Azelaic Acid in The Treatment of Acne Vulgaris

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Abstract ***Acne vulgaris is a common chronic skin disease involving blockages and inflammation when hair follicles plug with oil and dead skin cells. It may result in the formation of blackheads, whiteheads, pinheads, large papules, pimples and scarring. Azelaic acid is a naturally occurring saturated mineral carbon dicarboxylic acid. Azelaic acid is used to treat acne for the following reasons: it possesses a middle range of antityrosinase activity, is inexpensive and more soluble to be incorporated into a base cream that other dicarboxylic acids. Azelaic acid has antimicrobial activity may attribute to inhibition of microbial cellular protein synthesis and direct anti inflammatory properties due to its scavengers activity of free oxygen radical which make it effective in treatment of acne vulgaris. It is effective against a number of skin conditions such as mild to moderate acne, when applied topically in a cream formulation of 20%. It works in part by stopping the growth of skin bacteria that cause acne. Preliminary clinical studies proved effectiveness of topical azelaic acid can be considered an effective therapy chiefly for papulo pustular acne.***

Index Terms— ANTIMICROBIAL, ACNE VULGARIS, AZELAIC ACID, TOPICAL.

I. INTRODUCTION

Acne vulgaris is a human skin disease characterized by skin with scaly red skin (seborrhea), blackheads and whiteheads (comedones), pinheads (papules), large papules (nodules).Pimples and scarring [1]. Acne affects skin having dense sebaceous follicles in areas including face, chest and back [2]. Acne may be of inflammatory or non-inflammatory forms [3]. Due to changes in pilosebaceous unit's lessons are caused by androgen stimulation, acne occurs commonly during adolescence, affecting about 80-90% of teenagers in the western world and lower rate are reported in rural societies [4,7]. Management of adult acne requires a specific diagnostic and therapeutic approach; factors such as use of cosmetic products, certain medications and hormonal changes need to be taken into consideration when treating these patients [8]. Various forms of topical treatment have been established for the mild and moderate forms of acne vulgaris [9].Recommendations for the choice of therapy depends on pathogenic factors such as follicular hyperkeratosis, sebaceous gland hyperplasia accompanied by seborrhea, microbial colonization with propionibacterium acnes, and inflammatory immune responses, but the overall clinical presentation must also be considered [10]. Among available topical treatments antibiotics, azelaic acid, benzoyl peroxide and retinoids are often regarded as the most prominent choice. Azelaic acid is a saturated, straight chained c9 dicarboxylic acid. It was first described by nazzaro-porro and passi [11] in the 1970's and its effectiveness was first observed in hyperpigmentation. This finding was followed by evidence of its efficacy in acne vulgaris [12, 13].

II. ACNE

Acne develops due to blockage of follicles, hyper keratinization and keratin plug formation and sebum (microcomedo). With increased androgen production,

sebaceous glands are enlarged and sebum production is increased. The microcomedo may enlarge to form an open comedo (blackhead) or closed comedo. Comedones occurs as a result of clogging sebaceous glands with sebum, naturally occurring oil and dead skin cells. The acne spreading depends on pilosebaceous gland density and morphology [14]. Propionibacterium acnes a normal component of the cutaneous flora, invade the pilosebaceous unit using lipid rich sebum as a nutrient source and grow in the presence of increased sebum production leading to inflammation via complement activation and the release of metabolic byproducts, proteases and neutrophil attracting chemotactic factors [14,15]. When comedones ruptures, the contents of the pilosebaceous unit spread into the adjacent dermis and it leads to development of inflammatory acne vulgaris lesions such as; cysts, nodules, papules and pustule[14,16]. Also acne develops as a result of bacterial overgrowth and inflammation in the pilosebaceous units.The body's hormone level alter pilosebaceous gland function and causes acne. Follicular epithelial cells abnormally differentiated and forms tighter intracellular adhesions and shed less. That leads to the development of microcomedones or hyperkeratotic plugs which enlarge to form noninflammatory open or closed comedones [14]. Changes in the skin's natural flora are linked with androgen related sebum production. Diseases like congenital adrenal hyperplasia, polycystic ovarion syndrome and endocrine tumors result in a high level of androgen in body and associated with the development of acne vulgaris [17]

III. USES OF AZELAIC ACID

- Azelaic acid for acne:

Clearing skin pores of bacteria that may be causing irritation or breakouts.

Reducing inflammation so acne becomes less visible, less red and less irritated.

Gently encouraging cell turnover so skin heals more quickly and scarring is minimized.

- azelaic acid for skin lightening:

The same property that make azelaic acid more effective for the treatment of inflammatory hyperpigmentation also enables it to lighten skin that's discolored by melanin.

Using azelaic acid for skin lightening in patchy and blotchy areas of skin due to melanin has been effective.

- azelaic acid for rosacea

Azelaic acid can reduce inflammation, making it an effective treatment for symptoms of rosacea.
Clinical studies demonstrate that azelaic acid gel can continually improve the appearance of swelling and visible blood vessels caused by rosacea.

- azelaic acid for acne scars

Azelaic acid is used to treat acne scarring in addition to active breakouts. Azelaic acid encourages cell turnover, which is a way to reduce how severe scarring appears.

It also prevents melanin synthesis, the ability of skin to produce pigments that can vary skin's tone [18].

- Correlation between acne vulgaris and azelaic acid

Azelaic acid is a saturated dicarboxylic acid found naturally in wheat, rye and barley. It is natural substance that is produced by Malassezia furfur (also known as Pityrosporum Ovale), a yeast that lives on normal skin [18]. Acne is a chronic inflammatory disorder of the pilosebaceous unit. The physiopathological mechanism of acne seems to depend on several factors; a hyperkeratinization process of the follicular channels; microbial colonization of the pilosebaceous units; perifollicular inflammation; sebum production and excretion; and differential rates of conversion of testosterone to dihydrotestosterone. When compared to normal skin, acne bearing skin was found to produce from 2 to 20 times more dihydrotestosterone, generally considered to stimulate the pilosebaceous unit and a possible contributing factor in the pathogenesis of acne[19,20].Azelaic acid appear to retard the conversion of testosterone to dihydrotestosterone through competitive inhibition of 5 -alpha reductase[21]. This may be one mechanism that azelaic acid is effective in treating acne, but Nguyen et al. found that azelaic acid has no effect on the 5-alpha reductase activity in cells of human hair follicle. In

vivo animal studies also reported conflicting results: lipogenesis in sebaceous glands of the hamster ear was not significantly affected by topical application of azelaic acid up to a 4 month period [22,23]. In acne patients, application of 20% azelaic acid cream over a 3-to 6 month period did not affect the excretion rate, or composition of sebum, or morphology of sebaceous glands. Nevertheless, patients with acne reported subjectivity gradual and progressive reduction in skin greasiness after 1-2 months of treatment [24, 25, and 26]. Histologic findings showed normal skin possesses smaller sebaceous glands than seborrheic or acne skin, the later having larger sebaceous glands [24]. Mayer-da-Silva et al. demonstrated that azelaic acid is an antikeratinizing agent, displaying an antiproliferative cytostatic effect on keratinocytes (via inhibition of DNA synthesis) and modulating the early and terminal phases of epidermal differentiation (via inhibition of cytoplasmic protein synthesis). The infundibular epidermis of individual with acne showed marked reduction of thickness of the horny cell layer, widening of the horny cell cytoplasm, and normalization of filaggrin distribution. So far data accumulated have suggested that azelaic acid may achieve its antiacne activity through its antikeratinizing effects on the follicular epidermis and its antimicrobial action rather than by direct inhibition of sebaceous gland function. Cunliffe and Holland proposed that direct modification of comedogenesis, by normalization of the disorganized keratinization of the follicular infundibulum, may cause rapid reversal of noninflamed acne lesions in response to azelaic acid therapy. On the other hand, the antimicrobial action of the drug on cutaneous bacteria and its oxyradical scavenging properties may attribute to the reduction of inflamed acne lesions [24, 27].

IV. MECHANISM OF ABSORPTION

After topical application of 1g of 20% azelaic acid cream, a percutaneous absorption of about 3% and correlated plasma concentration of 0.038 ug/mL were estimated [28]. The formulation of the topical vehicle significantly affects the % amount being absorbed in a time-dependent manner. Absorption from 15% azelaic acid gel after 12 hours was higher (8%) than that from a water-soluble polyethylene glycol ointment base (3%) [29]. in normal cells, dicarboxylic acids penetrating the cell membrane undergo complete metabolism by beta-oxidation. Penetration of dicarboxylic acids through neoplastic cell membranes is about 3x higher with resulting higher intracellular concentration [30, 31]. Whether azelaic acid is transported across the cell membrane via a transport carrier system or by simple diffusion remains unknown. Other dicarboxylic acids (that is, malate, succinate, and oxaloacetate) are transported by specific protein carriers [32]. Twelve hours after oral administration, the higher concentrations of azelaic acid were estimated to occur in the liver, lungs and kidneys of rats. Azelaic acid continues to accumulate in adipose tissue for about 96 hours after a dose [33]. Of the total organ radioactivity, 90% was detected in fatty tissues and in fatty acids fractions of triglycerides and phospholipids [33, 34]. Azelaic acid can cross the blood-brain-barrier of dogs, after oral and intravenous administration with the cerebrospinal fluid concentration estimated at 2-5% of those of plasma [35]. The ocular distribution of azelaic acid after topical (retrobulbar) and intravenous administration in rabbits was also reported. Higher concentrations were found in the aqueous humor than vitreous humor, peaking at 2 hours after a dose [36].

V. THERAPEUTIC APPLICATIONS

- Disorders of pigmentation

Topical azelaic acid (15-20%) has no pigmentation effect on normal skin, solar freckles, senile freckles, lentigo simplex, pigmented seborrheic warts, and nevi; but has been reported to be effective against hypermelanosis caused by physical or phytochemical agents, postinflammatory melanoderma, melasma, chloasma, lentigomaligna, and primary lesions of lentigo maligna melanoma and malignant melanoma. These conditions are characterized by either hyperactivity or abnormal proliferation of melanocytes by inhibiting mitochondrial enzymes and DNA synthesis [37-43].

- Acne vulgaris

When compared to normal skin, acne bearing skin was found to produce from 2 to 20 times more dihydrotestosterone, generally considered to stimulate the pilosebaceous unit and a possible contributing factor in the pathogenesis of acne. Azelaic acid appears to retard the conversion of testosterone to dihydrotestosterone through competitive inhibition of

5-alpha reductase. So azelaic acid is beneficial in treating acne [19, 20].
Topical azelaic acid is Food and Drug Administration (FDA) approved for mild - moderate inflammatory acne vulgaris under the brand name Azelex as 20% cream [44].
It is also FDA approved for mild to moderate papulopustular rosacea under the brand name Finacea as 15% gel and 15 % foam [45].

- Types and severity of acne vulgaris

There are 3 types of acne: comedonal, papulo-pustular, and nodular, all of which result from a multifactorial pathophysiologic process in the pilosebaceous unit: (1) sebum production,(2)follicular hyperkeratinization, (3)proliferation and colonization by Propionibacterium acnes, and (4) the release of inflammatory mediators.2 The resulting lesions include noninflammatory open (blackheads) and closed (whiteheads) comedones, as well as inflammatory papules, pustules, and nodules. Acne severity is rated according to the Combined Acne Severity Classification that classifies acne into mild, moderate, and severe, based on the number and type of lesions.

- Comedonal (non-inflammatory)

Whitehead (closed): a dialated hairfollicle filled with keratin, sebum and bacteria, with an obstructed opening to the skin.
Blackhead (open): a dialated hair follicle filled with keratin, sebum and bacteria, with a wide opening to the skin clapped with a blackened mass of skin debris.

- Papulo-pustular (inflammatory)

Papule: small bump less than 5mm in diameter.
Pustule: smaller bump with a visible central core of purulent materia

- Nodular (inflammatory)

Nodule: bump greater than 5mm in diameter [46].

VI. COMBINED ACNE SEVERITY CLASSIFICATION

Severity	**Definition**
Mild acne	Fewer than 20 comedones, or Fewer than 15 inflammatory Lesions, or Total lesion count fewer than 30.
Moderate acne	20–100 comedones, or 15–50 inflammatory lesions, or total Lesion count 30-125.
Severe acne	More than 5 nodules, or Total inflammatory count greater Than 50, or Total lesion count greater than 125 [47].

VII. EPIDEMALOGY

In 2010, it was reported that acne affects approximately 9.4% of the population [48]. It affects about 90% of people during teenage years and sometimes in adulthood [5]. About 20% people have moderate and severe cases. Acne rates are low in rural areas and it may not occur in the non-westernized people of Paraguay and Papua New Guinea [7]. It is more common in females 9.8% compared to 9.0% [48]. In over 40 years old subjects about 1% of males and 5% of females have problems [5]. It affects all ethnic groups' people and it is not clear if race affects rates of disease [49, 50]. Acne affects 40 and 50 millions people which is about 16% in the United States and approximately 3 to 5 million people which is about 23% in Australia [51]. In the United States, it is more severe in Caucasians than African descent people [2].

VIII. SIGN AND SYMPTOMS

It includes papules, nodules (large papules), seborrhea (increased oil sebum secretion), comedones, pustules and scarring [1]. The appearance of acne varies with skin colour and it is also associated with psychological and social problems [5]. Acne scars shows inflammation within the dermis and it is created by wound healing resulting in collagen deposition at one spot [52]. The following types of scars are present.

Types of scars

Scars	Characteristics

Box car scars Angular scars occur on cheeks and can be either superficial or deep

Similar to chickenpox scars.

Ice pick scars Deep pits are most common, sign of acne scarring

Rolling scars Wave like appearance in skin

Hypertrophic scars Thickened or keloid scars

Pigmented scars True scars, Change in the skin's pigmentation, As a result of nodular

or cystic acne, inflamed red Marks.

IX. ADVERSE SIDE EFFECTS OF AZELAIC ACID

In numerous studies, including acute, chronic, those involving reproduction toxicology, investigations of the mutagenecity and sensitizing potential, and observations of local tolerance in various animals (that is, mouse, rat, guinea pig, rabbit, dog, and monkey), azelaic acid was found to be nontoxic[53,54]. Continuous infusion of 10g of azelaic acid over 80-90 min in healthy subjects posed no adverse effects [55]. Topical application of 20% azelaic acid is well tolerated in humans and overt systemic toxicity has not been reported. One isolated case of hypokalemia occurred following oral intake of 12g/day azelaic acid for 12 weeks [56]. The allergic reaction most commonly encountered is a local type of irritant, erythematous lesion that appears mild and transient [37]. The associated symptoms reported were burning, itching, and stinging, but they generally subsided after 2-4 weeks of therapy. Most of the local side effects were related to unsuitable cleansing, followed by excessive application and vigorous rubbing in of the azelaic acid cream. Mild scaling and absent phototoxic potential have been reported [43].

CONCLUSION

Azelaic acid is an effective drug in the treatment of acne vulgaris and in some other skin diseases like hyperpigmentation, melasma etc. Azelaic acid has antimicrobial, antiinflammatory and middle range of antityrosinase activity which help to treat acne bearing skin. For treatment of skin lightening, acne scars, rocasea, acne azelaic acid cream is used. It can be administered by both routes topically and orally. There are 3 types of acne vulgaris that is comedonal, papulo-pustular, nodular. The severity of acne is mild acne, moderate acne and severe acne. Acne affects about 90% of teenagers during adulthood. It may create psychological and social problems. Topical application is effective and tolerable for acne treatment.