A COMPARATIVE CLINICAL STUDY OF TOPICAL FINASTERIDE AS A NEW THERAPY OF ACNE VULGARIS

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Abstract

Background: Androgen regulation of sebum production requires the local conversion of testosterone to dihydrotestosterone catalyzed by 5 alpha-reductase; thus, its competitive inhibitor, finasteride, might be beneficial for treatment of cutaneous hyperandrogenism conditions like acne vulgaris.

Objective: To evaluate the efficacy and tolerability of topical finasteride as a new therapy for acne vulgaris.

Subjects & Method: Sixty patients with mild to moderate acne were enrolled and randomly assigned to receive topical solution of either 0.01 % finasteride (n=30) or 1.5% clindamycin (n=30) two times a day for 3 months. Efficacy was assessed by determining the patients' number exhibiting improvement per each recovery percentage.

Results: The initial response to finasteride or clindamycin was elicited at 4.15 ± 0.15 and 3.56 ± 0.13 weeks respectively ($p>0.05$) whereas the maximum response required 8.2 ± 0.23 and 8 ± 0.14 weeks respectively ($p>0.05$). Acne remissions were detected at week 12 of therapy in 66.67 % of finasteride group versus 80% of clindamycin group ($p>0.05$). Both drugs were well tolerated and safe.

Conclusion: 0.01% finasteride solution applied twice daily for 12 weeks has clinical efficacy and safety profile comparable to a similar regime of 1.5% clindamycin solution in treatment of mild to moderate inflammatory acne vulgaris.

Keywords: Finasteride, Clindamycin, Acne Vulgaris

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Introduction

Acne vulgaris is a multifactorial disease of the pilosebaceous unit of the skin. It may have profound psychological sequelae. Depending upon the degree of follicular hyperkeratinization, sebum production, *Propionibacterium acnes* (*P. acnes)* growth, and inflammation, the microcomedo evolves into a non-inflammatory lesions [closed comedo (a whitehead), and an open comedo (a blackhead)] or an inflammatory lesions [pustule, papule, or nodule]. In addition, scarring and hyperpigmentation may occur[1,2].

Mild cases of comedonal acne may respond to a topical retinoid or benzoyl peroxide, while inflammatory lesions such as papules and pustules benefit from topical antibiotics including topical clindamycin. More severe inflammatory acne is treated with systemic antibiotics. Recalcitrant cases often require oral isotretinoin or hormonal manipulation[1,3-5].

Topical clindamycin is thought to reduce free fatty acid concentrations on the skin and to suppress the growth of *P. acnes*, an anaerobe found in sebaceous glands and follicles. P. acnes produce proteases, hyaluronidases, lipases, and chemotactic factors, all of which can produce inflammatory components or inflammation directly[4].

Androgenic stimulation of sebaceous glands is an important factor in development of acne[6]. Most patients with acne do not overproduce androgens. Instead, they likely have sebaceous glands that are locally hyper responsive to androgens[7]. Nevertheless, androgens play a more important role in female than in male acne at the hormonal and at the peripheral level in skin[8]. The level of dehydroepiandrosterone sulfate, an androgen of adrenal origin, was significantly higher in prepubertal girls with acne[9].

Hormonal therapy is an alternative to systemic isotretinoin in women with acne that is unresponsive to other methods of treatment. Minimums of 3-6 months of therapy are required prior to evaluation of the efficacy of hormonal therapies that includes estrogens (oral contraceptives) or oral anti-androgens (spironolactone, cimetidine, flutamide, and ketoconazole); these act at the peripheral receptor level to decrease sebum production[7].

Finasteride is a competitive inhibitor of Type II 5(alpha)-reductase; it produces a rapid and

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significant reduction in serum and tissue dihydrotestosterone (DHT) concentration. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Type II 5(alpha)-reductase isozyme is responsible for two-thirds of circulating DHT. It is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver.

Studies with finasteride had indicated that the hypothalamic-pituitary-testicular axis was not affected. However, mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range. Finaseteride is indicated for treatment of benign prostatic hyperplasia and androgenic alopecia in men. Its adverse effects included breast tenderness and enlargement, as well as hypersensitivity reactions, including lip swelling and skin rash, has been reported. No drug interactions of clinical importance have been identified[10].

Aim of the Study:

Systemic and topical anti-microbials are effective in the treatment of inflammatory acne vulgaris; however, widespread use of these agents is becoming increasingly associated with the emergence of resistant pathogens indicating the need to develop strategies to minimize antibiotic use in acne therapy[11,12]; thus, this comparative clinical therapeutic trial aimed to evaluate the tolerability and clinical efficacy of topical finasteride as a new therapy for acne vulgaris in Iraqi patients.

Subjects & Methods

This prospective clinical study was performed on 60 patients with mild to moderate acne vulgaris among those attended the dermatologic consultation unit in Al-Kadhimiya Teaching Hospital. The study started in July 2001; patient admittance was completed in April 2002. The enrolled patients were randomly assigned into 2 treatment groups:

1. Topical finasteride group (n=30): Patients of this group received this tested drug at concentrations of 0.01 % as a thin film applied topically to the skin, twice daily to the affected areas; 70% ethanol was used as a vehicle in which finasteride was dissolved[10].

2. Topical clindamycin group (n=30): Patients of this group received a topical solution of 1.5% clindamycin phosphate, the routinely used topical antibacterial drug as a thin film applied topically to the skin, two times a day to the affected areas[4]; 70% ethanol was used as a vehicle in which clindamycin phosphate was dissolved[10].

The exclusive criteria included severe acne, pregnancy or a possibility of pregnancy, and cases of acne who were already receiving topical clindamycin or any type of hormonal therapy.

For each included patient, a detailed history was taken including: name, age, sex, residence, marital state, duration of acne, impact of the disease (whether disfigurement, occupational disability, psychological impact, or failure of previous treatment), aggravating factors (seasonal variation or stress), family history (regarding the acne), and previous anti-acne drug history.

Specific type of acne lesions whether non-inflammatory lesions [closed or open comedone] or an inflammatory lesions [pustule, papule, or nodule], or scarring and hyperpigmentation[1,2] were recorded at baseline (i.e., pre-treatment value) and then 4 weekly along the trial period of therapy which equal to 12 weeks.

Severity grades of inflammatory acne could be determined according the criteria shown in the table (1)[13].

Table 1: Severity grades of inflammatory acne[13]

Grade of severity	Factors that determine severity of inflammatory acne		
	Papules/pustules	Nodules	Additional factor
Mild	Few/several	0	Psychosocial circumstances
Moderate	Several/many	few/several	Occupational difficulties
Severe	Many/extensive	many	Inadequate therapeutic responsiveness

In each treatment group, the patients treated themselves twice daily for 3 months[14] to be seen at 4 weeks intervals during the follow up period (i.e., 12 weeks) in order to assess both clinical efficacy and tolerability (i.e., erythema, desquamation, dryness, itching, and burning[14,15] or any other noticeable side effects of the employed therapy).

According to Ersoy et al. (1996)[16], the efficacy of treatment in the present study was assessed by 4 weekly determination of number of the patients who exhibited drug-induced improvement per

each recovery percentage which was graded as follows: 0% (i.e., no improvement), < 25%, 25-50%, 50-75%, or 75-100%.

Staistical analaysis

Student paired t-test (for dependent data), student unpaired t-test (for independent data), or Chi- square (X^2) tests were used accordingly to assess whether the obtained differences could be accepted as insignificant (if P □ 0.05), significant (if 0.01 < P ≤ 0.05), or highly significant (if P ≤ 0.01)[17].

Results

With the aid of table 2, some characteristics of the 60 included acne cases are demonstrated. There was no significant difference (p>0.05) between the mean age of the 30 acne cases who received topical finasteride (22.0±0.7 years) (mean±S.E.M) and that of 30 acne cases who received topical clindamycin (21.33±0.8 years). The sex distribution pointed out that 20 (66.7 %) patients in each treatment group were females.

Table 2: Some characteristics of the included acne cases

Treatment group	No. of patients	Sex		Age (years)	
		Male	Female	mean±SEM*	range
Finasteride	30	10	20	22.0±0.7	15-30
Clindamycin	30	10	20	21.33±0.8	15-30

SEM = standard error of mean

Table 3, demonstrated the distribution of patients regarding aggravating factors (seasonal variation or stress) and family history of acne. Compared to clindamycin group, finasteride group significantly (P<0.05) had more patient with positive family history of acne whereas no significant difference (p>0.05) could be elicited regarding aggravating factors.

Furthermore, there were no significant differences (p>0.05) between the two treatment groups in respect of types of impact that induced by the acne vulgaris (Table 3).

When the included patients were distributed according their previous specific therapy of acne (Table 3), there were no significant differences (p>0.05) between the two treatment groups except in case of previous treatment with topical clindamycin where the difference was highly significant (p< 0.01).

Table 3: Distribution of patients regarding each of factors affecting acne presentation (&/or its severity), impact that induced by acne and their previous specific therapy

Parameters according to which the patients were distributed		No. of patients	
		Finasteride N = 30	Clindamycin N = 30
Factors affecting acne presentation &/or severity	Seasonal variation*	10	12
	Stress	16	15
	Family history	10[s]	8
Type of impact that induced by acne	Disfigurement	13	10
	Occupational disability	13	10
	Psychosocial impact	19	20
	Failure of previous treatment	11	7
Previous specific therapy of acne	**Topical**		
	Clindamycin	8[hs]	0
	Benzoyl peroxide	8	7
	Tretinoin	8	4
	Oral		
	Doxycyclin	3	5
	Tetracyclin	2	2
	Co-trimoxazol	1	1

* = increase severity during summer, S = significant difference (P<0.05) when compared with other group. hs = highly significant difference (P<0.01) when compared with other group.

According to sites of acne lesions (Table 4), no significant differences (p>0.05) could be elicited between the two treatment groups regardless the site itself, i.e., whether face, chest, or back.

Moreover, Patients presented with specific types of acne lesions whether non-inflammatory lesions [closed or open comedone] or an inflammatory lesions [pustule, papule, or nodule], or complications [scarring and hyperpigmentation] in a way that no significant differences (p>0.05) could be elicited between the two treatment groups (Table 4).

Besides, the differences between the two groups in respect of the grades of severity were found to be insignificant (p>0.05); the majority of patients presented with acne of moderate severity [24/30 (80%) patients in finasteride group Vs 22/30 (73%) patients in clindamycin group] whereas the remainders in each group had mild acne (Table 4).

Table 4: Distribution of patients regarding location and types of acne lesions and regarding grades of severity of acne

Parameters according to which the patients were distributed			No. of patients	
			Finasteride N = 30	Clindamycin N = 30
Location of acne lesions	Face		30	30
	Chest		10	7
	Back		10	7
Various types of acne lesions	Non-inflammatory	Comedones	15	18
	Inflammatory	Papules	30	30
		Postules	26	26
		Nodules &/or cysts	8	6
	Complicated	Atrophic scar	11	5
		Hyper-pigmentation	11	7
Severity grades of inflammatory acne lesions	Mild*		6	8
	Moderate**		24	22
	Severe***		0	0

Note: papules/pustules (*) = (+/++) (few/several) (**) = (++/+++) (several/many) (***) = (+++/++++) (many/extensive)
Nodules (*) = (0) (**) = (+/++) (***) = (+++)
Additional factors that determine severity:
(*) = Psychosocial circumstances, (**) = occupational difficulties, (***) = inadequate therapeutic responsiveness.

The initial response could be elicited at mean duration 4.15 ± 0.15 and 3.56 ± 0.13 weeks after commencement of topical therapy with either finasteride or clindamycin respectively; however, such difference was found to be insignificant ($p>0.05$). On the other hand, the maximum response required mean duration of 8.2 ± 0.23 and 8 ± 0.14 weeks of treatment by either finasteride or clindamycin respectively; this difference was also insignificant ($p>0.05$) (Figure1).

Finasteride reduced the sebum and skin greasiness within first 10 days whereas clindamycin could do so within first 2 weeks of therapy.

In this study, it was noticed that 0.01% Finasteride, like 1.5% clindamycin, had no effect on both whitehead and blackhead comedones and an only little effect on nodules; i.e., their effects particularly involved the papules and pustules.

Figures (2A, B, & C) illustrated the distribution of patients regarding their therapy-induced improvement per each recovery percentage throughout period of treatment with finasteride or clindamycin. Besides, tables (5A & B) outlined the significance of differences yielded from comparison of values of each follow-up interval with Pre-treatment (0 weeks) taking into account each recovery percentage within the same treatment group, i.e., finasteride (Table 5A) or clindamycin (Table 5B) accordingly. However, table (5C) revealed the results of comparison between finasteride and clindamycin groups.

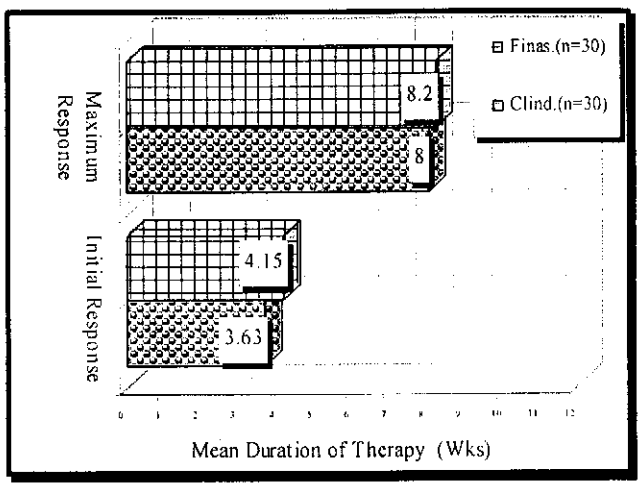
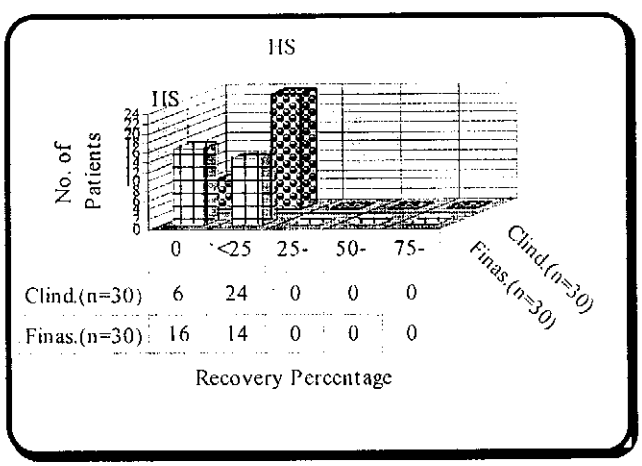
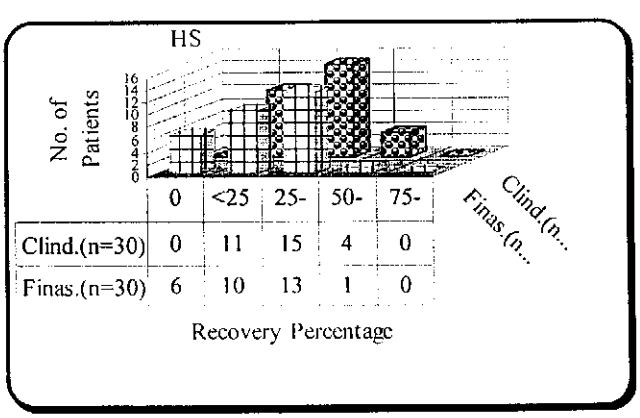


Figure 1: The mean duration (weeks) of therapy required for each group to show initial and maximum response



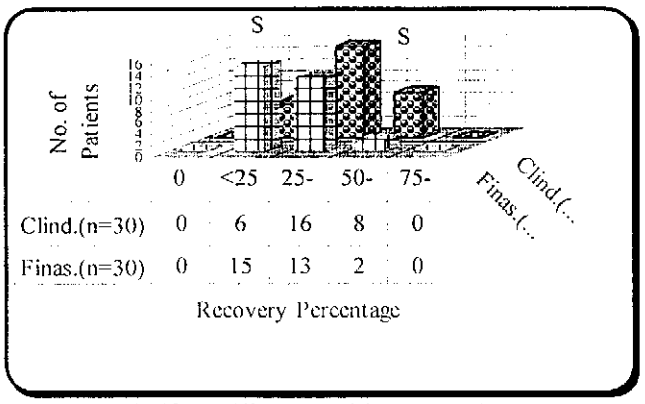
IIS = highly significant difference (P<0.01) betweenthe two treated groups

Figure 2A: Distribution of patients with acne treated for 4 weeks with finasteride or clindamycin regarding their therapy-induced improvement per each recovery percentage



HS = highly significant difference (P<0.01) betweenthe two treated groups

Figure 2B: Distribution of patients with acne treated for 8 weeks with finasteride or clindamycin regarding their therapy-induced improvement per each recovery percentage



S = significant difference (P<0.05) between the two groups

Figure 2C: Distribution of patients with acne treated for 12 weeks with finasteride or clindamycin regarding their therapy-induced improvement per each recovery percentage

Table 5A: Significance of difference yielded from comparison with baseline values regarding number of patients exhibited finasteride-induced improvement per each recovery percentage

Recovery percentage	Follow up intervals (weeks of treatment)		
	4th	8th	12th
0%	HS* (baseline)$	HS (baseline)	HS (baseline)
<25%	HS (4th week)	HS (8th week)	HS (12th week)
25-50%	NS**	HS (8th week)	HS (12th week)
50-75%	NS	NS	NS

HS* = highly significant difference (P<0.01), NS** = no significant difference, $ the highest value belongs to those of follow up interval mentioned between brackets

Table 5B: Significance of difference yielded from comparison with baseline values regarding distribution of patients according to clindamycin-induced improvement per each recovery percentage

Recovery percentage	Follow up intervals (weeks of treatment)		
	4th	8th	12th
0%	HS* (baseline)$	HS (baseline)	HS (baseline)
<25%	HS (4th week)	HS (8th week)	HS (12th week)
25-50%	NS**	HS (8th week)	HS (12th week)
50-75%	NS	S (8th week)	HS (12th week)

HS* = highly significant difference (P<0.01), NS** = no significant difference, $ the highest value belongs to those of follow up interval mentioned between brackets

Table 5C: Significance of difference between finasteride and clindamycin groups regarding the distribution of patients according to their therapy-induced improvement per each recovery percentage

Recovery percentage	Follow up intervals (weeks of treatment)			
	0	4th	8th	12th
0%	NS*	HS*** (F)#	HS (F)	NS
<25%	NS	HS (C)$	NS	S** (F)
25-50%	NS	NS**	NS	NS
50-75%	NS	NS	NS	S (C)

0 = baseline (pre-treatment), NS* = no significant difference, S** significant difference (P<0.01), HS*** = highly significant difference (P≤0.01), (F)# = the highest value belongs to finasteride group, (C)$ = the highest value belongs to clindamyci group.

As it was shown in figures (3A & B) and based on the overall response of each patient individually, by the end of 12 weeks of therapy, acne remissions were found in 66.67 % of finasteride group (Figure 3A) and 80% of clindamycin group (Figure 3B).

The difference between the two treatment groups was found to be insignificant (p>0.05).

When the patients of each group were differentiated into mild and moderate cases, acne remissions were found in 100% of those with mild acne in either treatment group. However, acne remissions of those with moderate acne were found in 58.33% in finasteride group versus 72.73% in clindamycin group; however, such difference was also found to be insignificant (p>0.05).

Finally, both topical drugs were well tolerated along the trial period, i.e., 12 weeks, without noticeable side effects among the included patients in this prospective study.

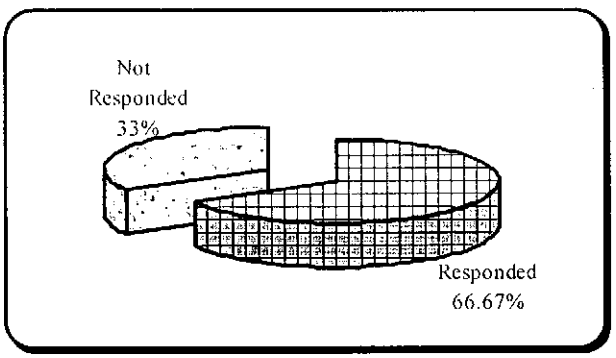


Figure 3A: The overall responses of patients with acne to 12 weeks of topical finasteride therapy

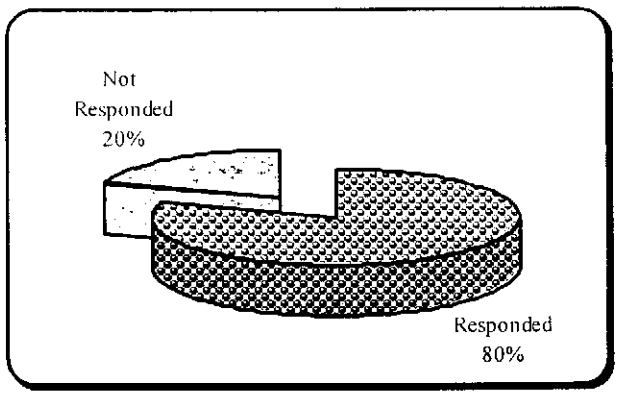


Figure 3B: The overall responses of patients with acne to 12 weeks of topical clindamycin therapy

Discussion

This prospective clinical study represents the first published work, at least in Iraq, which explores the role of finasteride as a new topical therapy for acne vulgaris.

Acne vulgaris is now recognized to be a disease that causes significant physical and emotional discomfort. Yet there is currently little consensus about the management of acne[18].

Androgens enhance lipogenesis, proliferation and terminal differentiation of human sebocytes by binding to nuclear androgen receptors[19]. The presence of 5 alpha-reductase in skin may indicate that the androgen regulation of sebaceous glands and sebum production requires the local conversion of testosterone to dihydrotestosterone[20]. Additionally, an exaggeration of this peripheral metabolism has been associated with acne in women[21].

Finasteride is the first available medication of a new class of drugs that is a competitive inhibitor of 5 alpha-reductase and therefore should be beneficial for medical treatment of cutaneous hyperandrogenism[22]. It has a 100-fold selectivity for the human Type II 5(alpha)-reductase over Type I isozyme (IC50=500 and 4.2 nM for Type I and II, respectively)[11].

Finasteride is freely soluble in lower alcohol solvents but is practically insoluble in water[10], in addition, alcohol aids in the removal of sebum from the surface of the skin[23]. Thus, we selected ethyl alcohol, the vehicle of clindamycin solution, to also be the vehicle used in preparation of fresh finasteride solution tested in this clinical trial.

Finasteride is contraindicated in women when they are or may potentially be pregnant. finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride[10]. Thus, in the present study, the exclusive criteria included pregnancy or its possibility.

Both groups seemed comparable when the various factors which could affect the clinical presentation of acne were taken into account, i.e., in respect of patients' mean age, patients' gender distribution (with predominance of females), aggravating factors, types of impact that induced by acne, and previous specific therapy of acne. However, patients with positive family history of acne were significantly more in finasteride group. Besides, regarding history of previous treatment, a highly significant difference ($p< 0.01$) between the two treatment groups was obtained in case of previous treatment with topical clindamycin; this difference was expected after exclusion every patient who previously received clindamycin from involving within clindamycin group.

It was interesting to discover that both groups of patients were presented in a comparable way, i.e., regarding severity of inflammatory acne, sites and types of acne lesions.

Thus, it became clear that unexpectedly, the conditions of this clinical trial were offering a suitable and more or less fair opportunity to explore the actual role of the applied topical therapy.

The duration of therapy in either group was decided to be continued up to 12 weeks since it takes 8 weeks for a microcomedo to mature; thus, any therapy must be continued beyond this duration in order to assess efficacy[7].

As it was discovered in this study, 0.01% finasteride had earlier and more obvious anti-sebum effect than 1.5% clindamycin. This probably explained as a consequence of finasteride-induced inhibition of an essential step required for sebum production which is the local conversion of testosterone to dihydrotestosterone mediated by 5 alpha-reductase in skin[20].

Another interesting finding in this study was the similarity between finasteride and clindamycin regarding the types of acne lesions which were responsive to their effects; i.e., the inflammatory lesions and namely both papules and pustules.

Approximately 4 weeks of treatment with either drug were enough for the initial response to evolve. However, as it was demonstrated in this study, in order to achieve the maximum response, continued treatment with either drug for further 4 weeks was mandatory. Furthermore, the maximum response seemed valid since it could also be maintained throughout the rest period of this clinical trial.

Every 4 weeks assessment of numbers of patients who showed improvement per each recovery percentage appeared to follow a manner that warrant a high significant difference when compared to the relevant pre-treatment values. The exceptions probably confined to the recovery percentage 50-75% where the differences were insignificant along the trial period of treatment with finasteride.

At 12th week of this clinical trial, finasteride treatment could increase the number of patients who showed improvement in recovery percentage (<25%) was significantly higher than

clindamycin did whereas the opposite was true regarding the recovery percentage (50-75%).

By the end of 12 weeks of topical therapy and based on the overall response of each patient individually, the number of patients who showed a valid response in finasteride group was comparable to that of clindamycin group regardless their grades of acne severity. Besides, all patients with mild acne in each group responded well; however, the non-responded patients were confined among those with moderate acne in each group. This probably pointed out the need for additive therapy since many times topical anti-acne therapy may be effective as maintenance therapy after initial control is achieved by combination of oral and topical therapy[24, 25].

Results of this study may represent an advanced step in accentuating the role of topical anti-androgen drugs in treatment of acne since topical 0.01% finasteride could achieve a comparable efficacy to that of topical 1.5% clindamycin whereas results of a previous study published by Erosy L. et.al. (1996)[16] revealed that topical 5% spironolactone, an anti-androgen drug, failed to do so and was less effective than topical 1.5% clindamycin.

The promising results obtained in this study counteract what was reported by Randall V.A. (1994)[26] who pointed out the availability of evidence that discounts the role of 5 alpha reductase II in sebaceous glands and acne.

Interestingly, treatment of 30 acne patients with topical finasteride solution (0.01%) for about 3 months seemed to maintain a good safety profile and lack any reported side effect from its oral use. This probably because of the too little dose of finasteride applied topically in this study compared to that of its oral use; thus, its amount reaching systemic circulation should be too little than that achievable from its oral use.

Conclusion

Finasteride solution 0.01% applied topically twice daily is as effective as the same regime of topical clindamycin solution 1.5% in the treatment of inflammatory mild-moderate acne vulgaris and has an excellent safety and tolerability profile.

Recommendations

1. Since finasteride seemed, from the present study, to have an excellent safety profile and because its efficacy might be a dose-related one so further comparative clinical studies with higher concentrations of topical finasteride solution are warrantable.
2. Clinical trials with combined therapy of topical finasteride solution with other anti-acne therapies appeared justified particularly for moderate-severe cases.
3. There is a need for studies that assess the effectiveness of topical finasteride solution in comparison to systemic hormones when the latter is indicated, for example, in treatment of acne of adult women happens when they are more than 20 years old and hadn't acne on their adolescence; this acne can be clinically classified as hypoestrogenic and hyperandrogenic[27].

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