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Review

A Review on the Advances in the Treatment of Moderate to Severe Acne Vulgaris

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Abstract

Acne vulgaris is a common, chronic inflammatory disease of the skin, and can lead to physical and psychological scarring. Treatment options are reviewed, including topical and oral medications, lasers and light therapies. There have been many advances in the management of moderate to severe acne vulgaris. Currently, oral isotretinoin remains the gold standard therapy. Most topical and systemic treatment modalities for patients with moderate to severe acne vulgaris are inconvenient and have side effects.

Introduction

Acne vulgaris is a multifactorial and frequently recurring inflammatory disease of pilosebaceous follicles in the skin, commonly affecting the face, neck, upper back, chest and upper arms, as these sites are densely populated with sebaceous glands [1-3]. It is clinically characterized by excessive greasiness of the skin[4] and polymorphic non-inflammatory lesions (open and closed comedones) and inflammatory lesions like papules, pustules, nodules, cysts and abscesses which are often painful with disfiguring scarring as a common sequel [5].

Acne vulgaris is a chronic skin disease with more than 90% prevalence during lifetime [6]. It is one of the most common reasons behind permanent facial scarring [7]. Acne vulgaris causes significant psychosocial morbidity [8]. It is no longer perceived as the 'disease of teenage years' since a subset of people experience the condition throughout their adulthood [9].

In acne vulgaris, the selection of treatment is difficult because assessing severity itself is challenging. Therefore, it should depend on a proper history, physical examination, previous treatment and response to it. In recent years, combination therapy has become an integral part of the acne regimen. There are various treatment modalities for acne vulgaris involving topical and systemic drugs, depending on the severity. Topicals used are Benzoyl Peroxide (BPO), Azelaic acid, salicylic acid, retinoids (vitamin A derivative-Tretinoin, Adapalene, Tazarotene, Isotretinoin) [10]. There are some minor side effects with topical retinoids such as skin dryness, peeling, burning, pruritus and erythema [11]. Topical antibiotics include tetracycline, clindamycin [13]. All of these are available in various formulations such as gels, creams or lotions [12]. Systemic drugs include isotretinoin and antibiotics [10,12]. Hormonal therapy is administered in females if the acne is associated with hormonal symptoms.The combined oral contraceptive (COC) helps in the treatment of acne due to its anti-androgenic effect [13]. Although oral isotretinoin is the standard treatment for moderate to severe acne vulgaris, post-isotretinoin acne can occur [14]. Therefore, maintenance therapy following treatment with systemic antibiotic or isotretinoin will be beneficial, by preventing *Propionibacterium* acnes (*P.acnes*) colonization and formation of new microcomedones [15].

Growing public health concern for antibiotic resistance, scarring, pigmentation and patient non-compliance due to the side effects of conventional drugs like excessive skin irritation and depression has lead to the development of alternatives. Physical methods generally include chemical peeling, laser ablation, and surgery for the treatment of acne in order to prevent acne scarring rather than the disease itself [10].

Discussion

Impact on quality of life

Acne vulgaris is one of the most common inflammatory skin diseases affecting about 80% of adolescents and young adults [16]. Acne vulgaris can significantly affect quality of life [8]. Besides physical symptoms like soreness, itching and pain, acne vulgaris can leave patients with psychological scars. Although acne is not life threatening, it imposes a huge negative impact on patients, leading to anxiety, depression, embarrassment, lack of self-esteem and self confidence, body dissatisfaction and social isolation [17]. Anger is inversely proportional not only to the patient's quality of life but also on treatment outcome satisfaction [18]. These issues can interfere with their physical and mental growth, since acne peaks during adolescence, a time that builds an individual's self confidence and self-esteem. Comparative studies have revealed that patients with acne vulgaris had similar levels of emotional, psychological and social disability as those seen in patients with chronic illnesses like asthma, atopic dermatitis, psoriasis, alopecia areata, epilepsy, arthritis and diabetes [10,19-21]. These patients have high levels of stress and stress itself is an aggravating factor. Hence, reducing psychological disability in these individuals is an integral part of acne management, besides assessing the negative impact caused by acne vulgaris [3].

Psychosocial disability can be measured using questionnaires such as the Cardiff Acne Disability Index, [22] Leeds Assessment of the Psychological and Social Effects of Acne [23] and Dermatology Life Quality Index (DLQI) [24].

Causes of acne vulgaris

There are several risk factors for acne such as genetic predisposition, influence of certain hormones, obesity and stress, and certain beliefs including diet, skin hygiene and sunlight, that are yet to be explored by researchers and might help to play a role in causing acne vulgaris.

Diet: Several studies have examined the association between acne and diet. A high prevalence of acne has been noted in western societies where food is typically rich in high glycaemic index (HGI) and hence is a disease of the western civilization [25,26,27]. This was proposed by Cordain et al. [28] whose study found an obvious absence of acne in individuals consuming a non-western diet in Papua New Guinea and Paraguay. A number of researchers have found a link between high glycaemic diet and hyperinsulinaemia causing androgen mediated sebum production and hyperkeratinisation [29,30,31]. Therefore, glycaemic load is the measure of raised blood glucose and insulin increasing the potential of food related hyperinsulinaemia and acne [32]. Smith et al. [33] conducted a randomized controlled trial that found an association between low glycaemic diet and reduced severity of acne study. However, a study by Reynolds et al. [34] did not achieve a significant difference in acne severity by altering glycaemic index and glycaemic load. Since this study was conducted over a short period of time of 8 weeks, well-designed prospective studies are required to answer the shortcomings. Previously there have been studies to examine the association between chocolates and acne; however, the results were insignificant [35]. A close link between moderate to severe acne and a high intake of milk, sweets and cakes and other dairy products have been found [36]. In addition, association between low intake of fish and obesity have been found [36]. On the other hand, BMI less than 18.5, high intake of fish, fruit and vegetables were all linked to limited or no acne [36]. The acne aggravating factor of milk and dairy products is multi-factorial. High milk intake increases insulin-like growth factor-1(IGF) and insulin concentrations [37]. On the opposite, inflammatory cytokine production is suppressed by diet rich in n-3 polyunsaturated fatty acids, including fish, thus limiting acne [38].

Genetic Factors: Numerous twin studies suggest that acne is an inherited disease [39-41]. A large twin study conducted by Bataille et al. [42] on adult acne patients revealed significant familial clustering and genetic predisposition. These results were similar to earlier twin studies done by authors Friedman et al. [43] and Kirk et al. [44] that reported heritability estimates between 50% and 90%. A study in the UK by Goulden et al. [45] found that acne was four times more prevalent amongst the first degree relatives of 204 patients with acne vulgaris than the first degree relatives of 144 controls. *Pilosebaceous* units are more sensitive to androgens in genetically susceptible individuals [46]. Hence, acne patients build up an immune response to *P. acnes* that is not seen in unaffected individuals [47]. Hence, there is a greater risk of developing acne in the presence of a positive family history [48].

Environmental Factors: Environmental factors have been implicated in acne but stronger evidence is required to confirm the association [49]. Most acne patients believe that dirt aggravates acne and end up with frequent face washing [41,50]. However, studies have shown that excessive face washing exacerbates acne [50]. Few studies suggest that sunlight is beneficial for acne [51], however, acne get worsened due to sunlight [52]. Furthermore, heat and humidity can trigger acne [41]. Therefore, it can be concluded that external factors related to environment can precipitate acne, however, these implications are not convincing. Hence, larger randomized studies are required for conclusive evidence.

Stress: A study by Chin et al. [53] showed that stress during examinations can aggravate acne; however, it did not have any effect on excess sebum production. In one survey conducted by Smith et al. [54] on 178 acne cases, stress was found to be a triggering factor for acne in about 74% cases. Acne itself precipitates stress and stress causes acne, and hence it is a never ending cycle.

Smoking: There have been contradictory studies linking smoking and acne. Earlier studies proposed that smoking was

inversely linked to acne [55]. However, recent studies suggest that smoking is directly proportional to the severity of acne [56,57]. This was revealed in a study conducted by Schafer et al. [56] that showed a significant association between smoking and increased rates of acne and severity. A study by Yang et al. [58] was done on 22 adult non-smokers and 21 adult smoker acne patients to investigate the relationship between Lipid peroxidase (LPO) and proinflammatory cytokines in the extracted comedones of smoking and non-smoking acne patients with clinical differences in terms of severity and acne lesions distribution. Study revealed relative higher levels of LPO and cytokine Interleukin-1 alpha (IL-1 alpha) in the extracted comedones of smokers than non- smoker acne patients suggesting positive correlation. However, there was no statistically significant difference in the acne lesions distribution, the severity of acne, and the levels of LPO and IL-1 alpha in the extracted comedones between the smoking and non-smoking acne patients. In conclusion, smoking may play an important role in the pathogenesis of acne only by inducing lipid peroxidation of sebum in comedones causing local increase in IL-1 alpha due to oxidative stress. Hence, smoking consequently leads to inflammation or abnormal follicular keratinization [58].The Similar results have been reported in a considerable number of studies; however, larger studies are needed to confirm this link.

Pathogenesis

The primary pathologic factors include excess sebum production, altered follicular keratinisation, follicular colonization of *Propionibacterium Acnes* (*P.acnes*), and inflammation [59].

Increased sebum production

Recent studies suggest that sebaceous glands are neuroendocrine inflammatory organs [59]. Hyperplasia of sebaceous glands in response to androgen hormones such as testosterone, adrenal dehydroepiandrosterone (DHEAS), androstenedione and dehydroepiandrosteronesulphate (DHEA-S) stimulates increased sebum production [60-63]. DHEAS is the chief regulator of androgenetic activity before adolescence and is responsible for non-inflammatory acne lesions in young acne patients [63]. In addition, insulin-like-growth factor 1 increases sebum production and vitamin D is also a regulator of sebum production like DHEAS [64].

Follicular hypercornification

Androgens, lipids, bacteria, cellular debris and cytokines induce hyperkeratinisation , leading to sebaceous gland obstruction [61]. Hence, the follicles become clogged and this produces a favourable microenvironment for *P.Acnes* bacterial growth [61,62]. This results in the formation of microcomedones which progresses to non-inflammatory lesions called 'macro-comedones', either open and/closed comedones. Closed comedones are whiteheads and open comedones are blackheads [61].

Propionibacterium Acnes (*P.acnes*) bacteria colonization

Propionibacterium acnes bacteria is a normal skin flora that flourishes in a triglyceride rich media [61]. Nonetheless, the severity of acne does not depend on the density of *P.acnes*. In a microcomedo, the bacteria breaks the lipid into free fatty acids causing further blockage of follicles and triggers an inflammatory response through activation of expression of Toll like receptors(TLRs) [61, 65].

Perifollicular inflammation

There is a cascade of inflammatory reactions of type 4 involving macrophages, neutrophils and CD4+ lymphocytes [61] and hence, formation of inflammatory acne lesions called papules, pustules, nodules and cysts [66-68]. However, the specific initial trigger that leads to the formation of acne is yet to be identified [65].

Free Radical Oxidation

Reactive oxygen species (ROS) and lipid peroxide (LPO) are the oxidative stress components, are involved in stages of the pathogenesis and progression of acne vulgaris. Free radicals are formed during the formation of ROS by oxygen acquiring an electron, and these free radicals has further the ability to form other ROS, such as peroxides. As a result, there is an oxidative damage to the skin such as lipid peroxidation and secretion of inflammatory cytokines as skin is always exposed to the ROS induced oxidative stress, both from internal and external sources [69].

Advances in the Treatment of Moderate to Severe Acne Vulgaris

Topical Therapies

Combination Therapy: Recent studies suggest topical retinoid and an antimicrobial agent combination therapy to be the first-line treatment for moderate and severe acne [59]. Greater efficacy is obtained through synergistic action as various drugs target more than one pathogenic factor and acne is a multifactorial disease.Among various fixed dose combinations, numerous double blind randomized controlled trials have shown the benefits of the fixed dose combination of topical retinoid adapalene 0.1% and the antimicrobial BPO 2.5% [70]. Retinoids normalize the abnormal follicular hyperkeratinisation and prevent scarring via transcription factors which are not exerted by the anti-microbial agents. Conversely, antimicrobials have superior anti-inflammatory effects. Combination treatment improves inflammatory acne in as early as 2 weeks with less irritation compared to monotherapy [59]. Therefore, effective combination treatment shortens the duration of treatment [59]. Moreover, combination of retinoid and/or BPO with oral antibiotic has been widely promoted, as both agents reduce the development of anti-microbial resistance [70]. Although oral isotretinoin is reserved for

severe recalcitrant acne vulgaris; for patients who cannot tolerate the side-effects or have contraindications to this treatment, combination therapy is justified and recommended as the first alternative [70].

A multi-center randomized double-blind controlled trial in 1670 patients was conducted by Gollnick et al. [71] in the USA, Canada and Europe in which subjects received adapalene 0.1%-BPO 2.5%, adapalene 0.1%, BPO 2.5% or vehicle (1:1:1:1), once daily in the evening for 12 weeks. 87.4% of subjects completed the trial. The authors concluded that a fixed dose combination gel adapalene-BPO was significantly more effective in decreasing lesion counts, observed as early as 1 week. An investigator evaluated the success rate as clear and almost clear, and the patients themselves as complete improvement and increased improvement at week 12. Increased patient compliance was noticed by decreased side effects in comparison to corresponding monotherapies. However, the limitations of this study were that firstly it had excluded patients who required oral isotretinoin due to severity of the disease. Secondly, it assessed lesions only on the face but excluded the nose. Thirdly, the sample size was large, but its calculation was based on the assumptions of a previous study. On the other hand, it produced strong evidence to support that combination therapy worked better. Another study by Feldman et al. [72] with the same combination produced the same outcome but was more efficacious in patients with higher baseline lesion counts. Adapalene has comedolytic and anti-inflammatory properties [72] while BPO is a potent bactericidal [72]. Hence both drugs complement each other and therefore, a more efficacious outcome is seen in both studies. The studies above illustrates that combination therapies can be more effective in treating acne vulgaris than monotherapies.

Thiboutot et al. [73] examined the efficacy of a combination of two antimicrobials; clindamycin phosphate (CL) 1.2% -BPO 2.5% gel and individual agents with once daily application in 2 large similar, multi-center, double blinded randomized controlled trials in 2813 subjects for 12 weeks. 2492 patients had completed the trial. Maximum subjects were from the CL-BPO 2.5% group. Intent to treat analysis included all patients who had participated. The study revealed that combination therapy was highly efficacious, well tolerated and safe in comparison to monotherapies. Several previous studies combining BPO with tetracyclines and macrolides showed similar efficacy, but greater antimicrobial resistance [73]. The strength of this study was that it had stratified subjects into 4 groups based on both Fitzpatrick skin phototypes (1-6) and acne severity before randomization. Another randomized study in Japan by Kobayashi and his colleagues [59] in January-December 2009 on 50 outpatients obtained a similar outcome but with the combination of the widely prescribed topical nadifloxacin cream (antibiotic) and adapalene gel (retinoid). All of the above studies included patients above 12 years of age with moderate to severe/only severe acne vulgaris and excluded all pregnant and nursing women. Several clinical trials, including the above studies, have established that the mentioned drugs when used in combination as part of an acne regimen are more effective than when used as monotherapy. Due to antibiotic resistance and limited action on comedogenesis, antibiotics are prescribed concomitantly with topical retinoid or BPO to enhance efficacy.

Topical Monotherapy: Multiple clinical trials have demonstrated azelaic acid to be effective in reducing lesion counts owing to its comedolytic and antimicrobial actions [10]. It alters epidermal keratinisation and reduces *P.acnes* population [74,75]. Advanced topical gel formulation of dapsone with greater efficacy and minimal side effects is available now. Previously, dapsone, a sulfone drug with antimicrobial and anti-inflammatory actions in nodulo-cystic acne, was prescribed but later became less popular due to systemic side effects [76]. It causes haemolysis of red blood cells especially in patients with glucose-6-phosphate (G6PD) enzyme deficiency who are more prone to develop haemolytic anaemia [77]. It is proposed that dapsone probably acts by directly inhibiting transfer and production of leucocytes and its chemical mediators in response to inflammation [76]. It is also suggested that it possibly acts indirectly by modulating the *P.acnes* level and/or it acts like other sulphonamides due to its structural similarity [76].

Systemic Therapies

Oral Antibiotic: Antibiotics are traditionally the first-line therapy in inflammatory acne. As primary treatment in moderate to severe acne vulgaris, careful prescription of oral antibiotic is important to achieve a higher therapeutic effect. Excessive use of antibiotics has led to increasing emergence of P. acnes antibiotic resistance universally, estimated at 51% -94% in Europe [78]. Several studies now suggest a greater use of topical and systemic retinoids than antibiotics [25]. Oral antibiotics act by reducing the *P.acnes* colony in the microcomedo, [79, 80] decreasing sebum free fatty acids and extracellular lipases along with neutrophil chemotaxis and their inhibitory effect on matrix metalloproteinase (MMP-9) and cytokines [81]. Most common antibiotics prescribed are first generation cyclines (tetracycline HCL and oxytetracycline) and second generation cyclines (doxycycline, minocycline and lymecycline). Second generation cyclines are more expensive [82] but have a better pharmacokinetic profile, hence thought to have better efficacy than first generation tetracyclines [82]. More recent studies suggest oral lymecycline to be the most suitable first-line treatment in moderate and severe cases of acne vulgaris [70].

Most tetracyclines are well tolerated; transient mild gastrointestinal disturbance being the most common side effect [82]. Doxycycline causes photosensitivity dependent on dose, skin phototype and UVA intensity [120]. There is no conclusive evidence that one antibiotic is better than the other or that combination therapy is less effective than oral

antibiotics for mild to moderate cases of acne [83]. Furthermore, there is no consensus on the optimal dosing of oral antibiotics in acne [84].

J Adawiyah et al. [78] examined oral antibiotic treatment outcomes in acne vulgaris on 250 outpatients in Malaysia between 2005 and 2009 and concluded that systemic antibiotic achieved a better response in combination with BPO and retinoid than on its own. Moreover, doxycycline as first line oral antibiotic is best due to its higher efficacy, rapid onset of action and lower resistance to *P.acnes* compared to tetracycline . In addition, he suggested that an antibiotic should be used for six to eight weeks at least and for a maximum of 12 to 24 weeks. In contrast, another study by Fernandez and colleagues [85] found antibiotics (doxycycline, tetracycline and minocycline) less effective compared to azithromycin(250 mg/day for 3 days/week) in reducing lesions by 77.1% and 85% respectively at the end of 4 weeks. In spite of antibiotic being the first line of treatment, it requires judicious use due to the emergence of *P.acnes* resistance. Moreover, the choice of antibiotic should depend on patient compliance, cost effectiveness and side effects of the drug.

Oral Isotretinoin: When acne vulgaris is severe nodulo-cystic and non-responsive to combined antibiotic or topical therapies, it demands oral isotretinoin [12]. Earlier, it was reserved for severe acne vulgaris but now it is recommended off label for moderate cases of acne [86]. Isotretinoin (13 cis-retinoic acid), is the single most effective drug that acts by targeting all four pathogenic factors [87] and has been approved by the Food and Drug Administration (FDA) for treating severe acne since 1982 [6]. It is also indicated in acne with severe scarring, acne with severe psychosocial impairment and extensive facial and truncal acne [88]. Daily dosage is 0.5-1.0 mg/kg of body weight per day for 4-8 months [89,12,86] with a clinical cure rate as high as 85% [90-92]. It needs to be taken after meals due to increased bioavailability and can be increased till a cumulative dose of 120-150 mg/kg has been achieved [12]. However, recent studies recommend a low dose regimen to overcome the serious side effects associated with the conventional high dose [12]. Furthermore, treatment may be initiated with conventional high dose for the first eight weeks followed by low dose maintenance since a low cumulative dose often results in relapse [86].

Authors Dhir R et al. [93] did a comparative study to determine the efficacy of oral isotretinoin with and without topical combination therapy, in which group A received oral isotretinoin 20 mg twice daily with topical clindamycin 1% during daytime and adapalene 0.1% at night. The other group B received oral isotretinoin only at the same dose 2 times daily. It was an open label and randomized study, carried out in India on 60 patients with nodulocystic acne for 24 weeks. Thirty five patients completed 6 months follow up. The comparison study revealed a reduction in lesions to 90.55% in group A and 88% in group B, with common and less severe side effects in both groups. The author concluded that oral isotretinoin alone showed excellent response. However, the limitation of this study is that the sample size was small and the cumulative dose was 120 mg/kg/wt which is high as recent studies show oral isotretinoin to be equally effective with lesser side effects in low doses.

A study was conducted by Lee et al. [94] in Korea on 60 patients with moderate acne and intervention included low dose (0.25-0.4 mg⁄kg⁄day), intermittent dose (0.5-0.7 mg⁄kg⁄-day for 1 out of every 4 weeks) and conventional dose (0.5-0.7 mg⁄kg/day) of oral isotretinoin. According to the authors, this study is the first of its kind that aimed to evaluate simultaneously the efficacy and tolerability of low dose and intermittent dose regimens and compare them directly with the standard dose of oral isotretinoin. Furthermore, a 1 year follow-up assessment was carried out to investigate the relapse rate and long term effectiveness of each therapeutic regimen for each group. It was a prospective, assessor blinded, open, randomized controlled trial of 24 weeks. The total period of treatment in the group receiving intermittent dose was 6 weeks and 24 weeks for other groups respectively. Double blinding was not possible; hence the therapists and the patients were not blinded. This could lead to some potential bias, despite this, the study has few strengths. Firstly, the assessor was blinded to group assignment during collection of data and while measuring the outcome. Secondly, patients were randomized in a 1:1:1 ratio using a computer generated randomization. Therefore, the authors ensured that selection bias was limited. All of the patients had given their consent. Out of 60 patients, 20 were men and 40 were women with moderate acne at baseline in all treatment groups, with twenty subjects being recruited to three different regimen groups. Patients who had not responded to antibiotic therapy previously or had relapsed following treatment with antibiotic were included. However, other forms of severe acne cases or with a previous history of oral isotretinoin and contraceptive or other anti-acne therapies were excluded as well as pregnant and lactating females. Evaluation included global acne grading system (GAGS) scores, lesion counts (inflammatory and non-inflammatory) at 0, 12 and 24 weeks; patient satisfaction at the end of the study on a four point scale (4, very satisfied; 3, satisfied; 2, slightly satisfied; 1 dissatisfied); and side effects at each visit. In addition, full blood counts, liver function tests and lipid profile of every patient were evaluated at 0, 12 and 24 weeks. Relapse rate at the end of 1 year following treatment was also assessed and Gags score measured for every patient. Statistically there was no significant difference between the low dose and the conventional high dose regimen groups. Maximum side effects were seen in the conventional treatment group. Moreover, highest patient satisfaction was noted in the low dose treatment group followed by intermittent dose therapy group due to fewer dose dependent side effects. However, recurrence rate was highest in the latter group. Despite limitations such as a small study group, the study has significant implications in clinical practice. Treatment with low dose oral isotretinoin is safe, tolerable and as effective as

conventional dose, including patient compliance. Therefore it can be recommended to patients with moderate acne for 6 months. However, future studies on larger groups are required to confirm the findings.

Oral isotretinoin has many mucocutaneous and systemic side effects such as erythema, severe dryness of lips, eyes, nose and skin, fatigue, muscle cramps, elevation of serum cholesterol, serum triglycerides, liver Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) [12,93,94]. Therefore, patients require regular clinical and laboratory monitoring before and during therapy. Tests include complete blood count, serum liver enzymes and lipids, urine pregnancy test in females because of its teratogenicity and patients should also be asked about mood swings [89,12,86,93]. Liver enzymes and serum lipids are checked before and 1 month after initiation of treatment, followed by monitoring every 3 months and a monthly pregnancy test in females throughout the entire course of therapy according to European Directive [95] Isotretinoin is teratogenic and therefore contraindicated in pregnancy; hence contraception in patients of reproductive age during the treatment is obligatory [12] Due to the side effects, patients often have difficulty in tolerating and continuing the conventional treatment [86,94].

Several cases of acne with higher risks of psychiatric adverse effects associated with isotretinoin have been reported by both the FDA and World Health Organization compared to other acne treatments. Furthermore, isotretinoin ranks 4th and 7th for all drugs causing depression and suicide respectively [6]. Many authors have stated psychological effects due to isotretinoin like anxiety, depression and suicidal tendency but sufficient evidence is currently unavailable [5,89,12,78,93]. This could be due to the fact that prevalence of depression in acne patients is 1% and 8-10% in the general population [6]. A study was conducted by Simic et al. [89] on 85 patients with moderate to severe acne vulgaris and found no significant link between isotretinoin and psychological impact. In another cohort study by Chia et al. [5] on 110 adolescent patients with moderate to severe acne vulgaris, authors evaluated the depressive symptoms in patients during their 4 months therapy with isotretinoin. However, there was no strong evidence to prove an association between isotretinoin and depression. Ergun and colleagues [6] conducted a prospective, multicentre study on 63 patients with severe/resistant acne receiving isotretinoin. The authors were aware of the studies done previously on animals that had showed negative effects of isotretinoin on memory and learning. However, sufficient data were lacking in humans, hence this study was aimed to assess the adverse effects of isotretinoin on cognitive functions, anger levels and its expression, short term memory and mood. Authors concluded that isotretinoin causes no detrimental effects. However, a major limitation of this study is that the sample size was small. Another limitation is that the tests used may not have been sensitive enough to identify the little changes on learning effects related to the drug and 'learning' is a very important aspect of cognitive function. On the contrary, a remarkable improvement was noticed in the patients' self confidence and interactive personality by author Kelly et al. [96] in a study on African- American patients with refractory nodulocystic acne.

Until now, isotretinoin has been the only drug that treats severe nodulocystic acne vulgaris successfully and is the single most effective advance in acne regimen. However, larger randomized controlled trials are required in future to confirm the possible link between isotretinoin and depression in acne patients.Recent studies have demonstrated that low dose and standard dose regimens have similar efficacy during, and 1 year after treatment [12,94]. The standard dose regimen is less tolerable due to many adverse effects, therefore, there is a low patient satisfaction score [94].

Hormonal Therapy: Several studies have revealed a link between Insulin like growth factor 1 (IGF), androgens and insulin particularly in women with polycystic ovary syndrome (PCOS) characterized by acne, hyperandrogenemia and hyperinsulinaemia [97]. Androgens responsible for causing acne are dihydrotestosterone (DHT), testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEA-S) [60].

Oral contraceptives: Oral contraceptive pills (OCPs) act by inhibiting the production of androgen from the ovaries and reducing testosterone levels in circulation [13]. In females with acne vulgaris and symptoms of hyperandrogenism (menstrual irregularity, hirsutism, alopecia, seborrhoea), combined oral contraceptive pills (COCs) are prescribed to control androgen mediated sebum production thereby reducing lesion counts [98]. In females with clinical signs of hyperandrogenism, a proper history, physical examination and investigations for hormone levels and pelvic organs ultrasonography are essential [99] Oestrogen component of COCs- ethinylestradiol (EE), and cyproterone acetate (CPA), an anti-androgen is a recognised hormonal anti-acne treatment [30]. Efficacy of CPA has been confirmed in numerous studies showing a reduction in acne lesions by 75-90% owing to its comedolytic property and ability in reducing sebum production. [100-102] OCPS consisting of cyproterone acetate in combination with ethinylestradiol improves acne by 50-75% [103,104]. A study by Kinne et al. [60] proved oral contraceptive pill (OCP) containing oestrogen (EE) and progesterone dienogest (DNG) to be more effective than placebo and equal to OCP containing EE/CPA.

Spironolactone (SL), an androgen receptor blocker, 100 mg daily dosage, is effective in treating acne, although not FDA approved [13]. The basis for dermatologists prescribing SL to female patients with acne vulgaris is that it inhibits the sebaceous gland activity and hence, lessens acne lesions by reducing androgen mediated sebum production [99]. It has been reported that patients with a greater tendency to have acne exhibit increased type 1-5-alpha reductase activity and

acne free skin of patients shows increased 17-beta-hydroxysteroid dehydrogenase activity [105]. Its mechanism of actions are clearing free circulating testosterone by increasing steroid hormone globulin binding (SHBG) with testosterone and enhancing liver hydroxylase enzymatic activity, consequently reducing 5-alpha reductase activity. In addition, locally, spironolactone inhibits testosterone and DHT binding by competing for androgen receptors [106]. In women, PCOS and congenital adrenal hyperplasia are frequent causes of high levels of circulating androgen with prevalence of PCOS being 3%-6% out of which apparently 23%-35% females have acne vulgaris [107,108]. Furthermore, one study had found that 83% of female patients with severe acne vulgaris had PCOS as an underlying cause [108]. Therefore, it can be concluded that in post-adolescent women or female patients with persistent acne or with clinical signs of hyperandrogenism; PCOS or other endocrinopathies should be highly suspected.Several studies have ascertained the effectiveness of spironolactone in female acne patients reporting 50-100% improvement with dosage 100-200 mg daily. [109-112]. Conversely, an effective outcome with less adverse effects with lower doses of 50-100 mg daily was also seen [113].

Insulin sensitizing agents: An association between hyperinsulinaemia and hyperandrogenism has been established. Insulin directly increases the sensitivity of androgen receptors on sebaceous glands. It has been found to be an important factor in PCOS cases. Therefore, any treatment such as a weight loss program or insulin-sensitizing agents like metformin and thiazolidinediones that decrease insulin levels would also decrease the state of hyperandrogenism. Hence, insulin sensitizing agents are helpful in the treatment of acne by improving PCOS [114-116].

Flutamide

Flutamide is a nonsteroidal androgen receptor blocker but since its affinity for the androgen receptor is less than that of spironolactone, higher doses, 500 mg/ day are required; although recent studies have proved lower doses of 250 mg/day to be effective as well [117-119]. A study by Paradesi et al. [120] was conducted on 230 Caucasian women with acne over a 15 year period to assess the long term efficacy and tolerability of flutamide in females with acne and seborrhoea. Patients received yearly reducing doses of 250, 125 and 62.5 mg of flutamide with or without OCPS. The study revealed that there was a significant decrease in acne in both groups; however, fewer side effects were seen in patients with lower doses of flutamide. Therefore, the author suggested low dose flutamide for treatment of acne to overcome serious side effects associated with flutamide such as hepatotoxicity. Side effects of flutamide include breast tenderness, hot flashes, gastrointestinal upset and decreased libido [121]. Treatment with flutamide warrants regular liver monitoring tests as cases of hepatic failure have been reported [122,123]. Nonetheless, side effects are dose dependent [124].

Corticosteroids: In adjunct to oral isotretinoin, potent corticosteroid is given orally, topically or Intralesionally only in nodulo-cystic acne during acne flare but for a very short period of time [98].

In conclusion, in hormone mediated and intractable acne, hormonal agents should be considered, particularly in females, by the dermatologists. Even in the absence of laboratory abnormalities, women respond well to hormonal therapy. Understanding the mechanism of action of various hormones on the sebaceous gland is important, therefore, more research is needed in future to help the emergence of newer treatments.

Maintenance Therapy

Maintenance treatment is noteworthy in patients with severe acne vulgaris due to its nature of relapse and chronicity [15]. A study by Leyden and his colleagues [125] examined the efficacy and safety of maintenance therapy with topical tazarotene and oral minocycline, or both, for 12 weeks on 189 patients with 99 drop outs. The authors concluded that patients with moderate to severe acne should be maintained on retinoid monotherapy so as to sustain improvement of acne lesions and minimize antibiotic exposure. Several similar studies concluded that, maintaining improvement following treatment with oral antibiotic or oral isotretinoin, was essential with retinoid / BPO or as a combination for preventing recurrences.

Physical Therapies

In recent times, some non-traditional treatments such as photodynamic therapy (PDT) and lasers have gained popularity over drugs.Physical therapies may be used concomitantly or as alternatives to traditional drugs [126] Photodynamic therapy is a disease site specific treatment modality. It is a two step process. The process involves application of a photosensitizer followed by irradiation of the target site with non-thermal visible light [126] PDT in combination with 5-aminolevulinic acid (ALA) is an effective treatment for facial acne vulgaris [2] ALA is the natural biosynthetic precursor of heme [126]. Topically applied ALA penetrates stratum corneum and is particularly absorbed by the target pilosebaceous unit and converted into protoporphyrin IX which can be activated by using Intense Pulsed Light (IPL), Pulsed Dye Lasers (PDL), blue light and 635 nm red light [2,126]. Some clinical trials demonstrated its application in moderate to severe acne vulgaris and found it to be effective [126]. Studies have shown that side effects can be reduced by using ALA-PDT with a short contact time [2]. Incubation time of 30-60 minutes has been recommended as a guideline for acne treatment since patients do not find long incubation time convenient [2]. Furthermore, there are side effects; including risk of oedema, crust formation, and pigmentation abnormalities associated with long incubation time [127]. However, the most successful incubation time of ALA-PDT is yet to be determined.

Light and Lasers	Mode of action	Reference	Patients and Time	Results
Non-Ablative Radiofrequency	Thermotherapy- Dermal heating inactivates P acne bacteria	Ruiz-Esparza et al. [10]	22 patients (20 pts-1 session, 2 patients- 2 sessions)	75% reduction in lesions in 18 patients, 25%-50 %-2 patients and no response in 2 patients
Intense Pulsed Light (IPL)	Light therapy (photo-inactivation of P acnes, photothermolysis of sebaceous glands)	Kawana et al. [13]	25 Japanese patients received 5 sessions at 1 week interval	Acne lesions reduced significantly to 12.9% (with dose 400-700 nm) and 11.7 % (870-1,200nm)
Topical ALA (5-aminolevulinic acid)-PDT	Suppression of bacteria in sebaceous follicles followed by its destruction	Wang et al. [126]	78 Chinese patients treated with 10% ALA for 3 hours followed by LED light	22% had excellent response after 1 session, 32% after 2 sessions and 44% after 3 sessions
Fractional 1320 nm Nd-Yag laser	Kills P acnes and destroys sebaceous glands	Deng et al. [129]	41 patients had 6 sessions at2 week interval (6 drop outs)	57% reduction in skin lesions and 30% decrease in sebum level

Table 1: Shows various types of physical methods examined on patients with severe acne vulgaris.

Recently IPL, with or without PDT has been suggested as an acne therapy due to its safety and efficacy. It is used in a variety of conditions including rosacea, hereditary benign telangiectasia, skin rejuvenation and solar lentigines. However, studies have shown its effectiveness with significant improvement in Caucasian skin only which was not reported in Asian skin. This difference in the result may be either due to an inappropriate waveband used on Asian skin or may be due to dissimilarity in skin response to light [128].

Lately, studies have shown that visible light activates endogenous porphyrins of *Pacnes* causing photo-destruction of the bacteria. Numerous studies have investigated the effectiveness of acne treatment with blue light with different success rates, since the wavelength of blue light is 415 nm is also the waveband for highest absorption of bacterial porphyrins [130].

In conclusion, several authors have suggested that the physical therapies like lasers and light are safe, efficacious and a good therapeutic option for treatment of moderate to severe acne vulgaris. However, such treatments require multiple sessions, are expensive, inaccessible and usually painful. Moreover, further well designed controlled studies are required to explore long term safety and efficacy.

Conclusion

Successful management of moderate-severe acne vulgaris requires consideration of individual patient factors like lifestyle and psychosocial impact, besides careful evaluation of severity of lesions. At present, there are various options for the treatment of acne vulgaris; however, none of them target all the pathophysiologic events except oral isotretinoin. Formerly, oral isotretinoin was the best drug of choice for severe cases only, although to be used with caution due to dose dependent side effects. Topical treatment may be limited by local side-effects and inadequate therapeutic response. However, combination treatment with various topical agents can improve the effectiveness and decrease the unwanted side-effects of topical monotherapy. Physical therapies like lights and lasers are novel treatments, effective in non-inflammatory and inflammatory acne, but cannot replace conventional drugs and are costly and less accessible to patients. In female patients, treatment failure is high despite many advances in acne therapy. Hence, hormonal treatment has been suggested as an alternative especially for those showing a hormonal pattern clinically. An antibiotic should be used with topical treatments such as BPO or retinoids, and not as monotherapy, in order to reduce potential resistance problems. Currently, oral isotretinoin remains the gold standard and the single most significant advance in terms of efficacy in the acne regimen for moderate to severe acne vulgaris that is not caused by primary underlying hormonal abnormality such as PCOS or prolactinoma. Lasers may be useful therapies for those patients who will respond to or tolerate conventional treatments. Alone, lasers may show efficacy, but complete clearance of acne is rarely achieved. Therefore, lasers show greater clinical improvements in combination with another modality of treatment. More studies are required in future to demonstrate significant synergistic effects among therapies such as topical agents, systemic treatment and laser therapies.

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