it showed not to be as successful [28].

Novel agents for acne management:

New Topical Agents for acne management:

1. Triafortene is a fourth-generation retinoid that has shown promise in the treatment of acne on the face and the trunk. It is a selective retinoic acid receptor (RAR) agonist [28].

2. Nitric oxide gels: Antimicrobial activity against Cutibacterium acnes is provided by the NVN1000 gel by the release of nitric oxide, also it exerts some immunomodulatory effect by inhibition of proinflammatory cytokines such as IL-1β, TNF-α, IL 8, and IL-6 [28].

3. Minocycline foam: In general minocycline and other tetracyclines have a lower resistance rate than erythromycin and clindamycin. Minocycline has the least resistance rate. There is a new topical tetracycline called minocycline foam which had been innovated for the treatment of nodulocystic acne. It is equally effective as systemic tetracyclines but has none of the adverse effects. It doesn't cause allergic reactions or inflammation, or phototoxic adverse effects [33].

4. Omiganon pentachloride: It is a cationic antimicrobial peptide. It is a topical bovine indolicidin derivative that has an antimicrobial (gram-positive and gram-negative) and antifungal spectrum. It also disrupts the cell membrane causing depolarization and cell death. Trials of using it as an anti-acne agent had been successful [29].

5.Epigallocatechin gallate (EGCG):

Green tea polyphenol is the active ingredient in this topical solution. It blocks sebogenesis by preventing the mTORC1 kinase from responding to Insulin growth factor-1 stimulation. It reduces the amount of IL-1 α and downregulates the nuclear factor-kappa B and activator protein pathways to control hyperproliferation. Additionally, it prevents the enzyme 5-α reductase from working [30].

6. Olumacostat glasaretil (OG): In studies on acne vulgaris, it was found to be an effective inhibitor of the acetyl CoA carboxylase (ACC) enzyme. The denovo fatty acid synthesis is inhibited when ACC is inhibited, and this prevents excessive sebum production. Cutibacterium acnes proliferation and biofilm formation could be inhibited by it, too [29].

7. Topical nicotinamide gel: It is the amide form of niacin which is a vitamin B3 derivative. It reduces acne through several processes. It reduces sebum production and enhances the barrier function of the epidermis against Cutibacterium acnes by increasing ceramide synthesis in the skin [29].

8. Topical Cortexolone 17α-propionate (C17AP) 1% cream: It is a synthetic steroidal antiandrogen that reduces androgen-induced sebum production by inhibiting androgen-to-androgen receptor peripheral binding. Because of its antiandrogenic qualities, this compound shows promise but it should only be used by women [30].

9. Topical probiotics: Lactobacillus genus species Enterococcus faecalis SL-5 was isolated from human feces and used in lotion form. It works against C. acnes as a bacteriocin [31].

10. Lupeol: Solanum melongena L. plant produces triterpene, a pentacyclic compound. Researchers found that taking Lupeol twice a day reduced the expression of several genes including Sterol regulatory-element binding proteins-1 (SREBP-1) and keratin 16. It was found that the inflammatory infiltration around the pilosebaceous unit (PSU) was reduced by its use,

proving that it can inhibit lipogenesis and Interleukin 1 driven comedone development [31].

11. Vitamin C loaded adapalene: Vitamin C is well-known for its ability to speed up collagen production. Post-acne hyperpigmentation may be helped by this new formula because it is an antioxidant and depigmenting agent. New adapalene-enriched vitamin C compositions have emerged, and they perform better than pure adapalene [32].

12. Next science acne gel (NAG): new gel containing isopropyl alcohol and a surfactant that solubilizes extracellular polysaccharide polymers encapsulated in biofilms, which reduces the risk of antibiotic resistance while having no negative effects on the skin of patients [32].

Novel systemic agents in the management of acne:

1. **Oral zinc:** Oral zinc supplementation has been shown in several trials to reduce the number of acne lesions. It also heals lesions and reduces inflammation [34].
2. **Sarecyclin:** Due to its relatively small spectrum, this new generation narrow-spectrum tetracycline demonstrates remarkable success in treating moderate to severe facial acne. When compared to standard tetracyclines, it has a lower resistance rate and fewer gastrointestinal side effects [22].
3. **Tyrothrin:** It is an experimental antibiotic generated by Bacillus brevis that targets C. acnes at a more precise structural level. It also has a broad spectrum of antibacterial activity against Gram-positive bacteria [14].
4. **Pentobra:** it is a brand-new antibiotic made from tobramycin conjugated to a short 12-amino-acid peptide to make a composite molecule. There was evidence that it was effective in killing Cutibacterium acnes while also suppressing some of the chemokines that lead to inflammatory changes in acnes [13].

Acne patients can now also benefit from Botox injections as a treatment option. In the sebaceous glands, acetylcholine (Ach) stimulates lipogenesis by binding to the Ach receptor α 7. Botox blocks the presynaptic release of acetylcholine, which reduces the quantity of sebum generated and the size of pores on oily skin [13].

Anti-IL17 and anti-IL-1 biologics theoretically can be of utility in the treatment of acne, but biological therapies are costly and have a wide range of adverse effects, therefore this line is only used in the most severe forms of the condition, acne fulminans for example, or research purposes [13].

Another method of combating the condition that is currently being developed is vaccines that target certain antigenic structures of the C. acnes bacterium. A vaccination targeting cell wall anchored sialidase, which is involved in the attachment of C. acnes to sebocytes. IL-8-induced inflammation is countered by a vaccination that targets the Calmodulin-regulated spectrin-associated protein 2 (CAMP2) factor protein that had been tested in mice. However, mice, unlike people, are not naturally colonized by the acne-causing bacteria, so the outcomes of these vaccine trials should be interpreted with care until adequate human studies have been conducted [13].

CONCLUSION

Several modalities have been introduced to treat acne vulgaris including topical, systemic, light assisted, and novel topical agents like Triafortene and Nitric oxide gels.

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