Assessment of efficacy and safety of dapsone gel 5% in the treatment of acne vulgaris

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ABSTRACTBackground : Acne vulgaris is a common skin disease, affecting more than 85% of adolescents and often continuing into adulthood. People between 11 and 30 years of age and up to 5% of older adults. For most patients acne remains a nuisance with occasional flares of unsightly comedones, pustules and nodules. For other less fortunate persons, the sever inflammatory response to Propionibacterium acnes (P.acnes) results in permanent

Methods: Disfiguring scars. [1, 2] Stigmata of sever acne cane lead to social ostracism, withdrawal from society and severe psychologic depression [1-4].

Result Pathogenesis of acne Traditionally, acne has been thought of as a multifactorial disease of the folliculosebaceous unit, involving excess sebum production, abnormal follicular hyperkeratinization, overgrowth of Propionibacterium acnes, and inflammation (Fig 2). Recent laboratory and clinical investigations into the roles of the innate immune system and extracellular matrix remodeling proteins have shed additional light on this pathogenetic process [5-7].

Role of androgens: Activity of type 1 5a-reductase enzyme was shown to predominate in human sebaceous glands and epidermis. This enzyme is responsible for the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). DHT in turn is thought to mediate androgen dependent skin diseases such as acne, hirsutism and androgenetic alopecia [13] The enzyme 5a-reductase type 1 has been studied in those with and without acne and it has been hypothesized that those with acne might have more active 5a-reductase type 1 .[2]

Conclusion : The prominent role of hormones in the pathophysiology of acne has long been recognized and corroborated by clinical and experimental observations and therapeutic experience [14]. Although acne is not considered a primary endocrine disorder, androgens, such as dihydrotestosterone, dehydroepiandrosterone sulfate, and testosterone, and growth hormone and insulin-like growth factors, have all been implicated in the pathogenesis of acne [15].

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Introduction

Increase in sebum production:

Adrenarche causes increased production of DHEAS from adrenal gland with subsequent rise in testosterone and DHT. This leads to sebaceous gland enlargement and increased sebum production.[23] Androgen stimulation drives the changes in both follicular keratinocytes and sebocytes that lead to the formation of microcomedones and subsequent development of inflammatory lesions and comedones[24] In acne patients, excess sebum production is mainly due to a difference in the response of the target organ (the pilosebaceous unit), increased circulating androgens or both. [25]

Follicular hyperkeratnization:

The cause of the hyperproliferation of keratinocytes and the abnormalities of differentiation and desquamation are unknown[27] Recent studies suggest that interleukin 1 alpha (IL-la) and androgens may be involved in this process[28,29]

Bacterial proliferation:

High sebum concentrations and follicular hyperkeratinization lead to a change of the follicular milieu which lead to consecutive proliferation of bacteria, chiefly P.acnes.[30,31] The organism metabolises sebaceous triglycerides, consuming the glycerol fraction and discarding free fatty acids. As a consequence of growth and metabolism, P.acnes produces neutrophil chemoattractants. Recent studies have shown that P.acnes affects both the differentiation and viability of sebocytes.[32] Immune response to P. acnes includes humoral and cell-mediated immunity as well as complement activation.[31,33]

Methods

Inflammation:

Toll-like receptors (TLRs) are ‘‘pathogen-associated pattern recognition receptors’’ that recognize particular pathogen-associated molecular patterns conserved among microorganisms and elicit specific immune responses [36] Expressed on many immune cells

and at sites of host-pathogen interaction, such as the skin , TLRs are instrumental in launching innate immune responses and influencing adaptive immunity. Recent results suggest that keratinocytes and sebocytes may be activated by P acnes by TLRs and CD14 leading to the production of inflammatory cytokines, such as interleukin (IL)-12 and IL-8 [37]. This cytokine response is a T helper-1–type immune response [38], and is mediated through increased expression of TLR-2 and TLR-4 by P acnes. Furthermore, because TLRs are vital players in infectious and inflammatory diseases, they have been identified as potential therapeutic targets [5].

TLR-2 is expressed on infiltrating inflammatory cells around the pilosebaceous follicle in those with acne. Its expression increases as the acne lesion ages and becomes more inflamed.[2,39] Keratinocytes and sebocytes, as major components of pilosebaceous unit, may act as immune cells and may be activated by P. acnes via TLRs and CD 14, and through GDI molecules may recognize altered lipid content in sebum, followed by the production of inflammatory cytokines[31,42]

Role of matrix metaloproteinases:

Although the precise inflammatory mediators activated in acne have not been fully described, advances in gene array expression profiling have helped to identify individual candidate genes [43]. Significant up-regulation of genes involved in mediating inflammation and extracellular matrix remodeling, such as the matrix metalloproteinase (MMPs), has been recently identified from acne lesional tissue [44,45].MMPs are a group of zinc-dependent endopeptidases that selectively degrade various components of extracellular matrix and nonmatrix proteins . MMP-1 and MMP-3 are up-regulated in skin lesions from acne patients [45], and down-regulation of some MMPs is seen in the setting of improving acne during isotretinoin treatment.

Diagnosis:

The diagnosis of acne is based on history and physical examination. [47] Acne is characterized by open and closed comedones (blackheads and whiteheads), which are present either alone or more commonly with pustules and erythematous papules[11] Lesions most commonly develop in areas with the greatest concentration of sebaceous glands, which include the face, neck, chest, upper arms and back.[27,48]

Classification:

Global Acne Assessment Score (Table1) .In 2003, Cunliffe[49] suggested a new classification for acne (Table2) and Acne also is classified by type of lesion into comedonal, papulopustular, and nodulocystic. Pustules and cysts are considered inflammatory acne [31]

Table (1): The Global Acne Assessment Score GAAS Severity Description

GAAS	severity	Description
0	None	No evidence of facial acne vulgaris
1	Minimal	A few noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
2	Mild	Several to many noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
3	Moderate	Many noninflammatory lesions (comedones) and inflammatory lesions (papules/pustules) are present; no nodulocystic lesions are allowed
4	Severe	Significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulocystic

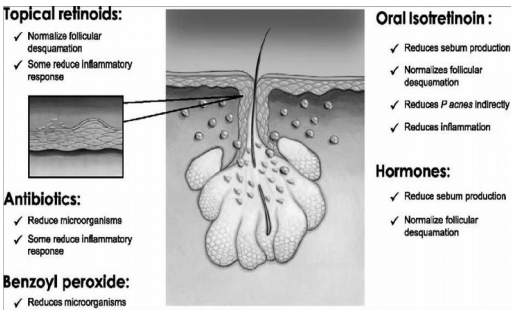
	lesions may be present; comedones may be present

Table (2): Acne classification according to Cunliffe (2003)[49]

Severity	*Description*
Mild	Comedones (non inflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally<10).
Moderate	Moderate numbers of papules and pustules(10-40) and comedones (10-40) are present. Mild disease of the trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasionally larger, deeper nodular inflamed lesions (up to 5). Wide spread affected areas usually involve the face, chest and back.
Sever	Nodulocystic acne and acne conglobata with many large, painful nodular or pustular lesions are present, along with many smaller papules and pustules and comedones.

Results : Treatment of acne:

It is necessary to consider the type of acne and the severity of symptoms to efficiently treat acne (Fig 3).[48,51,52] Treatment of acne is aimed at preventing the formation of comedones, papules, pustules, reducing inflammation, improving the adolescent's appearance, preventing scarring and avoiding the adverse psychological impact of acne (low self-esteem, loss of self-confidence, social isolation and depression)(48,53, 54)



Fig(3) treatment of acne [53]

Topical agents

Topical retinoids, benzoyl peroxide and azelaic acid are effective treatments for mild acne. Topical antibiotics and medications with bacteriostatic and anti-inflammatory properties are effective for treating mild to moderate inflammatory acne. Proper selection of topical formulations may decrease side effects and increase patient compliance. Fortunately, most acne medications are available in several forms. Creams and lotions typically are reserved for dry or sensitive skin, whereas gels are prescribed for oil-prone complexion. (56)

Combination topical agents e.g. clindamycin and benzoyl peroxide, erthromycin and benzoyl peroxide, or erythromycin and zinc oxide may be more effective than the topical antibiotic alone. Similarly, the addition of an antibiotic to benzoyl peroxide may be slightly more effective than benzoyl peroxide alone. However, they are generally more costy as well [56].

Most patients present with mild to moderate comedonal or papulopustular acne; in such patients, topical therapy is the first line of treatment. [57-59]

Results

Topical antibiotics

Topical antibiotics are indicated to treat mild inflammatory acne. The most commonly used are clindamycin and erythromycin. [68]Other topical antibiotics are used less often due to lower efficacy or increased side effects. Topical antibiotics reduce the population of *P. acnes* on the skin surface and particularly within the follicles, thereby reducing free fatty acids on the skin surface lipids—a marker of *P. acnes* lipase activity. [69-71] They demonstrate anti-inflammatory activity by suppressing chemotaxis.[72,73] Subsequently, an indirect

anticomedogenic effect can be observed,[74] which seems to be stronger with clindamycin. [69] Topical antibiotics have a relatively low cutaneous irritant profile.

One of the major setbacks in the use of topical antibiotics has been the dramatic increase in bacterial resistance over the past 20 years.[68,75-78] Antibiotic-resistant strains of *P. acnes* are found worldwide.[76,79], Therefore, combination therapies of topical antibiotics (e.g., with benzoyl peroxide, either alternating or as fixed combinations[76,8086], or alternating with azelaic acid[87] are now favored, because this reduces existing resistant *P. acnes*; counteracts the selection of new, resistant *P. acnes* strains; and reduces the risk of colonization with resistant *Staphylococcus aureus*. Topical antibiotics generally should not usually be used as monotherapy; if monotherapy is necessary, it should be maintained for only a short (3- to 4-week) period. Where possible, topicla antibiotics should be combined with topical retinoids to enhance efficacy against comedones and inflammatory acne lesions. Combination with benzoyl peroxide also reduces the risk of *P. acnes* resistance. Therapy with topical antibiotics should be discontinued when inflammatory lesions resolve adequately or, if this is not possible, switched to a combination of benzoyl peroxide and an antibiotic. [63]

Systemic treatment

Systemic treatment for acne includes antibiotics, hormones and isotretinoin.[101] Other drugs such as dapsone, clofazimine, and vitamin A (10-20 mg/day) are very occasionally used; there is very little evidence for their effectiveness. Oral treatment will be required in patients with moderate to severe acne, patients who are significantly depressed (even if the acne is physically mild), patients with body dysmorphic disorder and patients with scarring or who are prone to scarring [102]

MISCELLANEOUS THERAPY

Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.

There is limited evidence regarding the benefit of physical modalities including glycolic acid peels and salicylic acid peels[100].

COMPLEMENTARY THERAPY

Herbal and alternative therapies have been used to treat acne. Although these products appear to be well tolerated, very limited data exist regarding the safety and efficacy of these agents (100,141).

Dapsone

Dapsone and other sulphonamides have been used successfully in the treatment of patient with a variety of blistering skin diseases. The patient most likely respond to dapsone therapy have a predominantly nutrophilic infiltrate in there skin. There for the blistering disease with the most constant responses to dapsone therapy include dermatitis herpetiformis and linear IgA disease. Dapsone's precise mechanism of action is unknown in vitro studies have shown that dapsone can interfere with the production of and response to neutrophil chemoattractants and that it may impair the neutroplis' ability to localize to sites of inflammation and produce toxic oxygen intermediates. The safe use of dapsone requires an understanding of pharmacology and adverse effects of the drug. Hemolytic anaemia and methemoglobinemia are two of the dose-related adverse effects. Agranulocytosis, motor neuropathy, and dapsone hypersensitivity syndrome are some of the sever idiosyncratic effects that can occur in patients treated with dapsone. Dapsone is an effective drug for the management of patients with some blistering disease, especially those with predominant neutrophilic infiltrates in the skin. Carefull patient selection and close monitoring of patients with blistering skin diseases [142].

Pharmacology

Absorption /bioavailability

Dapsone is a lipid-soluble compound that penetrates well into cells and tissues. It is well absorbed from the gut with approximately 70-80% of a single oral dose absorbed. Its absorption half-life is about 1 hour [149,150]. Dapsone's greater effectiveness than other sulphonamides is probably related to its superior absorption from the gut and its effective penetration into the cell. Of note, patients with dermatitis herpetiformis do not demonstrate any significant impairment in the absorption of dapsone, with or without symptomatic intestinal involvement[151-154]. Dapsone is able to cross the placenta and its excreted into breast milk [150,155]. Hemolysis

has been demonstrated in nursing infants of mothers taking dapsone[155]. No harmful effects of dapsone have been demonstrated on development in-utro [156]. This is reassuring given its widespread use in developing countries for the treatment of leprosy.

Metabolism

Dapsone is primarily metabolized by N-acetylation and N-hydroxylation. There is significant variability in acetylation, with some individuals begin rapid acetylators. This variability, however, does not change the dose requirement or cause differences in steady-state plasma concentrations[154].

The second major pathway of dapsone metabolism is hydroxylation. N-hydroxylation of dapsone occurs in the liver, mediated by various cytochrome p-450 enzymes, including CYP2E1, CYP2C9 and CYP3A4 [157]. The hydroxylamine metabolite is thought to cause the hematologic adverse effects associated with dapsone, including methemoglobinemia and haemolytic anaemia [158,159].

Excretion

Dapsone and its metabolites are conjugated in the liver to glucuronides, which are water-soluble and rapidly excreted by the kidneys.

Mechanisms of action

While dapsone's mechanism of action in the treatment of leprosy has been shown to be duo to its inhibition of folic acid pathway, its mechanism in inflammatory diseases are not well understood [151]. Dapsone is most useful in treating diseases with neutrophilic infiltrates in the skin. In conditions effectively treated with dapsone, To produce this effect, it has been postulated that dapsone impairs neutrophil chemotaxis by inhibiting the production of neutrophil chemotactic stimuli and by blunting neutrophil responce to chemotactic signals. It has also been suggested that dapsone may inhibit the ability of neutrophils to function at the sites of inflammation. Despite dapsone's potential interference with neutrophil function, there appears to be no increased risk of opportunistic infections in patients taking the drug, suggesting that its effect on neutrophils is relatively selective.

Impairs neutropil chemotaxis

Dapsone affects neutrophil chemotaxis in multiple ways. It has been shown to block the production of and neutrophil response to chemoattractants. Dapsone has also been demonstrated in some studies to reduce the capacity of neutrophils to adhere to localizing signals.

To generate an inflammatory response, chemoattractants must first be produced[163]. Recently demonstrated that dapsone inhibits the release of IL-8, a known neutrophil chemotactic agent, from keratinocytes exposed to one of the pathogenic autoantibodes in bullous pemphigoid. These researchers saw no change in IL-8 mRNA levels and concluded that dapsone's effect on IL-8 release was posttranslational. In vivo studies addressing this effect have not been performed.

After chemoattractants have been produced, neutrophils must be able to respond to them. Dapsone has been shown to inhibit leukotriene B4 (LTB4)-neutrophil interactions. LTB4 is a chemoattractant generated from the 5-lipoxygennase family of inflammatory mediators. Dapsone inhibits neutrophil-LTB4 [164,165].

After neutrophils have sensed the inflammatory signal, they must be able to localize to the area of inflammation and migrate through the tissues. Although initial investigations showed no consistent inhibition of chemotaxis by dapsone[166-168] Harvath et al. were able to demonstrate selective inhibition of neutrophil chemotaxis to the chemoattractant Nformyl-methionyl-leucyl-phenylalanine (F-met-leu-phe)[169]. Thuong-Nguyen et al. showed that dapsone inhibits the migration and adherence of neutrophils to IgA- or IgGcoated normal epidermal basement membrane [170]. Booth et al. and Debol et al. demonstrated that dapsone affects integrin mediated neutrophil adherence to endothelium, a necessary step prior to diapedesisof those cells into inflamed tissue. Dapsone inhibits the signaling generated by the noncovalent association of CD11b with CD18. CD11b/CD18 coupling normally triggers the G-protein second messenger system, allowing neutrophils to move from the vascular space to an area of injury [171,172]. Dapsone did not inhibit the adherence response of neutrophils to all agonists utilizing the CD11b/CD18 system, suggesting that its effect was not adirectly toxic one. Modschiedler et al. showed that dapsone

decreased the adherence of neutrophils to interferon-gamma treated skin [173].

Impairs neutrophil function

Dapsone has been demonstrated in-vivo to impair the function of neutrophil myeloperoxidase and other lysosomal enzymes and thus the production of toxic oxygen intermediates [166,167]. Dapsone inhibits the myeloperoxidase-halide-mediated cytotoxic system. Dapsone could therefore modulate the degree of tissue destruction in lesion[166]. This effect was preferentially noted at a higher pH (unlike the microenvironment of the phagolysosome). Dapsone might have a greater effect on the myeloperoxidase that is actually secreted into the interstitium . The clinical revelance of dapsone's impact on neutrophil function is unclear, however, as patients treated with dapsone show an absence of neutrophils in the skin rather than neutrophils that are still present but less destractive[174].

Clinical uses

Dermatologic indications:

Dapsone has been approved by the U.S Food and Drug Administration (FDA) for the treatment of patients with dermatitis herpetiformis or leprosy. Dapsone responsive dermatoses can be divided into two general categories: those in which the response has been clearly documented and those in which the response has been noted only anecdotally or in a minority of treated patients. Due to the relative toxicity of Dapsone and the erratic nature of many inflammatory skin diseases, it is important that clear criteria be established for Dapsone responsiveness. If Dapsone is going to be effective in the treatment of an inflammatory dermatosis, the patient should experience a relatively rapid response (within 24-48hours), with a similar rapid recurrence of symptoms after withdrawal of the medication. iIn general, sulfasalazin (Azulfidine) and its active metabolite, sulfapyridine, have a similar but less effective profile of activity than Dapsone. This is likely duo to their less efficient absorption from the gastrointestinal tract.

Contraindication

Dapsone is contraindicated in patient with documented hypersensitivity to the drug. Sulfapyridine is also contraindicated when hyper sensitivity to that drug has been documented. It is important to note, however, that cross-sensitivity between dapsone and other sulfonamides is relatively rare [201]. A relative contraindication to the use of both drugs are their dose related, pharmacologic adverse events. Patients at increased risk for these events duo to cardiopulmonary or hematologic disease or glucose-6-phosphate dehydrogenase (G6PD) deficiency should be monitored with great care [202].

Adverse effects: pharmacologic **Hemolytic anemia**

The development of methemoglobinemia and hemolytic anemia have long been recognized as adverse events associated with dapsone and occure to some degree in all individuals taking the drug. There is, however, significant variability in the degree and significance of the hematologic changes. Athough dose-related, predisposed individuals can experience significant effecta after a single 100 mg dose of dapsone [158]. The observations that dapsone is not directly toxic to erythrocyte in vitro and that dapsone levels do not correlate with hematologic adverse effects led to the discovery that dapsone hematotoxicity is duo to its N-hydroxy metabolites [159,203]. These metabolites are potent oxidants. The ability of erythrocytes to tolerate oxidative stress is related to their supply of reduced glutathione and the ability of hexhexose mono-phosphate shunt to repair oxidative damage. Since red blood cells cannot synthesize new protein, the ability of the red blood cells to resist axidative stress decreases with time. Oxidative damage causes structural changes to the red cell membrane. The cell is then labeled as "senescent" by the body and removed from circulation by the spleen (extravascular hemolysis) [158]. This likely accounts for the initial decrease in hemoglobin seen in patients started on dapsone. A partial correction then supervenes duo to increased production of new red blood cells by the bone marrow. Some degree of intravascular hemolysis continues to be present duo to erythrocyte fragility, again a result of membrane membrane structural changes.

Susceptibility to dapsone's hematologic adverse effects is heightened in individuals who are deficient in G6PD. G6PD deficiency results in impairment of the hexose

monophosphate shunt and a diminished supply of glutathione [204]. It is important to remember that although this enzyme is more frequently absent in african Americans (about 10%of American black men), variability of enzyme function can exist those of Middle Eastern ancestry and Asians and results in significant hemolysis [205,206]. Methmoglobinemia.

The second major hematologic adverse event associated with dapsone is methemoglobinemia. Methemoglobin is formed when the iron within the heme molecule is oxidized to the ferric state by the hydroxylamine metabolite of dapsone. Reversing this reaction requires reduced glutathione and enzyme methemoglobin redactase [157,158]. There is no clear relationship between hemolytic anemia and the methemoglobinemia seen in patients taking dapsone. Methemoglobin cannot carry oxygen and impacts overall oxygen delivery only at concentrations greater than 30% in normal individuals. The clinical significance of the methemoglobinemia in an individual patient is related to their total hemoglobin and their cardiopulmonary reserve. For example a patient with 10% methemoglobin but a total hemoglobin of 15 g/dl will still have functional hemoglobin of approximately 13.5 g/dl. The same percentage of methemoglobin (10%) in patent with total hemoglobin of 10 g/dl, however, will produce a functional hemoglobin concentration of only 9 g/dl and the patient may develop symptoms. Symptoms and sings of toxicity include lethargy, head ache, dyspnea and cyanosis [207]. It is not possible to predict the degree of methemoglobinemia based on the degree of cyanosis of the patient.

In addition the clinician should be aware that methemoglobin can confound the measurements of pulse oximeters. Pulse oximeters measure oxyhemoglobin saturation based on the relative wavelength absorption of oxy- and deoxyhemoglobin. Methemoglobin's absorption spectrum is similar to deoxygenated hemoglobiun. |Thus the measured values will be low, although methemoglobin dose not have the same clinical impaction as deoxyhemoglobin. Vitamin E (800IU/day) has been demonstrated to improve subclinical markers of hemolysis and taking dapsone; however, clinical benefits have not been documented [208]. Cimetidine has also been shown to temporarily decrease methemoglobin formation in patients being treated with dapsone [161]. This was thought to be duo to cimetidine's inhibition of N-hydroxylation of dapsone. These investigators noted, however, that methemoglobin levels returned to baseline after 2 months of therapy, despite continued use of cimetidine. Cimetidine might be helpful for patients who require an increased dose for clinical effect but are limited by the hematologic side effects [209]. In sever methemoglobinemia, oral (100-300 mg/day) or intravenous (1 mg/kg over 5 minutes with a repeat dose in 30- 60 minutes) methylene blue can be used to acutely decrease methemoglobin levels. Methylene blue stimulates NADPH-dependent methemoglobin reductase activity, a reduction pathway that requires G6PD. G6PDdeficient patients are unable to respond to methylene blue [210].

Adverse effects: idiosyncratic

The mechanism of the idiosyncratic adverse effects of dapsone are less well understood than the pharmacologic adverse effects. These effects are not dose-related and there are no clinical criteria to predict their development.

Agranulocytosis.

Agranulocytosis is one of the most serious idiosyncratic reaction to dapsone [211,212]. The exact mechanism of agranulocytosis is not known, however, several hypotheses have been proposed. It is known that the hydroxylamine metabolite of dapsone is scavenged by erythrocytes. Cytotoxic metabolite might be delivered to the bone marrow in erythrocytes, where it leeches out and damages neutrophil precursors. Another hypothesis is that myeloperoxidase within the neutrophil precursors in the bone marrow produces the hydroxylamine metabolite locally. However, dapsone interferes with the function of myeloperoxidase and so it is unlikely that this mechanism could produce significant toxicity to the bone marrow. Perhaps the most

plausible explanation is the dapsone induces apoptosis in the neutrophil precursors. G-protein-coupled second messengers are important in a number of neutrophil regulatory systems. Dapsone, by inhibiting G-proteins, might block a highly specific mechanism of cell control rather than act as a direct toxin or produce a hapten-mediated immune response. This would explain why the bone marrow recovers so quickly upon drug withdrawal [213].

Incidence of agranulocytosis in patients with DH on dapsone at 1 case per every 3000 patient-years of exposure or approximately 1 in 240 to 1 in 425 patients. The median duration of therapy before the development of agranulocytosis is 7 weeks: however, cases have been reported as early as 3 weeks after starting the drug. Very rarely dose agranulocytosis develop after more than 12 weeks of therapy. The average dose in reported cases was 100 mg/day: there is no evidence for dose dependency in this effect [211,212]. Patients most often present with symptoms/signs of infection such as fever or pharyngitis. Occasionally there are signs of sepsis. With drug discontinuation, recovery is typical in 7-14 days if patients survive the presenting infection. Granulocyte colonystimulating factor (G-CSF) has been used successfully to speed hematologic recovery. Patients should have frequent complete blood counts (CBCs) within first 3 months of therapy and should be instructed to discontinue the medication if they develop sign/symptoms of infection [214].

Neuropathy.

Dapsone has been associated with several adverse neurologic events. The most common, although still rare, is a peripheral neuropathy [215-219]. This neuropathy primarily involves the distal motor nerves, with evidence of axonal degeneration by electrophysiology. Although a sensory component has been reported in a minority of patients, it has always been associated with motor findings [219]. Patients most typically present with weakness of their hands and/or legs, often with wasting of their hand muscles. Usually patients do not have oter signs of sever dapsone toxicity (sulfone syndrome, sever anemia, methemoglobinemia). The dose of dapsone associated with the development of neuropathy ranges from 75 to 600 mg/day, although most cases have been reported in patients taking more than 300 mg/day [218]. Most patients recover completely with discontinuation of the drug, although recovery may be delayed or incomplete [218]. For patients who cannot tolerate being off dapsone, a decrease in the dose, a temporary drug holiday, or switching to sulfapyridine might be viable options. Although the mechanism of dapsone neuropathy is unkown the patient's acetylator phenotype may play a role [218].

Conclusion

Permanent optic nerve atrophy has been reported in patients with sever dapsone overdose, thought secondary to ischemia induced by red cell fragments in the blood supply of retina [220]. Examined retinal blood flow in patients with DH taking 50-100 mg/day of dapsone and found no abnormalities [221]. Reported case of dapsone overdose with the development of both optic nerve atrophy and motor neuropathy. After 14 months the motor neuropathy had totally resolved. The optic nerve atrophy and visual imparment, however, persisted [222].

In addition a case of acute psychosis after treatment with dapsone has been reported [223-228]. The vast majority of these cases have been in individuals with leprosy. The mental status changes have resolved after discontinuation of the drug. Headache and nervousness have been reported in patients taking dapsone. It has been suggested that some patients are sensitive to even low levels of methemoglobinemia. In a trial evaluating the use of cimetidine to lower methemoglobin levels, a statistically significant improvement in headach was noticed [229].

Gastrointestinal effect

A variety of gastrointestinal adverse events have been associated with dapsone. Some patients experience mild gastrointestinal upset that is usually self-limited and can be controlled by taking the drug with meals.

Patients on dapsone have been reported to develop primary hepatocellular hepatitis as well as a cholestatic hepatitis; both resolves with discontinuation of drug in 10-14 days [226,227]. Elevated transaminases were associated with blood sulfone levels greater than 2 mg/dl, suggesting a direct hepatotoxic effect [227]. In

contrast, liver involvement in the sulfone syndrome is independent of dose. In this syndrome liver function abnormalities are often seen in association with leukocytosis, atypical lymphocytosis,and eosinophilia. Other rare gastrointestinal adverse events associated with dapsone include sever hypoalbuminemia (thought secondary to autoimmune reaction to albumin) and pancreatitis [228,229].

Dapsone hyper sensitivity syndrome

A more sever adverse event associated with dapsone has been called the dapsone syndrome or sulfone syndrome. It is an idiosyncratic, dose-independent, multiorgan disease that, unlike many drug reactions can begin after prolonged exposure to the drug. This syndrome usually appears after more than 4 weeks of therapy and occurs in less than 0.5% of treated patients [230]. The hydroxylamine metabolite has been postulated to be involved in the pathogenesis of this syndrome, perhaps acting as a chemical antigen in an autoimmune reaction. Older age and preexisting liver disease are thought to be somewhat protective, as the activity of the hepatic enzyme generating the metabolite is reduced. This has not, however been validated clinically or experimentally. The syndrome was initially described as an infectious mononucleosis like illness in patients bring treated for lepromatous leprosy [230,231].Patients present with fever, malaise, a generalized cutaneous eruption, lymphadenopathy and hepatitis. The skin eruption can range from maculopapular to toxic epidermal necrolysis and hepatitis shows a mixed hepatocellular and cholestatic pattern [227,230,232].

Patients often have leukocytosis, peripheral eosinophilia, and atypical lymphocytosis. Although most patients recover with discontinuation of the drug, fatalities have been reported. Systemic corticosteroids have been used in the syndrome; however, the benefit of this treatment is unclear. Some patients have been reported to develop hypothyroidism several months after hypersensitivity reaction [233].

Cutaneous hypersensitivity eruption

As with many drugs, dapsone has been associated with a wide variety of skin eruptions, ranging from the typical from the typical maculopapular drug eruptions to erythema multiform and toxic epidermal necrolysis [230]. No adverse effect clearly linked to dapsone in treated patients with previously documented adverse reactions to trimethoprim/sulfamethooxazole [201]. Although the mechanism of cutaneous hypersensitivity is unknown, Reilly et al. recently implicated keratinocyte hydroxylation of dapsone with local cytotoxicity [234]. Photosensitivity has been reported in some patients taking dapsone, often in the context of the dapsone hypersensitivity syndrome (235).

Carcinogenesis

Dapsone has been suggested to be a weak carcinogen. Animal studies have revealed a slightly increased incidence of malignancy in some animals treated for 2 years with high doses. No studies have been confirmed that dapsone is a human carcinogen [236]. Pregnancy and lactation.

The safety of dapsone during pregnancy has also been a concern, as many patients with skin disease require treatment during pregnancy. Although dapsone has not been proven safe in pregnancy, a series of patients with linear IgA dermatitosis and patients with leprosy suggest that dapsone can be safely used in pregnancy [156,237,238]. It should be remembered; however, that dapsone is secreted in breast milk and can rarely cause hemolytic anemia in breast-feeding infants of mothers on dapsone [155].

Drug interaction

Drug interactions are unusual in patients taking dapsone. Probenicid can reduce the renal excretion of dapsone, though the clinical significance of this finding has not been established. Rifampin can also decrease the functional half-life of dapsone secondary to induction of metabolizing liver enzymes. Again, the clinical significance of this interaction is unclear [150]. Potentially significant interactions may occur when

patients on dapsone take other drugs that are also oxidants. The increased oxidative stress to the erythrocyte may worsen the hemolysis that is normally seen with dapsone. Such drugs include other sulfonamides and antimalarials such as hydroxychloroquine [205,239].

Pretreatment considerations

The most important step in minimizing the toxicity associated with dapsone therapy is to evaluate the patient before initiating the drug and providing close follow-up. Understanding the Pharmacology of dapsone and the pathogenesis of the disease being treated will allow the clinician to use dapsone when the likelihood of success is high and the risk of significant adverse effects is as low as possible. Patients being considered for therapy with dapsone should be screened for preexisting cardiopulmonary disease that would increase their risk if significant hemolysis or methemoglobinemia were to develop. Lower initial doses are recommended in these patients. Preexisting anemia, liver or kidney disease offers a more narrow therapeutic window and requires closer laboratory monitoring. A CBC with differential, liver, and renal function testing should be performed prior to initiating therapy. G6PD level should be determined in many, if not all, patients being considered for treatment with dapsone. G6Pd deficiency most often occurs in African Americans and those of Middle or Far East ancestry. It is important to remember that a screening test for G6PD deficiency may be falsely normal if the patient has an elevated reticulocyte count, is heterozygous for enzyme deficiency or has a variant of enzyme that is less capable of handling oxidative stresses in red cells [240].

Quantitative G6PD levels will overcome the limitations of the screening test. Particular attention should be paid to the patient's baseline hemoglobin level. Patients that have a preexisting mild iron, foliate or vitamin B_{12} deficiency will not be able to mount an adequate reticulocyte response to the initial dapsone induced hemolysis, leading to more significant hemolytic anemia.

Theraputic guidelines

Most patients require 100-200 mg/day for adequate control of their skin disease. An initial dose of10 mg/day taken as a single daily dose. Patients can be started on lower doses if necessary; however, it will take longer to determine if dapsone is effective for their skin disease. Dapsone doses can be adjusted at 2-week intervals until control of the skin disease is obtained, while monitoring for dose dependant adverse events. In patients under good control, it is recommended that dapsone dose be gradually decreased to the lowest effective dose to minimize adverse effects.

Monitoring during therapy

A CBC should be obtained frequently during the first 3 months of therapy to evaluate hemolysis and agranulocytosis. Recommendations vary from weekly to monthly for the first 3 months; after this time, hemolysis has usually stabilized and agranulocytosis is rare. Patients on chronic dapsone should probably have CBC every 34 months and whenever dose increases occur. Checking for liver and renal function is recommended every 3-6 months. Methemoglobin levels need not be measured unless the patients experiencing symptoms such as excessive fatigue, headaches or cardiopulmonary symptoms. Evaluation of methemoglobin levels may also be useful for patients in whom noncompliance is the suspected cause of a suboptimal response. Patients should carry medication cards that state that they are on dapsone so other clinicians won't embark on a work-up for their methemoglobinemia and decreased pulse oximetry readings. Patients should be regularly reminded not to increase the dose of dapsone on their own due to the increased risk of dose dependant side effects. They should also be reminded to stop the drug if a prolonged febrile illness occurs and to alert their physician if they experience a mono-like illness. At all follow-up visits, patients should be evaluated for symptoms/signs of worsening cardiopulmonary disease and for development of distal motor neuropathy.

AIM OF THE WORK

The aim of this work is to evaluate the efficacy and safety of Dapsone 5% Gel in the treatment of acne.

METHODS Two hundred and fifty patients 14 years of age or older with a clinical diagnosis of acne vulgaris involving the face were included in this study. Patients were selected from the attendants of the Dermatology Outpatient Clinic of the Alexandria Main University Hospital and private Dermatology Clinic. **Inclusion and exclusion criteria for patients are the following:** Inclusion criteria:Patients who had 20 to 50 inflammatory lesions (defined to include papules and pustules) and/or 20 to 100 noninflammatory lesions (comedones) (Grade 2 or 3 by global acne assessment score) at baseline.Patients who had given an informed consent to participate in the study. Patients with reasonable, realistic outcome expectations about the treatment.

Exclusion criteria:

1. atient with severe cystic acne, acne conglobata, or any active or developing nodules (Grade 4 global acne assessment score).
2. Patients with a history of using topical drugs or treatments with anti inflammatory agents; use within 4 weeks before baseline of systemic medications or therapy known to affect acne or inflammatory responses; use of isotretinoin within 3 months of baseline. .
3. Patients with allergy or hypersensitivity to dapsone, sulfa drugs, or excipients of the dapsone gel product.
4. Women of childbearing planning to be pregnant or pregnant.
5. Women using hormonal contraception (Systemic contraceptive).
6. Patients with impaired complete blood picture (CBC) or bleeding time disorder [50].

Patients were divided in to two groups:

Group I : Includes 200 acne patients used Dapsone Gel 5% twice daily for 6 weeks.

Group II: Includes 50 acne patients used base used in the preparation of Dapsone Gel 5% without Dapsone twice daily for 6 weeks**.**

Each patient was subjected to:

Thorough history including personal history, present history and family history of the same condition.

1- **Past history of** a

2- polycystic ovary. b- Menstrual irregularity. c- Drug intake

3- specially previous isotretinoin therapy

d-Glucose 6 phosphate Dehydrogenase deficiency or anemia if positive Glucose 6 phosphate dehydrogenase level and complete blood count, including a reticulocyte count should be obtained at base line and every 2 week during treatment.

4- **The patient's**

5- complaint. 4- Examination:

- ***General examination:***
- ***Local examination:***

1-Evaluation of the type and morphology of acne.

2-The overall severities of the acne were graded on 4-point scale as follows, Global acne assessments score (Table 1 copied)[i]

GAAS	severity	Description
0	None	No evidence of facial acne vulgaris
1	Minimal	A few noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
2	Mild	Several to many noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
3	Moderate	Many noninflammatory lesions (comedones) and inflammatory lesions (papules/pustules) are present; no nodulocystic lesions are allowed
4	Severe	Significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulocystic lesions may be present; comedones may be present

We used a personal evaluation scheme developed on the basis of this 4 point scale to evaluate the effectiveness of the therapies.

6- Investigations:

- Complete blood count (CBC).
- Glucose 6 phosphate Dehydrogenase level

If there is a history of Glucose 6 phosphate dehydrogenase deficiency anemia or other forms of anemia.

7- Informed consent:

It was obtained once the patient was appropriately selected. The informed consent includes a thorough discussion of any possible complications.

Therapy:

Dapsone 5% gel were prepared in the Pharmaceutical Department Lab. Faculty Of Pharmacy, Alexandria University.

Method for Dapsone 5% preparation:

The present invention also provides methods for preparing the dermatological compositions described above. In a general form, the method for producing a dermatological gel composition having dissolved dapsone and microparticulate dapsone precipitates comprises the steps of completely dissolving dapsone in a solvent or solvent mixture; adding and adequately dispersing a polymeric thickener in water; and combining the dissolved dapsone with the dispersed polymeric thickener. Alternatively, water may be slowly added to the dissolved dapsone, followed by the addition of a polymeric thickener. Ethoxydigylcol and 1_methyl-_2-_pyrollidone are preferred solvents for use

in the topically applied dermatological composition [241].

In one preferred embodiment, the method for preparing a topically applied dermatological composition having dissolved and microparticulate dapsone comprises the steps of forming a homogenous dispersion by stirring purified water vigorously enough to form a vortex and sifting gel polymer into the vortex formed in the water while continuing to stir; forming a pharmaceutical component by dissolving methyl paraben and propylparaben in ethoxydiglycol by mixing to form a solution, and mixing dapsone with the solution until the pharmaceutical is dissolved; mixing the pharmaceutical component with the homogenous dispersion to form a microparticulate dapsone dispersion; and adding a caustic material.

The order in which reagents are combined may be important, depending on the particular reagents necessary for the target mixture. For example, after a pharmaceutical such as dapsone is dissolved in a solvent such as ethoxydiglycol, water may be slowly added to the dapsone in the ethoxydiglycol solution, or the dapsone in ethoxydiglycol solution may be added to the water with mixing. Adding the dapsone in ethoxydiglycol solution to water may result in less polydispersity in the size of the microparticulates than adding water to the dapsone in ethoxydiglycol solutions. The carbomer is generally dispersed in the water component of the formulation, while the remaining ingredients will be dissolved or dispersed in whichever of the two components are best for dissolving or dispersing the ingredient. For example, it is suggested to dissolve methylparaben, propylparaben in ethoxydiglycol. After the ethoxydiglycol component and water component are combined, neutralizer is added to formulate the gel [242].

Patients were informed to apply Dapsone 5 % gel twice daily for 6 weeks or the base used in the preparation of Dapsone Gel 5%for group II.

Monitoring of adverse events, local signs and symptoms (adverse reactions of facial oiliness, peeling, dryness and erythema), physical examination including vital signs. Patient will be monitored at base line and at each study visit .

RESULTS

This study was carried out on 250 patients suffering from acne, they divided into two groups, group I includes 200 patients used Dapsone Gel 5%, while the other 50 patients in group II used placebo treatment as a control group.

The following data was collected and analysis:

I. Demographic data:

a. Age:

The age ranged from 14-35 years in group I with a mean of 23.21±6.25, while in group II the age of the patients ranged from 15-36 years with a mean of 24.1±7.21, there was no significant difference between the two studied groups regarding age (p =0.39), the most frequent age group was less than 20 year in the two studied groups. (Table 3).

b. Sex:

In group I, 122 of the patients (61.0%) was female, and in group II also 32 was female (64.0%), there was no significant difference between the two studied groups regarding sex (p 0.19) (Table 3).

II. Skin type:

The most frequent skin type in group I was type III (90 patients, 45.0%), while in group II the most frequent skin type was type II. Type IV shows the lowest frequent in the two groups, it was found that there was no significant difference between the two studied groups regarding skin type (p 0.136). Table (4).

Sun exposure:

It was found that the most of the patients in the two studied groups were not frequently exposured to the sun (116 patients, 58.0%) in group I and (31 patients

62.0%) in group II, there was no significant difference between the two studied groups regarding sun exposure (p 0.25) (Table 4).

Type of acne:

In group I, there was 158 patients (79.0%) their acne was non inflammatory, while the other 42 (21.0%) was inflammatory, in group II the non inflammatory acne was found in 32 patients (64.0%), while the other 18 patients (32.0%) was inflammatory, on comparing the two groups it was found that there was no significant difference between the two studied groups regarding type of acne. (p =0.19) (Table 5) **Global Acne Assessment Score (GAAS):**

a. At base line:

In group, 92 of patients (46.0%) had a score 2, while the 108 patients (54.0%) had score 3, on the other hand in group II, 25 patients (50.0%) had score 2, while 25 patients (50.0%) had score 3, there was no significant difference between the two studied groups regarding GAAS at the base line (p 0.068) (Table 6).

b. After 2 weeks:

After 2 weeks it was noticed that there was a slight improvement in GAAS in patients in group I, only one patients (0.5%) had score 0, 75 patients, (37.5%) had score 1, 95 patients (47.5%) had score 2, and the other 29 patients (14.5%) had score 3. In group II there was no change in the score of the patients, there was a significant difference between the two studied group after 2 weeks of treatment, there was an improvement in group I, while no change in group II (p 0.0124) (Table 6).

c. After 4 weeks:

After 4 weeks, there was a significant improvement in Global Acne Assessment Score, 7 cases (3.5%) their score was 0, while 92 patients (46.0%) their score was 1, 75 patients (37.5%) their score was 2, while only 26 patients (13.0%) had score 3. Group II show a very slightly insignificant improvement as follow, 29 patients had score 2, 17 cases (34.0%) has score 3, while 4 cases (8.0%) had score 4, there was a significant difference between the two studied groups after 4 weeks, group I show a high significant improvement than group II (p 0.0027) (Table 6).

After 6 weeks:

After 6 weeks it was found that 12 patients (6.0%) had score 0, while more than 50.0% of the patients had score 1 (103 patients (51.5%), 74 patients (37.0%) had score 2, while only 11 patients (5.5%) still had score 3. On the other hand in group II a very slightly change was occurred in this group, the difference between the two studied groups was highly significant, (p 0.001) (Table 6).

Table (7), show the comparison between the level of improvement in the two studied groups at different period of follow up, in group I it was found that the significant improvement in the Global Acne Assessment Score was noticed after 2 weeks, also, there was a significant improvement after 4 and 6 weeks, while in group II, there was no significant change in group II.

Complications:

Incidence of complication in the studied group are presented in table 9. It showed that, in group I, there were 16 cases (8.0%) suffering from mild erythema, 8 (4.0%) moderate erythema and only one patients (0.5%) was severe erythema. 21 cases (10.5%) were mild dryness, 2 (1.0%) were moderate dryness. While 20 cases (10.0%) were mild oiliness, 10 (5.0%) were moderate oiliness and only one patients (0.5%) were severe oiliness. On the other hand, 10 (5.0%) cases were mild peeling, 6 (3.0%) were moderate peeling. while in group II there were 4 cases (8.0%) suffering from mild erythema, 3 (6.0%) moderate erythema and no patients (0.0%) was severe erythema. 4 cases (8.0%) were mild dryness, 2 (2.0%) were moderate dryness. 5 cases (10.0%) were mild oiliness and 3 (6.0%) were moderate oiliness and no patients (0.0%) were severe

oiliness. On the other hand, 4 (8.0%) cases were mild peeling, 2 (4.0%) were moderate peeling. There were no statistical significant differences between the two studied groups regarding complications.

Relation between GAAS in group I at end of follow up and sun exposure: Table 9, shows that there was a significant relation between sun exposure and bad improvement in GAAS score, in the sun exposure patients, no one had score 0, while most of the patients (10 from 11 patients) who had score 3 was sun exposure patients, there was a significant relation between out come and exposed to sun (p 0.0025).

Relation between GAAS in group I at end of follow up and nature of acne: It was found that there was a very significant association between nature of acne and out come, almost all patients which had score 3, their acne was inflammatory, on the other hand no one of inflammated acne patients had score 0 or 1, from table (10) it was found that there was a significant relation between nature of acne and out come (p 0.0001)

Table (3): Demographic data of the studied patients group.

	Group I "n=200"		**Group II "n=50"**	
	No.	%	No.	%
Age < 20 >20 – 25 > 25-	79 69 52	39.5 34.5 26	25 15 10	50.0 30.0 20.0
Range Mean S.D.	14-35 23.21 6.25		15-36 24.1 7.21	
t p	1.06 0.39			
Sex Male Female	78 122	39 61	18 32	36.0 64.0
X^2	2.06 0.19			

p	

Table (4): Comparison between the two studied groups regarding skin type and sun exposure.

	Group I "n=200"		**Group II "n=50"**		**p**
	No.	%	No.	%	
Skin type					
II	42	21. 0	11	22.0	
III	90	45.0	19	38.0	0.136
IV	68	34.0	20	40.0	
Sun exposure					
Yes	84	42.0	19	38.0	0.25
No.	116	58.0	31	62.0	

Table (5): Comparison between the two studied groups regarding type of acne

Type of acne	**Group I "n=200"**		**Group II "n=50"**		**p**
	No.	%	No.	%	
Inflammatory	42	21.0	18	32.0	
Non inflammatory	158	79.0	32	64.0	0.19

Table (6): Comparison between the two studied groups regarding global acne assessment score at 0, 2, 4 and 6 weeks.

	Group I "n=200"		**Group II "n=50"**		**p**
	No.	%	No.	%	

At base line					
2	92	46.0	25	50.0	0.068
3	108	54.0	25	50.0	
4	0	0.0	0	0.0	
After 2 weeks					
0	1	0.5	0	0.0	
1	75	37.5	0	0.0	0.0124 *
2	95	47.5	26	52.0	
3	29	14.5	19	38.0	
4	0	0.0	5	10.0	
After 4 weeks					
0	7	3.5	0	0.0	
1	92	46.0	0	0.0	0.0027 *
2	75	37.5	29	58.0	
3	26	13.0	17	34.0	
4	0	0.0	4	8.0	
After 6 weeks					
0	12	6.0	0	0.0	
1	103	51.5	0	0.0	0.001*
2	74	37.0	30	60.0	
3	11	5.5	17	34.0	
4	0	0.0	3	6.0	

Table (7): Comparison between base line global acne assessment score and different period of follow up in the same group.

	Group I "n=200"		**Group II "n=50"**	
	No.	%	No.	%
At base line 2	92	46.0	25	50.0
3	108	54.0	25	50.0
4	0	0.0	0	0.0
After 2 weeks 0	1	0.5	0	0.0
1	75	37.5	0	0.0
2	95	47.5	26	52.0
3	29	14.5	19	38.0
4	0	0.0	5	10.0
p	0.0001*		0.28	
After 4 weeks				
0	7	3.5	0 0.0	
1	92	46.0	0 0.0	
2	75	37.5	29 58.0	
3	26	13.0	17 34.0	
4	0	0.0	4 8.0	
p	0.0001*		0.196	
After 6 weeks 0	12	6.0	0	0.0
1	103	51.5	0	0.0
2	74	37.0	30	60.0
3	11	5.5	17	34.0
4	0	0.0	3	6.0
p	0.0001*		0.122	

Table (8): Comparison between the two studied groups regarding complication.

	Group I "n=200"		**Group II "n=50"**		**X^2 p**
	No.	**%**	**No.**	**%**	
Erythema					
Mild	16	8.0	4	8.0	0.51
Moderate	8	4.0	3	6.0	0.7754
Severe	1	0.5	0	0.0	
Dryness					
Mild	21	10.5	4	8.0	0.55
Moderate	2	1.0	1	2.0	0.458
Severe	0	0.0	0	0.0	

Oiliness Mild Moderate Severe	 20 10 1	 10.0 5.0 0.5	 5 3 0	 10.0 6.0 0.0	 0.31 0.854
Peeling Mild Moderate Severe	 10 6 0	 5.0 3.0 0.0	 4 2 0	 8.0 4.0 0.0	 0.03 0.856

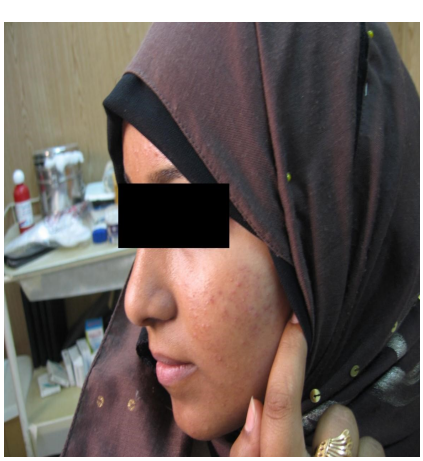
Table (9): Relation between GAAS in group I at end of follow up and sun exposure.

	Sun exposure			
	Frequently exposed		**Not frequently exposed**	
	No.	**%**	**No.**	**%**
0	0	0.0	12	10.34
1	14	16.7	89	76.72
2	60	71.4	14	12.07
3	10	11.9	1	0.86
Total	84		116	
X^2 p	15.65 0.0025*			

Table (10): Relation between GAAS in group I at end of follow up and nature of acne.

	Nature of acne			
	Inflammatory		**Non inflammatory**	
	No.	**%**	**No.**	**%**
0	0	0.00	12	7.59
1	0	0.00	103	65.19
2	31	73.81	43	27.22
3	11	26.19	0	0.00
Total	42		158	
X^2 p	25.31 0.0001*			

Figure.(11): Relation between GAAS in group I at end of follow up and nature of acne.



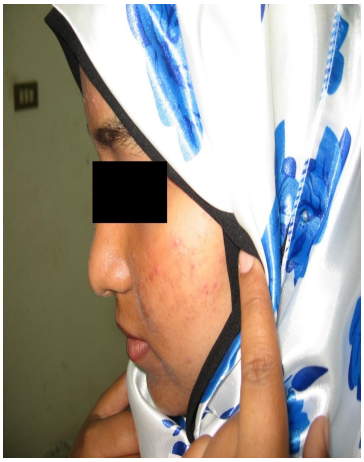
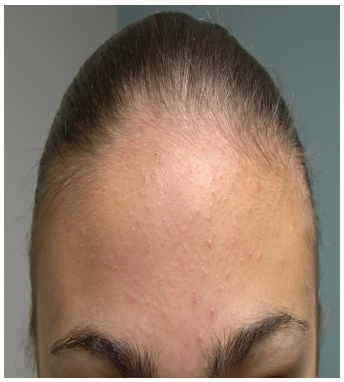


Fig (12-A) A case of acne GAAS III before the treatment

Fig (12-B) GAAS I after 6 weeks



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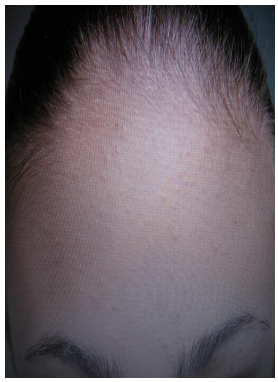
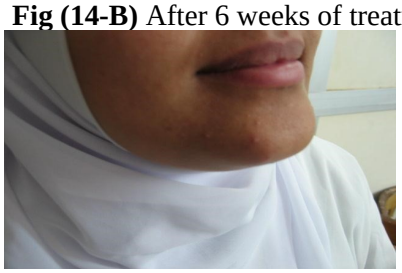


Figure : (13-A) A case of acne GAAS II before
Fig (13-B) After 6 weeks of treatment GAAS0

Figure : **(14-A)** A case of acne GAAS II
Fig (14-B) After 6 weeks of treatment GAAS 0



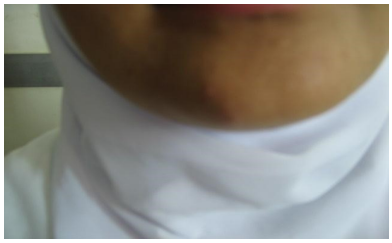
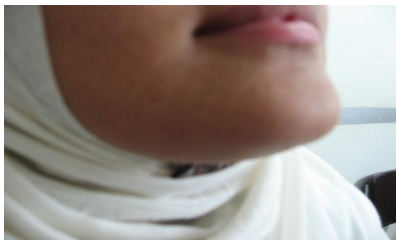


Fig (15-A) A case of acne GAAS I before the treatment



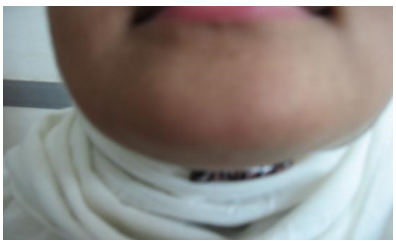


Fig (15-B) A case of acne GAAS 0

Fig (17-A) A case of acne GAAS I before the treatment

Fig (17-B) after 6 weeks treatment GAAS 0

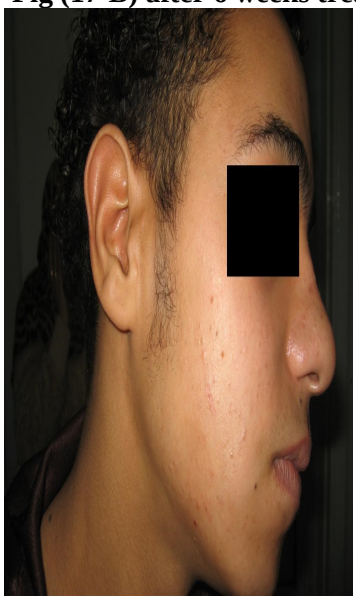


Fig (18-A) A case of acne GAAS II before the treatment
Fig (18-B) after 6 weeks treatment GAAS I

Fig (19-A) A case of inflammatory acne GAAS III before the treatment

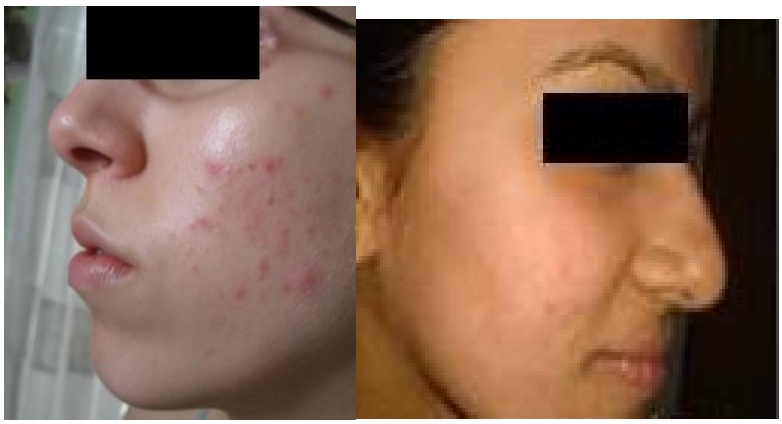


Fig (19-B) after 6 weeks treatment GAAS 0

Fig (20-A) A case of inflammatory acne GAAS II before the treatment

Fig (20-B) after 6 weeks treatment GAAS I

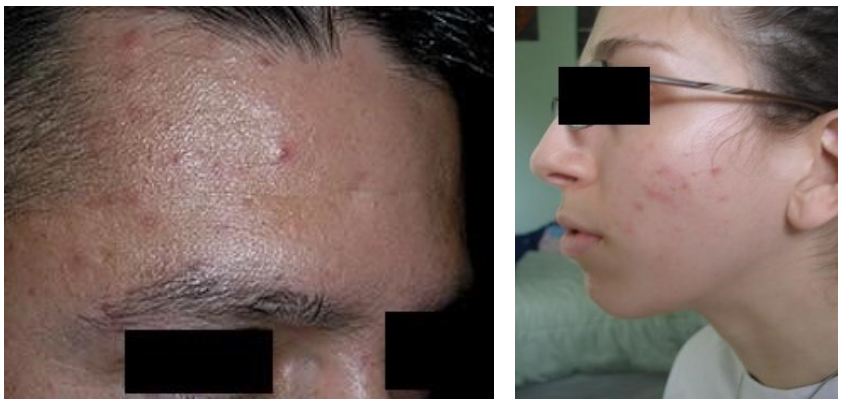


Fig (21-A) A case of acne GAAS II before the treatment

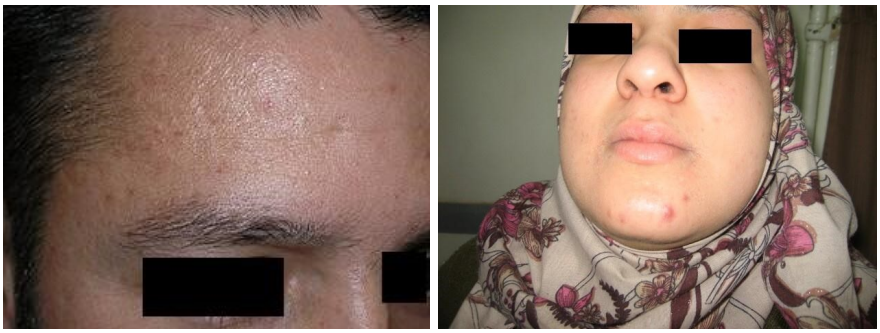


Fig (21-B) after 6 weeks treatment GAAS 0

Fig (22-A) A case of acne GAAS I

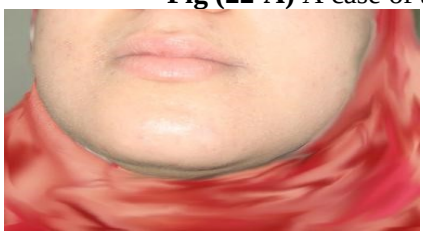


Fig (22-B) after 6 weeks of treatment GAAS 0

Fig (23-A) A case of acne GAAS II

Fig (23-B) after 6 weeks treatment GAAS I

DISCUSSION

Acne vulgaris is a common skin disease with onset in adolescence, characterized by papules and pustules (inflammatory

lesions), and open and closed comedones (non inflammatory lesions). The prevalence of acne increases through adolescence, affecting 39% of people at age 12 and 86% at age 17; nearly half of boys and one third of girls experience moderate to severe facial acne with extensive inflammatory lesions.[243] The prevalence subsequently decreases from 18 to 45 years of age with little change from 55 to 74 years,[244] but acne is also not uncommon in individuals as young as 8 years of age and in elderly patients.[245] Twenty-one percent of patients seeking treatment for acne from physicians in office-based settings are between the ages of 25 to 34, 10% between ages 35 and 44, and 5% older than 45 years of age.[246]

Dapsone, a sulfone that has both anti-inflammatory and antimicrobial properties, was shown to be an effective treatment for acne, including inflammatory nodulocystic acne, in the era predating the availability of isotretinoin. However, the use of oral dapsone for acne was never widespread because of its potential to cause systemic toxicity, and recently, efforts to develop a topical formulation of dapsone allows clinically-effective dose of dapsone to be administered topically with minimal systemic absorption.[247,248]

This study was carried out on 250 patients suffering from acne, they divided into two groups, group I contain 200 patients and used the drug, while the other 50 patients in group II used placebo treatment as a control group.

The present study showed that, there was no significant difference between the two studied groups regarding age; the most frequent age group was less than 20 year in the two studied groups.

Anne, et al., (2007) found that, Most patients were female (54.3%) with an overall mean age of 20 years. Three patients were over 50 years of age; these patients met inclusion criteria for a diagnosis of acne vulgaris and minimum lesion counts. At baseline, patients had a greater number of inflammatory (mean of 48.1) than noninflammatory (mean of 38.5) lesions.[249]

Patients applied dapsone gel for a mean of 253 days (mean 491 applications) over the 12-month study period (N=506). Based on the reconcilable drug weights, the average daily use of dapsone gel was 1.35 grams. [249]

The present study, comparison between the level of improvement in the two studied groups at different period of follow up, in group I it was found that the significant improvement in the Global Acne Assessment Score was noticed after 2 weeks, also, there was a significant improvement after 4 and 6 weeks, while in group II, there was no significant change in group II.

On the other hand, Michele, 2005 study 496 patients aged 12-44 years with mild to severe facial acne. The patients were randomized to either dapsone 5% gel (330 patients) or vehicle (166 patients), applied twice daily for 12 weeks. At baseline, the patients had a mean lesion count of 33 inflammatory lesions and 55
35
noninflammatory lesions. Significant differences in lesion count reduction were apparent by week 4 of treatment. By week 12, success as measured by a Global Acne Assessment score of less than 2 occurred in about 28% of the treatment group and 19% of the placebo group.

At end of follow up we found some complication in a small number of patients in both groups, the most common complications was adverse reactions of facial oiliness, peeling, dryness and erythema. In group I there was 13 cases (6.5%) suffering from adverse reactions of facial oiliness, while in group II there was 2 patients (4.0%) suffering from the same complication, peeling was noticed in 8 patients (4.0%) in group I and 3 cases (6.0%) in group II, dryness was found in 10 patients (5.0%) in group I, and in 1 patients (2.0%) in group II, finally the erythema was found in 11 patients (5.5%) in group I and in 2 patients (4.0%) in group II. There was no significant

difference between the two studied groups regarding incidence of complication.

Recently authors demonstrated that, these randomized, double-blind, vehiclecontrolled studies show dapsone gel to be effective in the treatment of acne, as demonstrated by significantly greater success based on the investigator's GAAS and by the reduction of inflammatory, non inflammatory, and total lesion counts at the end of treatment. A significantly greater number of patients treated with dapsone gel than patients treated with vehicle gel had no acne or minimal acne on completion of treatment. Combined results from these two studies were consistent with the results obtained from the individual studies. The responses seen in the dapsone gel-treated patients for the percent reduction of acne lesion counts at week 12 fall within the range of those observed in clinical trials of currently available topical acne therapies.(250-252)

Although clinical improvement was observed with both inflammatory and noninflammatory lesions, dapsone gel was particularly effective for inflammatory acne lesions. Reductions in inflammatory lesions occurred earlier and were of greater magnitude by the end of treatment. These findings were not unexpected, given the known anti-inflammatory properties of dapsone, which has long been used in dermatology for treatment of inflammatory dermatoses, particularly those characterized by neutrophilic inflammation such as dermatitis herpetiformis and linear lgA bullous dermatosis.[253] A potential mechanism of action of dapsone in acne could be the direct inhibition of leukocyte trafficking and the generation by leukocytes of chemical mediators of inflammation. However, it is also possible that, as a sulfone with structural similarities to trimethoprim-sulfamethoxazole and other sulfonamides, topical dapsone may act indirectly in acne by altering the levels and/or activity of propionibacteria located in the upper third of the follicles.

The onset of action of dapsone in these studies was rapid, with some difference in the mean decreases in inflammatory lesions of active versus vehicle occurring as early as 2 weeks after beginning treatment; the difference in favor of dapsone gel became highly significant by the fourth week of treatment. Counts of both inflammatory and noninflammatory lesions fell throughout the 12 weeks of treatment and may not have reached their nadirs by the end of the studies. This observation is consistent with the findings of a 12-month, long-term safety study of dapsone gel, in which acne lesion counts steadily fell for the first 6 months before reaching a plateau that was maintained for the remaining 6 months of the study.[254] Topical dapsone was exceptionally well tolerated in these studies. Rates of overall adverse events as well as application-site adverse events were similar between dapsone gel-treated patients and the control group, and few patients discontinued treatment because of adverse events or lack of efficacy. Most of the adverse events associated with dapsone gel were local application-site events. The few non-application-site adverse events observed were consistent with what would be expected for a healthy young population.

Local signs and symptoms of acne and cutaneous irritation such as skin dryness and erythema were also comparable between the two treatment groups throughout the studies and declined markedly in both groups over the course of treatment, suggesting that the emollient base of the vehicle gel itself may have been of therapeutic value. The use of a noncomedogenic cleanser by all of the study participants also may have favorably affected the incidence of local signs and symptoms, leading to further improvement in acne.[255,256]

Oral dapsone has been associated with adverse hematologic reactions; individuals with G6PD deficiency are particularly susceptible to these reactions. However, because dapsone gel, 5%, is a topical formulation, minimal systemic absorption was expected.[253,257] Overall, in these studies there was no significant change in

hemoglobin or other laboratory values, even among the 44 patients with G6PD deficiencies.

Topical dapsone gel, 5%, as a single agent has a rapid onset of action, is minimally irritating, and appears to be safe and effective in the treatment of acne vulgaris. Furthermore, this new antiacne treatment affords the opportunity to target the inflammatory aspects of acne by mechanisms that may differ from conventional antibiotics, the efficacy of which may he diminished by the rising prevalence of antibiotic-resistant strains of *Propionibacteriu;n acues.*

Our data demonstrated that, there was a very significant association between nature of acne and out come, almost all patients which had score 3, their acne was inflammatory, on the other hand no one of inflammated acne patients had score 0 or 1.
there was a significant relation between nature of acne and out come.

Zoe et al., 2007 studied that, Dapsone gel-treated patients achieved superior results in terms of the investigator's global acne assessment and the mean percentage reduction in inflammatory, noninflammatory, and total lesion counts at week 12. Reductions in inflammatory lesion counts favoring dapsone gel over vehicle were apparent as early as 2 weeks and reached statistical significance by 4 weeks.[50]
The present study showed that, most of group I were suffering from mild dryness (10.5%), oiliness (10%), erythema (8%) and peeling (5.0%) respectively. The same trend were found in group II most of patients were mild oiliness (10.0%), mild erythema (8.0%), mild dryness (8.0%) and mild peeling (8.0%). There were no statistical significant differences between the two studied groups and complications.
In according to our results, Hall, et al.,[258] was evaluated the Aczone Gel, 5%, for 12 weeks in four controlled studies for local cutaneous events in 1819 patients. The most common events reported from these studies include oiliness/peeling, dryness, and erythema, they found that, 14%, 13%and 9% from the patients were mild dryness, oiliness/pelling and 9% were erythema respectively. The same results were supported by other previous reports.[50,259-262]

They found that, no clinically significant changes in laboratory parameters, including hemoglobin, even among glucose-6-phosphate dehydrogenase-deficient patients, were observed. Adverse events were comparable between the treatment groups and rarely led to discontinuation.[50]
SUMMARY Acne is a common condition experienced by up to 80% of people between 11 and 30 years of age and by up to 5% of older adults.[1] For most patients acne remains a nuisance with occasional flares of unsightly comedones, pustules and nodules. For other less fortunate persons, the sever inflammatory response to Propionibacterium acnes (p.acnes) results in permanent disfiguring scars.[1,2] Stigmata of sever acne cane lead to social ostracism, withdrawal from society and severe psychologic depression.
It is necessary to consider the type of acne and the severity of symptoms to efficiently treat acne.[24,26,27] Treatment of acne is aimed at preventing the formation of comedones, papules, pustules, reducing inflammation, improving the adolescent's appearance, preventing scarring and avoiding the adverse psychological impact of acne (low self-esteem, loss of self-confidence, social isolation and depression)[24,28, 29]

The aim of this work was to study the efficacy and safty of the use of topical Dapsone 5% Gel in the treatment of acne.
In the present study is carried on two hundred and fifty patients (154 female and 96 male) suffering from acne.
Patients were subdivided into two unequal groups, according to the use of Dasone 5% Gel or vehicle .

I. **First group (G I):** This group included 200 acne patients were using Dapsone 5% Gel.

II. **Second group (G II):** This group included 50 acne patients were using a vehicle

The patients had been subjected to use Dapsone 5% Gel twice daily for 200 patient (Group I) and the use of vehicle for 50 control patient (Group II). Patients who fulfilled the inclusion criteria were included in the study. For each patient,

Methods:

- All patients were assessed history taking, assessment ,general examination, dermatologic examination, and local examination of acne lesions.
- Digital photography of the patients, pre, 2 weeks, 4 week and 6 weeks.
- Assesment of the patient using global acne assessment score (GAAS) from 0 to IV.
- Instracting the patient to use Dapsone 5 % Gel or vehicle twice daily.
- Monitoring for the addvers effect of Dapsone 5% at every visit.

Results:

-The age of patients ranged from 14 – 35 years with a mean of 23.21±6.25 in pataints group I While,the age of the patients ranged from 15-36 years with a mean of 24.1±7.21 in the control group II.

- In group I, 122 of the patients (61.0%) was female, and in group II also 32 was female (64.0%) - The most common skin types encountered were skin type III , IV, II respectively.

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SUMMARY

-In group I, there was 158 patients (79.0%) their acne was non inflammatory, while the other 42 (21.0%) was inflammatory, in group II the non inflammatory acne was found in 32 patients (64.0%), while the other 18 patients (32.0%) was inflammatory

- It was found that the most of the patients in the two studied groups non exposure to the sun (116 patients, 58.0%) in group I and (31 patients 62.0%) in group II.
- **Global Acne Assessment Score (GAAS):**

i. **At base**

(46.0%) had a score 2, while the 108 patients (54.0%) had score 3, on the other hand in group II, 25 patients (50.0%) had score 2, while 18 patients (36.0%) had score 3 and finally the rest 7 cases (14.0%) had score 4.

ii. **After 2**

noticed that there was a slight improvement in GAAS in patients in group I, only one patients (0.5%) had score 0, 75 patients, (37.5%) had score 1, 95 patients (47.5%) had score 2, and the other 29 patients (14.5%) had score 3. In group II there was no change in the score of the patients.

iii. **After 4**

was a significant improvement in Global Acne Assessment Score, 7 cases (3.5%) their score was 0, while 92 patients (46.0%) their score was 1, 75 patients (37.5%) their score was 2, while only 26 patients (13.0%) had score 3. Group II show a very slightly insignificant improvement as follow, 29 patients had score 2, 17 cases (34.0%) has score 3, while 4 cases (8.0%) had score 4.

er 6 weeks: After 6 weeks it was found that 12 patients (6.0%) had score 0, while more than 50.0% of the patients had score 1 (103 patients (51.5%), 74 patients (37.0%) had score 2, while only 11 patients (5.5%) still had score 3. On the other hand in group II a very slightly change was occurred in this group.

It was found that the significant improvement in the Global Acne Assessment Score was noticed after 2 weeks, also, there was a significant improvement after 4 and 6 weeks, while in group II, there was no significant change in group II.

At end of follow up it was found some complication in a small number of patients in both groups, the most common complications was adverse reactions of facial oiliness, peeling, dryness and erythema. In group I there was 20 cases (10.5%) suffering from adverse reactions of mild facial oiliness, while in group II there was 4 patients (8.0%) suffering from the same complication, mild peeling was noticed in 10 patients (5.0%) in group I

and 4 cases (8.0%) in group II, mild dryness was found in 21 patients (10.5%) in group I, and in 4 patients (8.0%) in group II, finally the mild erythema was found in 16 patients (8.0%) in group I and in 4 patients (8.0%) in group II. There were no statistical significant differences between the two studied groups and complications.

CONCLUSION

From the results of this study and in addition to reviewing related internationally published literature, we have the following conclusions and recommendations:

- Dapsone 5% gel is effective for inflammatory acne with little effect on non inflammatory acne with rapid result as early as 3 weeks.
- Dapsone is safe to use with very minimal local adverse reaction and not causing photosensitivity.
- Recommended to use dapsone 5% gel with mild to moderate inflammatory acne.
- It is recommended that, further research studies done on dapsone gel combination with other acne treatment.

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