Original Article

Efficacy and safety of once-daily dapsone 7.5% gel monotherapy for mild to moderate acne vulgaris: A comparative study with adapalene 0.1% gel monotherapy.

Fatima Wahida[1], Shah Zaman[2], Md. Noor Nabi Sayem[3], Md. Anwarul Haq[4], Sabbir Muhammad Shawkat[4], Mohammed Saiful Islam Bhuiyan[5]

1. Consultant, Dept. of Dermatology and Venereology, Dhaka Medical College, Dhaka, Bangladesh.
2. Assistant Professor, Dept. of Dermatology and Venereology, Care Medical College, Dhaka, Bangladesh.
3. Data analyst, National heart foundation Bangladesh, Dhaka, Bangladesh.
4. Consultant, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
5. Associate Professor, Dept. of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Abstract

Objective: To see the efficacy and safety of once daily dapsone 7.5% gel for mild to moderate acne vulgaris compared with adapalene 0.1% gel monotherapy. **Methods:** This was a randomized, open-label, comparative study, conducted over 47 patients with mild to moderate acne (lesional count 3-30). Patients were randomly enrolled into two 2 treatment groups (A and B). They were instructed to apply a thin layer of dapsone 7.5% gel (group A, n=23) or adapalene 0.1% gel (group B (n=24) on face. Inflammatory, non-inflammatory and total lesions were counted and adverse effects were assessed at weeks 0, 4, 8 and 12. **Result:** All forms of acne lesions were reduced from baseline to onwards in both groups. Percent reduction of total lesions and non-inflammatory acne lesions were statistically similar in both groups ($p>0.05$) but for inflammatory lesions, dapsone 7.5% gel is less effective than adapalene 0.1% gel ($p<0.05$). Adverse effects were also indifferent between the two groups ($p>0.05$). **Conclusion:** Dapsone 7.5 gel is effective and safe as monotherapy for acne vulgaris.

Key words: Dapsone, Adapalene, Acne vulgaris

Introduction:

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous gland that mostly affects teenagers irrespective of gender.[1] According to the Global Burden of Disease Study 2010 acne vulgaris is the eighth most common skin disease, with an estimated global prevalence (for all ages) of 9.38%.[2] Prevalence of acne ranges from 26.8% to 96% in different regions and age groups.[3-4] Major pathogenic factors responsible for acne are i. raised sebum production related to androgen stimulation of sebaceous glands; ii. altered follicular keratinization (hyperkeratinization); iii. Increased follicular colonization of Propionibacterium acnes or other bacterial infection and iv. complex inflammatory process along with both innate and acquired immunity.[5] Another factor that causes increased chances of acne is oxidative stress induced by reactive oxygen species (ROS) of both endogenous and external origin. ROS has a significant contribution in the production of inflammatory mediators such as interleukin-8 (IL-8) and tumour necrosis factor- α (TNF-α) by monocytes/macrophages during the progression of acne. Also, excessive and repeated stimulation by invading organisms such as P. acnes and S. epidermidis causes overproduction of ROS.[6]

Though acne is not a life-threatening disease causing only a few minor features including itching, stinging,

Corresponding author
Dr. Fatima Wahida, Consultant, Dept. of Dermatology and Venereology, Dhaka Medical College, Dhaka, Bangladesh.
Email: fatimawahida1983@yahoo.com
Received: 25 November 2021 Accepted: 15 December 2021 Available Online: 30 January 2022

Cite this Article:
Wahida F, Zaman S, Sayem MNN, Haq MA, Shawkat SM, et al. Efficacy and safety of once-daily dapsone 7.5% gel monotherapy for mild to moderate acne vulgaris: a comparative study with adapalene 0.1% gel monotherapy. J Ban Acad Dermatol. 2022; 2 (1): 11-16

Available at: www.jbadbd.com
An official publication of Bangladesh Academy of Dermatology (B.A.D.)

pain and rashes; it imposes a significant psychological burden due to scarring and pigmentation. It creates a negative impact on the relationship, friendships and job; reduces self-esteem; initiate shame, anger, concern, withdrawal and feeling stigmatized.[7] Acne is associated with significant psychiatric comorbidities include anxiety, depression and suicidal ideation.[8]

Acne can be presented as seborrhea (increased oil-sebum secretion), comedones, papules, nodules, pustules and scars.[9] In acne management topical agents are considered as the mainline therapy for mild to moderate disease. The most used topical drugs for acne include benzoyl peroxide, clindamycin, and retinoids (tretinoin, adapalene, isotretinoin, etretinate, retinaldehyde, tazarotene, ɷ-retinoylglucuronideare). Though these have been proved effective in the treatment of acne of mild to moderate severity, they have limitations due to irritation, unfavourable tolerability and low patient adherence.[10] Other topical agents include salicylic acid and azelaic acid, which have antibacterial, comedolytic, and anti-inflammatory properties. None of these treatment modalities can achieve the complete cure of the disease. They can control the disease with a variable rate of success.

The exact mechanism of action of dapsone in the treatment of acne is unknown. In addition to antimicrobial/antiprotozoal function, dapsone has anti-inflammatory activities similarly to non-steroidal anti-inflammatory drugs.[11] The efficacy of systemic dapsone in acne was described long ago in 1961 in a placebo control study where 9 patients out of 23 showed remarkable improvement of acne.[12] Systemic dapsone have some serious adverse effects including met-Hb formation, haemolysis and agranulocytosis.[11] Moreover its efficacy was proved less compared with isotretinoin in a later study.[13] But dapsone still have a position to consider for some special situations include acne fulminans.[14] Considering the serious adverse effects of systemic dapsone and its potential antibacterial and anti-inflammatory role, the use of a topical formulation was rationally attempted.

Methods:

Efficacy and safety of topical dapsone 7.5% gel in mild to moderate acne was assessed compared with topical adapalene 0.1% gel. This randomized, open-label, comparative study was conducted in Dhaka medical college hospital and Bangabandhu Sheikh Mujib Medical University (BSMMU) between July 15, 2019 and 20, November 2021. From the outpatient department (OPD) of dermatology attended patients with acne vulgaris 25 individuals were randomly enrolled into each of two monotherapy groups (group-A, dapsone) and (group-B, adapalene). Two subjects from group A and one from group B were withheld themselves from the trial and were excluded. Efficacy and safety were assessed at weeks 0, 4, 8 and 12. Written and verbal consent to take medications as directed and come for the follow up was taken before enrolment to the study. Patients of both sex and age 12 years or older were included who had newly diagnosed (by a dermatologist) acne having ≥2 to ≤30 total lesions which could be inflammatory (papules and pustules) and/or non-inflammatory (open or closed comedones) over face with investigator's global assessment score (IGA) 2 or 3. Cases of nodulocystic acne, acne conglobation, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne, or any other acne requiring systemic treatment) were not enrolled in the study.

Individual patients with severe acne vulgaris and who had a prior history of treatment with topical agents (15 days), oral antibiotics (one month), or oral isotretinoin (six months) were excluded from the study. Pregnant and lactating women, women who have menstrual irregularities, who are on hormonal contraception or individuals on any drugs having hormonal influence were also excluded.

Socio-demographic information and associated medical history were taken from all participants. Patients were instructed to apply a thin film of 7.5% dapsone gel (Group A) and 0.1% adapalene gel (Group-B) in the evening. No other medication was used during the treatment period.

The primary efficacy was assessed by the percentage of changes of non-inflammatory (open and closed comedones), inflammatory (papule and pustule) and total lesional counts and comparing between two groups. Only facial lesions were counted and photographs were taken from those who gave consent. Itching, burning, stinging and scaling were also observed for assessment of adverse effects at weeks 4, 8 and 12. Data were analyzed in SPSS. Unpaired t-test and Chi-square test were done to compare the demographic and clinical parameters of two groups. Mann-Whitney U test was done to test the changes in the lesional counts at each follow-up. Mann-Whitney U test was done to see the percent reduction of inflammatory, non-inflammatory and total count of acne in both groups. A p-value <0.05

was considered significant.

Result:

Table I: Demographic and clinical parameters of patients with acne vulgaris.

Demographic/ clinical parameter	Dapsone 7.5% gel n=23	Adapalene 0.1% gel n=24	Total	p value
Age				
Mean ± SD	25.57 ± 9.52	22.33 ± 9.07	23.91 ± 9.34	0.240[a]
Minimum, maximum	14-45	12-50	12-50	
Gender				
Male	7 (30.4%)	7 (29.2%)	14 (29.8)	0.942[b]
Female	16 (69.6%)	17 (70.8%)	33 (70.2)	

[a]Unpaired t test was done to measure the level of significance

[b]Chi-square test was done to measure the level of significance.

Over all mean age of patients with acne was 23.91 ± 9.34 years ranging from 12 to 50 years and their age distribution between two groups was statistically comparable (p>0.05). Male to female ratio of two groups has no significance difference (p>0.05) Table I. Gender distribution of two groups was also statistically similar. Table II: Lesional count of two groups at week 0, 4, 8 and 12.

Table II: Median lesion count at week 0, 4, 8 and 12.

Lesional count (Median)	Dapsone 7.5% gel (Group A) n=23	Adapalene 0.1% gel (Group B) n=24	Total	p value[a]
Total				
Baseline	22	23	23	0.949
4th weeks	20	20	20	0.369
8th weeks	15	12	14	0.183
12th weeks	10	8	9	0.098
Inflammatory				
Baseline	5	7	7	0.304
4th weeks	6	6.5	6	0.814
8th weeks	4	4	4	0.966
12th weeks	2	2	2	0.290
Non inflammatory				
Baseline	16	14	15	0.306
4th weeks	15	12	12	0.198
8th weeks	11	8	9	0.060
12th weeks	7	5	7	0.129

[a]Mann-Whitney U test was done to measure the level of significance.

Median of lesional counts at baseline, 1st, 2nd and3rd follow up of two groups had no significant difference. (Table II)

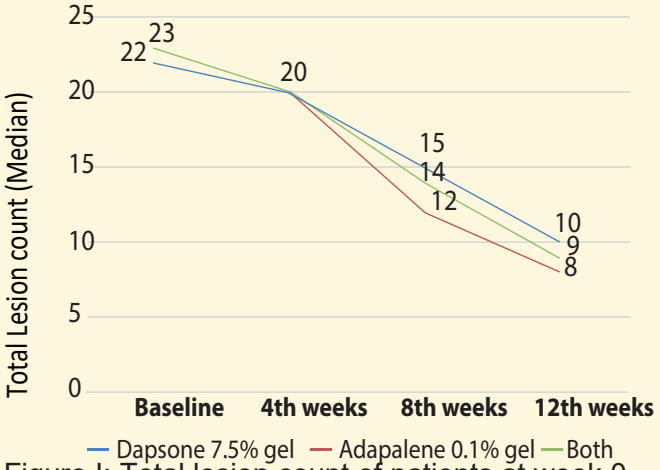

Figure I: Total lesion count of patients at week 0, 4, 8 and 12.

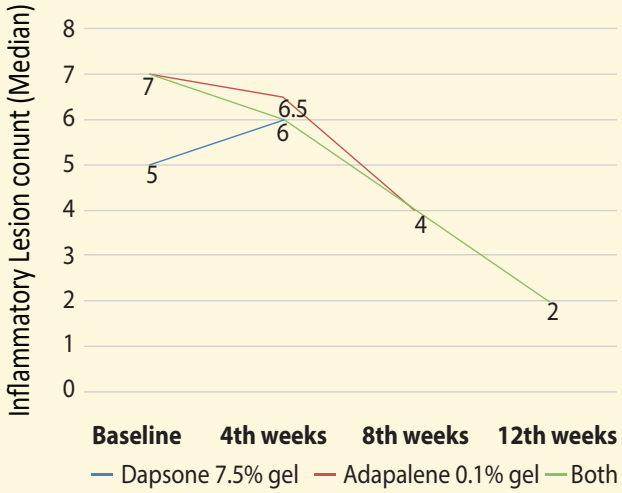

Figure II: Inflammatory lesion count (Median) of patients at week 0, 4, 8 and 12.

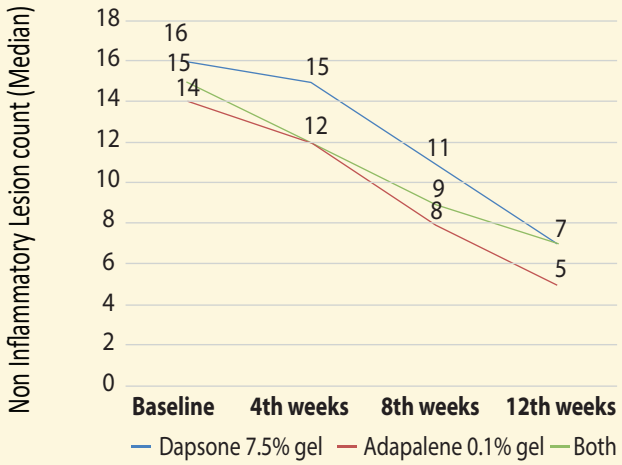

Figure III: Non-Inflammatory lesion count (Median) patients at week 0, 4, 8 and 12.

Table III: Changes of lesional count at week 12 (n=47)

Change of lesion count (median)*	7.5% Dapsone gel (Group-A) (n=23)	0.1% Adapalene gel (Group-B) (n=24)	P value
Total	-48.3	-59.5	0.011[a]
Inflammatory	-52.3	-76.9	0.008[a]
Non-inflammatory	-47.2	-52.6	0.102[a]

[a]Mann-Whitney U test was done to measure the level of significance.
*Percent change

Percent changes of lesional count of total and inflammatory acne from baseline to 12th week was significantly more in group B (p<0.05). Percent changes of lesional count of non-inflammatory acne from baseline to 12th week was comparable in both groups (p>0.05) (table III).

Table IV: Adverse event of the drugs (n=47)

	7.5% Dapsone gel (Group-A) (n=23)	0.1% Adapalene gel (Group-B) (n=24)	P value
Itching	3 (13.0%)	4 (16.7%)	0.740[b]
Burning	2 (8.7%)	1 (4.2%)	0.543[b]
Redness	1 (4.4%)	2 (8.3%)	0.999[b]
Scaling	1 (4.4%)	2 (8.3%)	0.494[b]
No adverse effects	18 (78.3%)	17 (70.8%)	0.464[a]

[a]Chi-square test was done to measure the level of significance.
[b]Fisher's Exact test was done to measure the level of significance.
*Multiple responses

Itching is the most common adverse effects in both groups of dapsone (13.0%) and adapalene (16.7%). Other adverse effects were burning, redness and scaling. No adverse effects was found in 78.3% of group A and 70.8% of group B (p>0.05) (table IV).

Discussion

Dapsone having both antibacterial and anti-inflammatory activities is rationally considered as a treatment option for acne vulgaris. Single daily topical use of 7.5% gel is approved by the United States Food and Drug Administration (FDA) for acne vulgaris in patients aged nine years and older.[15] In 2005, topical dapsone 5% gel was approved by the FDA for twice-daily topical 10 treatment of acne vulgaris in patients aged 12 years and older.[16] To see the efficacy of 5% dapsone gel in acne vulgaris on face Draelos et al. carried out 2 same type studies over 3010 patients. Dapsone gel was applied two times daily as a single agent for twelve weeks on 1506 person and vehicle gel containing in the same-looking tube was also applied on the same number of patients. All patients were assessed with the investigator's global acne assessment (IGA) and count of lesions (inflammatory, non-inflammatory and total) at weeks 0, 4, 8 and 12. Dapsone gel treated participants had a significant reduction of IGA and lesional number (percent change) at final follow up (week 12) (P<0.001).[17] Moore et al. in a study demonstrated that dapsone 7.5% gel was effective, safe, and well-tolerated for the treatment of acne in pediatric patients aged nine to 11 years.[18] In the current study the efficacy once-daily application of dapsone 7.5% gel was tested in acne vulgaris patient of age ranging from 12 to 50 years.

In a randomized, double-blind, vehicle-controlled, Phase III clinical trials over a similar age group by Thiboutot et al. once daily application of 7.5% dapsone gel was found effective.[19] Here in the current study non-inflammatory, inflammatory and total number of acne lesions were significantly reduced from baseline to subsequent weeks. (table I, Fig I, II and III). In a study by Jawade SA et al. total lesions, inflammatory lesions and non-inflammatory lesions were reduced were by 57.8%, 63.1% and 52.4% respectively after 12 weeks of treatment.[20] In our study at 12 weeks all forms of acne lesions were significantly reduced from baseline(table III). The percent reduction of total, inflammatory and non-inflammatory acne lesion count in the dapsone at week 12 was 48.3%, 52.3% and 47.2%. Though we included mild to moderate with a total lesional count less than thirty. In the study by Stein Gold et al. mean inflammatory lesions decreased by 55.5%, non-inflammatory lesions decreased by 44.4% and total lesions decreased by 48.7% with the dapsone 7.5% gel.[21]

All these studies are compared with vehicle only but in the current study efficacy and adverse effects of topical dapsone 7.5% gel was compared with 0.1% adapalene gel. Topical adapalene 11 gel has a good track record of safety and efficacy in the treatment of acne vulgaris both as monotherapy and in combination. We used only adapalene 0.1% gel for the treatment of inflammatory and non-inflammatory lesions of acne vulgaris in 24 patients on the face. Karan et al. in one study found

a significant reduction of inflammatory and non-inflammatory lesions from the baseline. After completing treatment of 12 weeks the total lesional count was reduced by 65.54%, non-inflammatory lesions were reduced by 56.60% and inflammatory acne was reduced by 69.98%.[22] In a study by Rao et al. on same type of acne severity (mild to moderate) found a significant decrease ($P < 0.05$) in the mean inflammatory and non-inflammatory lesion and total lesion counts from the 1st week onward. At 12 weeks, the total reduction was 66.7% for inflammatory lesions and 70.3% for open and around 50% for closed comedones. The decrease in total lesion count was 69% at 12 weeks.[23] In the current study patients treated with either dapsone gel or adapalene gel showed gradual reduction of total lesion count, inflammatory and non-inflammatory lesions from baseline toonward. The efficacy of both dapsone 7.5% gel and adapalene 0.1% gel was statistically significant after 12 weeks (table III). In the current study a 12 weeks treatment with adapalene 0,1% gel the reduction of the total lesional count, inflammatory acne and non-inflammatory acne were 59.5%, 76.9% 52.6%.

In the group of patients treated with dapsone 7.5% gel, after the treatment of 12 weeks reduction of total lesional count (48.3%) is statistically indifferent (p=0.011) to the adapalene group (59.5%). Reduction of non-inflammatory acne in the dapsone group (47.2%) and adapalene group (52.6%) were also very close and statistically comparable (p=0.102). But percent reduction of inflammatory lesions was 52.2% with the treatment of dapsone which is significantly lower than 0.1% adapalene (p=0.008).

Most of the patients in both dapsone (78.3%) and adapalene (70.8%) had no adverse effects. In both groups there were only some mild adverse effects among them itching was the most common followed by burning, redness and scaling. In a study by Thiboutot et al. dryness, 12 pruritus and pain were the reported adverse effects.[19] None of our cases had to discontinue the treatment due to adverse effects. In previous studies by Draelos et al., Lucky et al. and Raimer et al. dapsone was found safe and well-tolerated.[17,24-25] Here the tolerability profile of 7.5% dapsone gel was compared with adapalene 0.1% gel and there was no significant difference considering safety.

Conclusion:

Dapsone 7.5% gel is effective and safe in the treatment of mild to moderate acne vulgaris. Its efficacy on acne vulgaris especially non-inflammatory lesions is similar to adapalene 0.1% gel, but on inflammatory acne, dapsone gel is less effective than adapalene.

References

1. Willians C, Layton AM Persistent acne in women. Am. J. Clin. Dermatol. 2006;7(5): 281-290.
2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012 Dec 15;380(9859):2163-96.
3. Schäfer T, Nienhaus A, Vieluf D, Berger J, Ring J Epidemiology of acne in the general population: the risk of smoking. Br J Dermatol. 2001;145(1):100–4.
4. Bagatin E, Timpano DL, Guadanhim LR, Nogueira VM, Terzian LR, et al. Acne vulgaris: prevalence and clinical forms in adolescents from Sao Paulo, Brazil. An Bras Dermatol. 2012;89(3):428–35.
5. Williams HC., Dellavalle RP, Garner S Acne vulgaris. Lancet. 2012;379(9813):361–372.
6. Akamatsu H, Horio T The possible role of reactive oxygen species generated by neutrophils in mediating acne inflammation. Dermatology. 1998;196(1):82-5.
7. Hazarika N, Archana M The psychosocial impact of acne vulgaris. Indian J Dermatol 2016;61:515-20.
8. Stamu-O'Brien C, Jafferany M, Carniciu S, Abdelmaksoud A Psychodermatology of acne: Psychological aspects and effects of acne vulgaris. J Cosmet. Dermatol. 2021Apr;20(4):1080-1083.
9. Adityan B, Kumari R, Thappa DM Scoring systems in acne vulgaris. Indian J Dermatol Venereol Leprol. 2009;75(3):323–326.
10. Kawashima M, Nagare T, Doi M Clinical efficacy and safety of benzoyl peroxide for acne vulgaris: comparison between Japanese and Western patient. J Dermatol. 2017; 44(11):1212-8.
11. Wozel G, Blasum C Dapsone in dermatology and beyond. Arch Dermatol Res. 2014;306(2):103-124.
12. Ross CM The treatment of acne vulgaris with dapsone. Br J Dermatol 1961;73:367-70.
13. Prendiville J, Logan R, Russel-Jones RA Comparison of dapsone with 13-cis retinoic acid in the treatment of nodular cystic acne. Clin Exp Dermatol. 1988 Mar;13(2):67-71.
14. Tan BB, Lear JT, Smith AG Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. Clin Exp Dermatol. 1997;22:

26-7.
15. Aczone Gel, 7.5% [package insert]. Exton, PA: Almirall; 2018.13
16. Aczone Gel, 5% [package insert] Dublin, Ireland: Allergan plc; 2015.
17. Draelos ZD, Carter E, Maloney JM, Elewski B, Poulin Y, et al., for the United States/Canada Dapsone Gel Study Group. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol. 2007;56(3):439.
18. Moore AY, Lain EL, McMichael A, Kircik L, Zaenglein A, et al. Once-daily Dapsone 7.5% Gel for the Treatment of Acne Vulgaris in Preadolescent Patients: A Phase IV, Open label, 12-week Study. J Clin Aesthet Dermatol. 2021;14(4):43-48.
19. Thiboutot DM, Kircik L, McMichael A, Cook-Bolden FE, Tyring SK, et al. Efficacy, safety, and dermal tolerability of dapsone gel, 7.5% in patients with moderate acne vulgaris: a pooled analysis of two phase 3 trials. J Clin Aesthet Dermatol. 2016;9(10):18–27.
20. Jawade SA and Singh A Efficacy of Dapsone 5% gel in treatment of Acne vulgaris Int J Res Dermatol. 2016 Dec;2(4):77-81
21. Stein Gold LF, Jarratt MT, Bucko AD, Grekin SK, Berlin JM, et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: First of Two Identically Designed, Large, Multicenter, Randomized, Vehicle controlled Trials. J Drugs Dermatol. 2016 May 1;15(5):553-61.
22. Karan S, Vikrant J, Anil G A comparative study between topical adapalene (0.1%) versus a combination of topical adapalene (0.1%) and intense pulsed light therapy in the treatment of inflammatory and noninflammatory facial acne vulgaris: A split-face randomized controlled trial. Indian J Drugs Dermatol 2019;5:19-25.
23. Rao GR, Ghosh S, Dhurat R, Sharma A, Dongre P, et al. Efficacy, safety, and tolerability of microsphere adapalene vs. conventional adapalene for acne vulgaris. Int J Dermatol 2009;48:1360-5.
24. Lucky AW, Maloney JM, Roberts J, Taylor S, Jones T, et al. Dapsone gel 5% for the treatment of acne vulgaris; safety and efficacy of long term (1 year) treatment. J Drugs Dermatol. 2007;6(10):9817.
25. Raimer S, Maloney JM, Bourcier M, Wilson D, Papp K, et al. Efficacy and safety of dapsone gel 5% for the treatment of acne vulgaris in adolescents. Cutis. 2008;81:171-8