Emerging Role of Dapsone in the Management of Acne Vulgaris: Review Article

Gehad Nabil Mohamed*, Khaled Mohamed Gharib, Mai Ahmed Samir
Department of Dermatology, Venereology & Andrology, Faculty of Medicine, Zagazig University, Sharkia, Egypt
***Corresponding author:** Gehad Nabil Mohamed, **E-Mail:** gehadnabil6244@gmai.com

ABSTRACT

Background: Skin illness Acne Vulgaris (AV) is characterized by excessive sebum production, follicular hyperkeratinization, and long-term pilosebaceous unit irritation. Acne can persist into adulthood in 12-14% of instances, resulting in deformity and chronic scarring that can have psychological and social consequences. Acne scars, feelings of negative effects on psychology, isolation from society, and depression can all be long-term repercussions of the condition. In a small percentage of patients with nodulocystic acne, the anti-inflammatory drug Dapsone, developed in the 1950s, was found to be beneficial. However, the risk of systemic side effects has limited the use of dapsone in clinical practice. Topical dapsone gel was licensed for acne treatment following two double-blind, randomized trials that established its therapeutic efficacy.

Objective: Summarize the role that Dapsone plays in the treatment of Acne Vulgaris.

Methods: The databases were searched for articles published in English in 3 databases [PubMed – Google scholar-science direct] and Boolean operators (AND, OR, NOT) had been used such as [Management of Acne Vulgaris AND Dapsone OR Acne Vulgaris] and in peer-reviewed articles between March 2001 and April 2020.

Conclusion: Acne vulgaris can be effectively treated with topical Dapsone, according to clinical trials.

Keywords: Dapsone, Acne Vulgaris.

INTRODUCTION

Chronic inflammation of the pilosebaceous unit and excessive sebum production mediated by hormones are the hallmarks of acne vulgaris, a common skin disorder [(1)].

AV is most common in adolescents, however, it can afflict people of any age range. An estimated 85 percent of persons aged 12 to 25 suffer from AV, and 15 to 20 percent of those with acne have moderate to severe cases. Acne vulgaris affects people of all socioeconomic backgrounds, ethnicities, and genders due to the production of androgens and the commencement of face sebum production during adolescence [(2)].

Puberty is the time when most cases of AV occur, however it can afflict people of any age in varying degrees. A study of the global burden of disease found that AV affects roughly 86% of people aged 12 to 25 years, and acne affects 15% to 20% of the same young people. Androgens are produced, and facial sebum production begins throughout adolescence. This helps explain why acne vulgaris affects so many people, no matter what their socioeconomic situation, country, or gender may be [(3)].

Adolescence and early adulthood are the most typical times for men to get acne, although women are more likely to get it later in life [(4)].

Acne Vulgaris Treatment with Dapsone:

In dermatology, the antibacterial agent Dapsone is commonly used for inflammatory dermatoses because of its anti-inflammatory properties. Using a new topical form of the drug, acne vulgaris has been successfully treated [(5)].

Dapsone was first synthesized in 1908 by German dye industry experts, but it wasn't until the 1930s that its therapeutic potential was fully realized when sulfonamides, a new class of sulfur-containing chemicals, were found**.** Dapsone, a sulfone that shares chemical similarities with sulfonamides, was first tested in mice in 1937 and found to be effective in treating artificially produced streptococcal infections [(6)].

Dapsone was found to be more hazardous than sulfonamides in animal studies, resulting in anemia and methemoglobinemia, as well as a wide range of other side effects, such as septic shock [(7)].

In animal studies in 1941, Dapsone was discovered to be effective against leprosy as well as tuberculosis [(8)]. The oral formulation for the treatment of leprosy was introduced in 1949. Dermatitis herpetiformis sufferers received sulfones the following year, based on the false notion that the ailment was infected [(9)].

This original conclusion was supported by further research once the patients' symptoms had significantly improved. The noninfectious inflammatory, bullous, and auto-immune diseases, including dermatitis herpetiformis, can now be treated with dapsone, thanks to FDA approval [(10)].

Dapsone was the subject of a randomized, double-blind, placebo-controlled experiment in the treatment of acne, 9 out of 23 patients saw significant improvement, however, the other 9 exhibited no improvement [(11)].

Later, a study was conducted [(12)], although the benefits of dapsone were classified as minimal, a comparison was made between it and 13-cis-retinoic acid (isotretinoin). Isotretinoin, which was introduced in the 1980s, has superseded almost all prior therapies for severe acne.

Acne fulminans with erythema nodosum, a particularly severe and unusual form of acne, may benefit from dapsone treatment, even if some research suggests the drug's efficacy in treating acne fulminans may be limited when administered alone. Dapsone's potential negative effects have limited its usage as an oral acne treatment [(13)].

Received: 8/10/2021
Accepted: 6/12/2021

Mechanism of action:

In the same way, as sulfonamides suppress folate formation in bacteria's deoxyribonucleic acid, dapsone's antibacterial effect is mediated by competitive suppression of this enzyme. Sulfones are bacteriostatic compounds like dapsone and other sulfonamides. A poor bacteriostatic activity of dapsone against propionibacterium acnes (P. acnes) suggests that dapsone's role in acne is more important than its anti-inflammatory properties. Exactly how the drug works is still a mystery. Acne lesions are thought to be triggered by inflammation, and at the inflamed site, dapsone appears to inhibit chemo-attractant signaling, limiting neutrophil recruitment [(14)].

Dapsone prevents neutrophils from producing reactive oxygen species, which are harmful to tissues and trigger inflammation in addition to killing bacteria [(14)].

As data suggests, the anti-inflammatory effects of dapsone may be achieved through numerous pathways [(13)].

Form: Dapsone comes in a 50 mg gel format with a 5 percent concentration of dapsone (Aczone) [(15)].

Pharmacology: Antimicrobial drug in the sulfonamide class, Dapsone [(13)].

Pharmacokinetics:

Sulfur links two aromatic amine rings in the diaminodiphenyl sulfone or dapsone molecule. Dapsone is available in tablets (50 and 100 mg), an oral suspension (2 mg/mL), and a gel for topical use (5 and 7.5 percent). DDS is lipid-soluble and water-insoluble because of its two aromatic rings. Because of its high lipophilicity, it can easily pass through the lipid bilayer of cells. As a result, obesity may diminish its plasma levels in such a large way [(13)].

About 70–80 percent of the drug enters the enterohepatic circulation and is mainly bound to proteins when taken in tablet form. To get into the breast milk, its lipophilicity permits it to pass across the placenta barrier. Dapsone has a half-life of 30 hours or less when taken orally. An N-acetyltransferase enzyme and an N-hydroxylase enzyme in the liver convert dapsone into monoacetyl and diacetyl byproducts, which are eliminated in the urine and bile as waste products. [(13)].

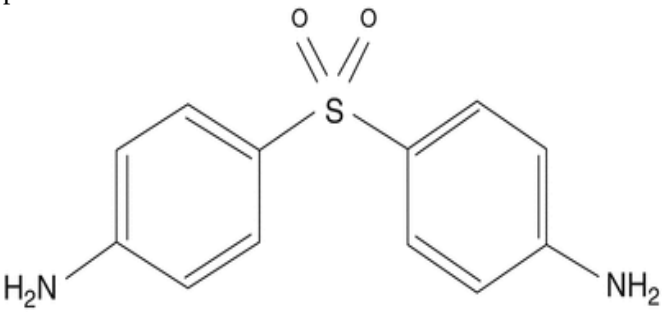

Figure (1): Dapsone (diaminodiphenyl sulfone) $C_{12}H_{12}N_2O_2S$[(13)].

Dapsone in Dermatology:

Acne:

As a result of the possibility of side effects, oral dapsone has lately been resurrected as a topical treatment for acne. After being authorized by the FDA in 2008 for treating acne vulgaris, it was made available to consumers in North America in 2009 [(5)].

Studies into the efficacy and safety of Aczone have been conducted in two separate but linked randomized trials [(16)].

After a 12-week course of aczone therapy, the number of inflamed lesions was decreased by half, while the number of noninflamed lesions was reduced by a third. But even though these drops were regarded as statistically significant, just a slight improvement was seen compared to the vehicle when it came to reducing the number of inflamed and noninflamed lesion counts. Benzoyl peroxide and adapalene have both been studied in conjunction with dapsone [(17)].

Only when dapsone and placebo were administered together did there appear to be a difference in the number of lesions. Dapsone added to tazarotene 0.1 percent was recently compared to tazarotene alone in research for acne treatment. The combination reduced the total lesion count by 63 percent compared to tazarotene alone, according to the study. To summarize, these efficacy trials demonstrate the effectiveness of topical dapsone as an anti-acne treatment, but until comparison studies can provide data, it is unclear under what conditions doctors should prescribe the medication [(18)].

Jawade & Singh [(19)] topical dapsone 5 percent gel for the treatment of acne vulgaris was the subject of research, After 12 weeks, the success rate was 31.54 percent. Overall lesions were reduced by 57%, non-inflammatory lesions by 52%, and inflammatory lesions by 63% with the use of Dapsone 5 percent gel, respectively. Dapsone gel side effects were minor and short-lived.

Helpful and well-tolerated Dapsone 5 percent gel was found to be effective in both non-inflammatory and inflammatory acne lesions [(19)].

Dapsone is available as a topical gel in concentrations ranging from 5% to 7.5%. Acne may be effectively and safely treated with these concentrations, and the 5% concentration is said to be gentle enough for delicate skin [(13)].

When it comes to treating acne, women may be more likely to adhere to twice-daily regimens because of their hormonal differences or because they are more inclined to apply the gel twice a day [(20)].

In the early phases of both comedonal and noncomedonal acne, the 5 percent gel may be particularly helpful, especially when taken in conjunction with a retinoid [(20)]. When administered once a day, the 7.5 percent gel is helpful for 30–40 percent of patients who are unable to adhere to twice-daily regimens [(20)].

By 12 weeks, the 7.5 percent formulation is well tolerated. This method of acne treatment has been reserved for those with severe nodulocystic acne or those who have been unsuccessful with other treatments [20].

Dermatitis Herpetiformis:

Gluten-sensitive enteropathy (GSE) is related to Dermatitis herpetiformis (DH), an autoimmune blistering illness. It's more common for people who have autoimmune disorders like thyroiditis to also suffer from anemia and type 1 diabetes [21]. Gluten-free diets and dapsone are the current standard of therapy for DH [21].

Leprosy:

The bacteria Mycobacterium leprae is the source of leprosy. Granulomas of the skin and mucous membranes, as well as peripheral nerve involvement, are hallmarks of chronic leprosy. Pregnancy can increase the risk of developing leprosy. Skin, nerves, limbs, and eyes can all be permanently damaged if untreated. Antibiotics such as dapsone are commonly used in treatment [22].

Erythema Elevatum Diutinum:

Rarely occurring brown or red-purple papules, nodules, or plaques describe Erythema elevatum Diutinum (EED). Dapsone is an effective treatment method [13].

Hidradenitis Suppurativa:

Although it is most common in intertriginous areas, such as the axilla, inner thighs, groyne, and pendulous breasts; it can also arise on any follicular skin, such as the back of the neck. It is possible to treat mild HS with a combination of topical dapsone and clindamycin [22].

Autoimmune Bullous Diseases (AIBD):

Skin and mucosal surfaces with autoimmunity to basement membranes or intercellular adhesion molecules make up AIBD, a group of disorders [23].

DOSAGE in acne:

It's recommended that you use Aczone for up to 12 weeks, using it twice daily [24].

Contraindications:

Aczone can be used without fear of side effects. Oral dapsone, on the other hand, has been linked to hemolysis (abnormal breakdown of red blood cells) and hemolytic anemia (a blood disorder). If a person has glucose-6-phosphate dehydrogenase deficiency, hemolysis is more likely to occur (G6PD). Hemolysis can be triggered by infections and the use of medications like dapsone [25].

Aczone was tested for hematological safety in acne patients with G6PD deficiency for 12 weeks, and some patients experienced minor hemolysis, as seen by a hemoglobin reduction of 0.32 g/dl, but no clinical or laboratory evidence of hemolytic anemia was found overall [26].

Do not use Aczone gel if you have back discomfort, dyspnea, fatigue/weakness with daily tasks, dark brown urine, and high temperature when using the gel (the firm recommends halting use if these symptoms arise). Patients using antimalarials such as dapsone should also avoid aczone as it may produce a hemolytic reaction [5].

Pregnancy and lactation:

Pregnant women are advised to only use Aczone if the benefits outweigh the risks, even though oral dapsone has been demonstrated to be embryocidal in animal studies at extremely high concentrations. Although topical administration of dapsone has very low systemic levels, the company nonetheless advises nursing moms to stop nursing or stop taking the medicine [27].

Drug interactions:

The combination of trimethoprim-sulfamethoxazole (160/800 mg) and Aczone resulted in a rise in dapsone and its metabolite, N-acetyl-dapsone, although systemic levels were still 100-fold lower than oral dapsone at therapeutic doses [28].

Side Effects:

For the most part, adverse reactions to this treatment are predictable and localized to the area where it is applied, like with many other topical treatments. Skin peeling is one of the side effects of erythema. Only 6% of patients who used Aczone had moderate side effects, according to the study. Alternating days of use (or even less frequently) and gradually raising the frequency of application to daily may lessen the severity of such side effects. As with any medication, patients need to be aware of any side effects and share any concerns with their doctor [5].

CONCLUSION

Acne vulgaris can be effectively treated with topical Dapsone, according to clinical trials.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Suppiah T, Sundram T, Tan E *et al*. (2018):** Acne vulgaris and its association with dietary intake: a Malaysian perspective. Asia Pac J Clin Nutr., 27 5:1141-1145.
2. **Lynn D, Umari T, Dunnick C *et al.* (2016):** The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther., 7:13-25.
3. **Gulliver W, Zouboulis C, Prens E *et al.* (2016):** Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the

European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord., 17:343-351.

4. **Skroza N, Tolino E, Mambrin A *et al.* (2018):** Adult Acne Versus Adolescent Acne: A Retrospective Study of 1,167 Patients. J Clin Aesthet Dermatol., 11:21-25.
5. **Radley K, Tucker R (2013):** Dapsone in the Management of Acne Vulgaris. Journal of the Dermatology Nurses' Association, 6:316-319.
6. **Zhu Y, Stiller M (2001):** Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol., 45(3):420-34.
7. **Barr J (2011):** A short history of dapsone, or an alternative model of drug development. J Hist Med Allied Sci., 66(4):425-67.
8. **Sago J, Hall R (2002):** Dapsone. Dermatol Ther., 15:340-51.
9. **Wolf R, Matz H, Orion E *et al.* (2002):** Dapsone. Dermatol Online J., 8(1):2-6.
10. **Gordon R, Mays R, Sambrano B *et al.* (2012):** Antibiotics used in nonbacterial dermatologic conditions. Dermatol Ther., 25(1):38-54.
11. **Pickert A, Raimer S (2016):** An evaluation of dapsone gel 5% in the treatment of acne vulgaris. Expert Opin Pharmacother., 10: 1515-21.
12. **Stotland M, Shalita A, Kissling R (2014):** Dapsone 7.5% gel: a review of its efficacy and safety in the treatment of acne vulgaris. Am J Clin Dermatol., 10:221-7.
13. **Abramovits W (2018):** Dapsone in Dermatology. In, Yamauchi P. (eds): Biologic and Systemic Agents in Dermatology. Springer, Pp. 517-524. https://www.ellibs.com/fi/book/9783319668840/biologic-and-systemic-agents-in-dermatology
14. **Debol S, Herron M, Nelson R (2002):** Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. J Leukoc Biol., 62:827–836.
15. **Gorle A, Pawara K (2017):** Formulation, development, and evaluation of antiacne dapsone gel. W J Phar And Pharmaceutical Sci., 8:1664-1679
16. **Draelos Z, Carter E, Maloney J *et al.* (2007):** Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol., 56: 439-4.
17. **Fleischer A, Shalita A, Eichenfield L *et al.* (2010):** Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. J Drugs Dermatol., 9(1):33-40.
18. **Tanghetti E, Kawata A, Daniels S *et al.* (2011):** Understanding the burden of adult female acne. J Clin Aesthet Dermatol., 7(2):22-30.
19. **Jawade S, Singh A (2016):** Efficacy of Dapsone 5% gel in the treatment of Acne vulgaris. International Journal of Research in Dermatology, 2(4):77-83.
20. **Yin N, McMichael A (2014):** Acne in patients with skin of color: practical management. Am J Clin Dermatol., 15(1):7-16.
21. **Dreno B, Gollnick H, Kang S *et al.* (2015):** Understanding innate immunity and inflammation in acne: implications for management. J Eur Acad Dermatol Venereol., 29: 3-11.
22. **Kundakci N, Erdem C (2020):** Leprosy: A Great Imitator. Clinics in Dermatology, 37: 200-212.
23. **Alghamdi H, Alhemel A, Bukhari I (2017):** Effect of milk and dairy products consumption on acne risk and severity in young adult patients with Acne vulgaris attending the dermatology clinics at King Fahd hospital of the university in Alkhobar, Saudi Arabia. Science Rise, 4: 4-8.
24. **Al-Salama Z, Deeks E (2017):** Dapsone 7.5% Gel: A Review in Acne Vulgaris. Am J Clin Dermatol., 18(1):139-145.
25. **Pamba A, Richardson N, Carter N *et al.* (2012):** Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. Blood, 120(20):4123-33.
26. **Piette W, Taylor S, Pariser D *et al.* (2008):** Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol., 144(12):1564-70.
27. **Zaenglein A, Pathy A, Schlosser B *et al.* (2016):** Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol., 74(5): 945–973.
28. **Molinelli E, Paolinelli M, Campanati A *et al.* (2019):** Metabolic, pharmacokinetic, and toxicological issues surrounding dapsone. Expert Opin Drug Metab Toxicol., 15(5):367-379.