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Review Article

An Overview about Possible Roles of Dapsone and Adapalene in Treatment of Acne Vulgaris: A Review Article

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ABSTRACT

Background: Inflammatory lesions such as papules, pustules, or nodules, as well as open or closed comedones, defined as acne, which is a chronic inflammatory disease. A lot of young people get this skin condition, which is why it's so frequent. Several factors may influence the choice of therapy including age of the patient, extent, severity of the disease and sites involved. Topical treatment can be used alone or with combination to other topical or oral agents. We intended to provide an outline of possible roles of Dapsone and Adapalene in Treatment of Acne Vulgaris.

Conclusions: Nodulocystic acne and other severe forms of acne frequently necessitate systemic medication. Although systemic isotretinoin is widely considered the best treatment for stubborn acne, it comes with a range of well-known adverse effects. Applying a thin layer of 5% dapsone gel to afflicted lesions is indicated for the treatment of acne vulgaris, and the product has FDA approval. Adapalene (ADP) and other retinoids are used to treat acne vulgaris with the goal of removing these causes and reducing or eliminating acne lesions. In comparison to benzoyl peroxide, a 0.1% ADP is more effective at keratolysis. These effects of ADP have been found to be effective in treating hyperkeratosis. Also, ADP's corneum layer has poor percutaneous absorption, so it stays active in the skin and hair follicles for longer—an important area for treating acne vulgaris.

Keywords: Dapsone; Adapalene; Acne Vulgaris.

INTRODUCTION

The open or closed comedones and inflammatory lesions that manifest as papules, pustules, or nodules define acne, a chronic inflammatory illness. Among the most prevalent skin illnesses, it primarily affects young people [1].

Acne's incidence is over 90% among adolescents and it could persist into adulthood in 12% - 14% of cases. This may result in high psychological and social implications**.** However, most cases are seen during early teenage years [2].

Seborrhea, comedones, papules and pustules are characteristic features of this disease. Equal incidence of this disease occurs in males and females; however, the more severe form usually appears in men from the hormonal effect [1].

Open and closed comedones, which are non-inflammatory lesions, together with papules, pustules, and nodules, are the hallmarks of acne vulgaris. (inflammatory lesions). A white head (closed comedo) is formed when the opening of hair follicle is blocked by oil and skin cells. This presents on the skin as small, whitish bumps and under the surface of the skin. A blackhead (open comedo) is a kind of acne lesion that does not cause inflammation and is packed with sebum and dead skin cells. The open comedo shape is characterized by a dark hue, such black or brown, and the fact that the skin's surface stays visible [3]. Several factors may influence the choice of therapy including age of the case, extent, severity of the disease and sites

involved. Topical treatment can be used alone or with combination to other topical or oral agents [4].

An antibacterial agent, dapsone is a lifesaver for several severe diseases. To treat long-term skin disorders without the risk of steroid-related side effects, it is prescribed by dermatologists [5]. Because of its anti-inflammatory actions, dapsone is applied topically (and has sometimes been applied systemically) to treat acne [6]. Dapsone (4,40 diaminodiphenylsulphone) is a sulfone derivative that had been used orally for the treatment of leprosy and several inflammatory dermatoses, including dermatitis herpetiformis, pyoderma gangrenosum, bullous lupus erythematosus, straight immunoglobulin A dermatosis, and bullous pemphigoid [7].

Chemistry and pharmacokinetics

An aromatic amine ring is joined to two phenylsulfone (DDS) or dapsone (another name for the same compound) molecular structure. Dapsone comes in a variety of forms, including 50 and 100 mg tablets, a 2 mg/mL oral suspension, and a topical gel (5 and 7.5 percent). A lipid solubilizer and a water insoluble compound, DDS has two aromatic rings. Its ability to easily traverse the lipid bilayer of cells is due to its high lipophilic activity. This could be the reason why its plasma levels are drastically decreased in obese people [8].

Protein binding accounts for the majority of the 70–80% absorption of DDS in tablet form, with the remaining 30–40% entering the enterohepatic circulation. It can enter breast milk thanks to its lipophilic activity, which enables it to breach the placental barrier. About 30 hours is the half-life of dapsone. The by-products of monoacetyl and diacetyldapsone, which are produced by the liver enzymes N-acetyltransferase and N-hydroxylase acetylate dapsone, are subsequently degraded and eliminated in the digestive fluids and urine [9].

To achieve its antibacterial effects, dapsone competes with para-aminobenzoic acid (PABA) and functionally inhibits PABA's ability to generate folic acid. DDS and PABA are rivals for the same active site on the dihydropteroate synthase enzyme found in bacteria. Dapsone stops the production of amino acids, the building blocks of proteins, by blocking this enzyme. Myeloperoxidase inhibition is the mechanism by which dapsone exerts its anti-inflammatory effects [10].

In addition to killing germs, neutrophils employ myeloperoxidase to transform hydrogen peroxide into hypochlorous acid, which has the potential to oxidize and inflame nearby tissues. Preventing the buildup of hypochlorous acid, myeloperoxidase is rendered inactive at its intermediate stage. [10]. Dapsone inhibits neutrophil chemotaxis and function, which is how it functions in conditions like erythema elevatum diutinum and dermatitis herpetiformis. The chemotactic factors that prevent neutrophil accumulation may be restored by dapsone.[11].

Dapsone in acne:

Oral Dapsone:

Systemic medication is frequently necessary for severe cases of acne, including nodulocystic acne. Patients frequently experience aversion to systemic isotretinoin due to its many well-known side effects, which include teratogenicity, hepatotoxicity, photosensitivity, and mood disturbance. Despite its reputation as the gold standard treatment for recalcitrant acne, this option is not without its drawbacks. When it comes to nodulocystic acne, oral isotretinoin works better than oral dapsone [12].

Topical Dapsone:

1. The 5% formulation

The Food and Drug Administration (FDA) has authorized a topical formulation of 5% dapsone for the treatment of acne vulgaris in the US. A thin coating of 5% gel applied to afflicted lesions is suggested [13].

In two massive randomized controlled trials, 1506 patients received topical 5% dapsone and 1500 patients received vehicle control. The investigator's overall assessment for acne showed that treatment success was more common in the treatment group compared to the vehicle group (P >.001). The treatment group showed better results regardless of the acne findings at the beginning, with a reduction of noninflammatory and total lesion counts at 12 weeks (P <.001) and, most importantly, a reduction of nearly 50% in inflammatory lesion counts in the treatment group after 12 weeks. Oiliness and erythema were common side effects across both groups. Research like this provides credence to the idea that topical dapsone can be an effective acne treatment. The emollient foundation of the carrier gel may have therapeutic effects, as it decreased the numbers of inflammatory lesions by 41.8% [13].

2. The 7.5% formulation

Patients with moderate acne vulgaris have also shown success with dapsone 7.5% gel once day, which outperformed a vehicle treatment with minimal reported adverse effects [13]. A total of 4,340 patients participated in two separate double-blind controlled trials that randomly assigned them

to receive either a vehicle or topical dapsone 7.5% gel. The treatment group showed a considerable improvement in the global acne evaluation score after 12 weeks compared to the vehicle group in both investigations. Additionally, there was a decrease in the number of inflammatory and noninflammatory counts from baseline ($P \leq .05$). The results showed that adults and females, as opposed to teenagers and boys, experienced the greatest improvement in acne scores with a dose of 7.5% dapsone when all the trials' data was combined and evaluated ($P \leq .029$) [14].

Over the course of 12 weeks, dapsone gel, 7.5% used topically once daily, effectively and safely treats acne with few side effects. There was no significant difference in local tolerance between the vehicle and dapsone gel, 7.5% used once daily, and the safety and tolerability profile was comparable to that of dapsone gel, 5% applied twice daily [15].

Adapalene

There are few negative effects associated with adapalene, a retinoid of the third generation. Due to its good tolerability profile and comparable efficacy to other topical retinoids, adapalene has become widely utilized. loca1 decreased photo instability and skin irritation, and it had the right amount of comedolytic and anti-inflammatory action [16].

Discovering vitamin, A in a lipid extract from egg yolk in 1909 marks the beginning of the contemporary retinoids' history. The retinoids family includes retinol, retinyl ethers, retinaldehyde, and several synthetic analogues of vitamin A. The toxicity and negative effects of the first generation of retinoids limited their use in treating acne and keratinization illnesses. The first retinoid applied topically to treat acne was tretinoin, which had a high rate of side effects. Hence, it has been critical to enhance the safety of administration to improve these compounds. In 1996, the U.S. Food and Drug Administration (FDA) authorized a retinoid called adapalene (ADP) to treat acne. Compared to tretinoin, it has fewer negative effects [17]. Generational classification is the gold standard for retinoids. Vitamin A and its synthetic derivatives, including the widely used tretinoin and isotretinoin, make up the first generation. Acitretin, a retinoid of the second generation with an aromatic cyclic component in its chemical structure, and polyaromatic compounds make up the third generation of retinoids (ADP, tazarotene). The third generation was developed following the identification of retinoid receptors. Its selective receptor binding has been enhanced using diverse chemical configurations. One subset of nuclear receptors is the retinoid X receptors, while another subset is the retinoic acid receptors (RAR- retinoic acid is a natural ligand) (RXR-9-cis- retinoic acid is natural ligand) [18].

The fourth-generation representative, trifarotene, was recently approved. The new selective RAR-γ agonist trifarotene is 20 times more selective than RAR-α and RAR-β receptors. An increasing number of illnesses, including lichen spinulosus, plantar warts, alopecia areata, and childhood acanthosis nigricans, are being treated with ADP off-label because of positive clinical observations. In addition to treating acne vulgaris, the recognized biological effects are helpful for a variety of other dermatological issues. Some research on the therapy of acanthosis nigricans has recently shown a depigmenting effect [19].

Inhibiting melanogenesis and having a positive effect on hair follicle maintenance and differentiation made it an effective photoaging therapy. The antiproliferative impact of ADP has not been thoroughly investigated, and its exact mechanism of action remains unclear. Some forms of cancer can benefit from ADP's antiproliferative impact. We also reported new therapeutic combinations with orally delivered APIs that were just as efficacious as topical combinations of ADP and other APIs. It is still a struggle to develop novel ADP analogues that show promise as medicinal agents [20].

Physiochemical properties of ADP:

ADP is a retinoid family member and a stable synthetic derivative of naphthoic acid. The structural components of ADP that impart specific biological and physicochemical characteristics are the adamantane (tricyclo [3.3.1.1] decane) and methoxyphenyl groups [19]. When combined with benzoyl peroxide, ADP offers the added benefit of light stability, making it an ideal ingredient in acne treatments. Compared to tretinoin, ADP maintains its stability better when exposed to light and oxidation processes [21].

Mechanism of action:

Specific binding to retinoid receptors is the basis of retinoids' action mechanism. Targeting RARs with retinoids influences cell proliferation and differentiation. Tretinoin and tazarotene, which are effective against acne, psoriasis, and photoaging, are also in this class with ADP. Retinoids like alitretinoin and bexarotene, which target RXRs, induce cell death and are effective against mycosis fungoides and Kaposi sarcoma [22].

By selectively attaching to RARs rather than the retinoic acid cytosolic binding proteins, ADP activates the genes that are important for cell differentiation. Trifarotene is a highly selective RAR-γ agonist, whereas ADP is not as selective, despite its high affinity for RAR-γ receptors found in the epidermis and RAR-β primarily in dermal fibroblasts [19].

In the same way as tretinoin slows cell proliferation, ADP does the same thing by binding specifically to RARs (RAR-γ and RAR-β). Topical ADP regulates keratinization, inflammation, and follicular epithelial cell differentiation; however, the exact mechanism is still unclear. Microcomedones and inflammatory lesions linked to acne vulgaris are thereby decreased [23].

Evidence from an experiment using hamster sebocytes showed that ADP inhibited sebum accumulation. This effect is coupled with perilipin 1 and the transcriptional repression of diacylglycerol acyltransferase 1, the enzyme responsible for triacylglycerol production (lipid droplet-associated protein). Moreover, ADP inhibits the production of sebum storage droplets by mechanisms involving insulin, 5α-dihydrotestosterone (5α-DHT), and peroxisome proliferators activating receptors (PPARγ) at the level of differentiated sebocytes.[24].

Biological effects:

Treatment of acne vulgaris with ADP has received official approval. ADP's stability and lipophilicity make it comparable to tretinoin in terms of efficacy.[19].

1. **Anti-inflammatory and comedolytic effects:**

ADP possesses anti-inflammatory and comedolytic properties. By blocking lipooxygenase and arachidonic acid oxidative metabolism, ADP disrupts the inflammatory process [20]. Some research has shown promising results in treating inflammatory acne using topical ADP treatment. [25]. The number of teenage girls affected by acne is decreasing, whereas the percentage of teenage girls affected by acne is rising [26].

2. **Keratolytic effect:**

Acne vulgaris treatment with ADP or other retinoids aims to diminish or eradicate acne lesions by removing these causes. In comparison to benzoyl peroxide, a 0.1% ADP is more effective at keratolysis. These effects of ADP have been found to be effective in treating hyperkeratosis. Also, ADP's corneum layer has poor percutaneous absorption, so it stays active in the skin and hair follicles for longer—an important area for treating acne vulgaris [27].

3. **Immunomodulatory effect:**

Polymorphonuclear leukocytes release oxygen free radicals, and ADP inhibits these pathways as well as leukotriene formation, which is how it modulates the immune system (derived from rabbits). Furthermore, ADP blocks the expression of the mammalian toll-like receptor 2 (TLR-2) on human monocytes and the chemotaxis of polymorphonuclear leukocytes in humans. This mode of action complements the targeting of RAR receptors [28].

Therefore, ADP has been found to be effective in treating a variety of conditions, including alopecia areata, pigmentary disorders, epidermolytic ichthyosis, molluscum contagiosum, Darier disease, Fox-Fordyce disease, Dowling-Degos disease, molluscum contagiosum, epidermolytic ichthyosis, alopecia areata, and various others. For rosacea and perioral dermatitis that mimics it, ADP is an effective therapy option [29].

4. **Antiproliferative effect:**

Every retinoid is recognized to have a crucial function in cell proliferation and differentiation. Results showed that ADP was effective in treating cervical intraepithelial neoplasia. When it came to treating level 2 cervical intraepithelial neoplasia, ADP was the clear winner [30]. Using ADP to treat colorectal cancer in humans was mentioned in a recent paper [30]. It was demonstrated that ADP inhibited glutamic-oxaloacetic transaminase 1 without competing with it; as a result, ADP inhibited ovarian cancer ES-2 cells [20].

Comparatively, ADP was more effective than other retinoids in inhibiting melanoma cell growth than isotretinoin, acitretin, bexarotene, and all-trans-retinoic acid. S phase cell cycle arrest was the method by which apoptosis was induced. Apart from being the best retinoid, ADP also inhibited the HaCat cells (all-trans-retinoic acid and isotretinoin from first-generation, acitretin from the second generation, and tazarotene and bexarotene from the third generation). In response to ADP, the protein expression of the DNA damage marker γ-H2AX was increased [20].

5. **Neuroprotector effect:**

Both normal adult central nervous system function and neurodevelopment depend on retinoid signalling. It is possible that disruption of retinoid signalling causes several neurodegenerative disorders. The bioactivity of nanoparticles containing ADP delivered intravenously in the

central nervous system was revealed in a study involving healthy mice (minimum 24 h). Potentially replacing current methods of treating central nervous system illnesses are ADP and retinoid-modulating treatments [31].

6. **Antibacterial activity:**

Researchers looked examined the effectiveness of a nano-emulsion containing ADP and tea tree oil in killing Propionibacterium acnes. A much lower minimum inhibitory concentration (MIC) value is presented in the results. Furthermore, adamantane intercalates into the lipidic bacterial membrane, which likely explains why one ADP analogue exhibits antibacterial action against methicillin-resistant Staphylococcus aureus (MRSA) [32].

The antibacterial properties of ADP can serve as a foundation for the development of more effective compounds that may one day be used to treat infections of the skin. Two ADP analogues, CD437 and CD150, which differ in that they contain a 4-hydroxyphenyl group rather than a 4-methoxyphenyl one, were discovered to possess antibacterial properties against MRSA. When combined with gentamicin, these two compounds had synergistic effects [32].

Adapalene Combination Therapies in Acne Treatment

Combining adapalene with antibiotics—whether systemic, topical, or benzoyl peroxide—has been beneficial in several studies [33].

Combination adapalene and BPO (adapalene-BPO)

A new and powerful combination regimen combines a retinoid called adapalene with a bactericidal and anti-inflammatory drug called BPO. This allows the retinoid to target both comedonal and inflammatory lesions simultaneously, eliminating the need for antibiotics [33].

There have been evaluations of the safety and effectiveness of adapalene-BPO gel in comparison to monotherapies of the medication or its vehicle. They found that the combo product was more effective than the individual drugs when used alone [33].

Combination of adapalene and topical antibiotics like clindamycin

For mild to severe acne vulgaris, clinical research found that a regimen consisting of 1% clindamycin topical lotion and 0.1% adapalene gel was far more effective than clindamycin alone. We observed a marked decrease in the number of all types of acne lesions (inflammatory and noninflammatory), an increase in the speed and magnitude of the therapeutic response, and no increase in the reported tolerability load when using the adapalene combination [34].

Combination of adapalene and oral antibiotics

In two 12-week, multicenter, randomized, and investigator-blinded studies, the effectiveness of adapalene gel 0.1 percent combined with oral antibiotics was examined. 242 patients with moderate to moderately severe acne (EBM-level 2b, n = 242) and 467 patients with severe acne (adapalene 0.1 percent gel plus doxycycline 100 mg/d) were included in the studies [35]. There were 467 participants (EBM-level 2b). At weeks 8 and 12, the combination medication showed a far higher decrease in inflammatory lesion counts than the systemic antibiotic alone [36].

Adverse Effects

The most common side effects of adapalene include redness, peeling, dryness, burning, and itching in the affected area of the skin. Plus, a pustular flare could happen to certain people. There is a small risk of skin irritation when using adapalene. However, adapalene 0.1 percent gel compares favorably to tretinoin 0.025 percent gel in terms of tolerability, and both products have at least the same level of effectiveness [36].

CONCLUSIONS

Nodulocystic acne and other severe forms of acne frequently necessitate systemic medication. Although systemic isotretinoin is widely considered the best treatment for stubborn acne, it comes with a range of well-known adverse effects. Applying a thin layer of 5% dapsone gel to afflicted lesions is indicated for the treatment of acne vulgaris, and the product has FDA approval. Adapalene (ADP) and other retinoids are used to treat acne vulgaris with the goal of removing these causes and reducing or eliminating acne lesions. In comparison to benzoyl peroxide, a 0.1% ADP is more effective at keratolysis. These effects of ADP have been found to be effective in treating hyperkeratosis. Also, ADP's corneum layer has poor percutaneous absorption, so it stays active in the skin and hair follicles for longer—an important area for treating acne vulgaris.

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