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Original Article

Topical 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream alone and their combination in older children with atopic dermatitis - an open randomized comparative study

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Abstract

Background Atopic dermatitis, a chronic recurring inflammatory skin disease, often requires long-term use of topical corticosteroids that may cause serious adverse effects. Therefore, steroid sparing topical agent is needed.

Objective In this open, randomized and comparative study, the efficacy and safety of 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream and their combination were evaluated in patients with AD.

Patients and methods 45 patients with moderate to severe AD involving with moderate to severe AD involving ≤50% of the total body surface area (BSA) were randomly assigned to three groups. 15 patients in each group received 0.03% tacrolimus ointment twice daily (arm A) or 0.05% clobetasone butyrate cream twice daily (arm B) or 0.05% clobetasone butyrate cream in the morning and 0.03% tacrolimus ointment in evening (arm C). The treatment duration was 4 weeks and was followed-up for 6 weeks. The modified eczema area and severity index (mEASI) and the extent of the affected BSA were assessed and evaluated.

Results All treatment groups showed significant improvement throughout the treatment period. At the end of 4 weeks treatment, a median improvement of ≥75% in mEASI was observed in 53.3%, 73.3% and 93.3% of patients in arms A, B and C, respectively (endpoint analysis 1) and at the end of follow-up this improvement remained at the rate of 87.5%, 63.6% and 85.7% respectively (endpoint analysis 2). Only 13.3% patients who received 0.03% tacrolimus ointment experienced excellent improvement and clearance by the end of the treatment compared with 66.7% patients who received 0.05% clobetasone butyrate and 93.3% patients who received combination regimens. Skin burning was common in the 0.03% tacrolimus treatment group than in the 0.05% clobetasone butyrate group (7/15 vs. 1/15, p=0.010) and in the combination regimen group (7/15 vs.2/15, P=0.042).

Conclusion The overall therapeutic effectiveness and safety were in favor of combination regimens.

Key words Tacrolimus, FK506, clobetasone butyrate, atopic dermatitis, efficacy, safety.

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Introduction

Atopic dermatitis is a Th2-mediated chronic pruritic recurring inflammatory skin disease

in children and adults associated with substantial morbidity. Topical application of corticosteroids often produces dramatic suppression of atopic dermatitis in which inflammation is a prominent feature. However, the disease may return or be exacerbated when these topical agents are withdrawn. The chronicity and recurring nature of the condition often require long-term use of these preparations. The consequences of prolonged use of topical corticosteroids are well documented. Depending on strength, many cause cutaneous atrophy, pigmentary disturbances, telangiectasis and transient pituitary adrenal suppression.[1] Therefore, a steroid sparing topical agent suitable for the management of atopic dermatitis in terms of safety and efficacy is needed.

Tacrolimus (FK 506) is a non-steroid inhibitor of inflammatory cytokines with potent immunomodulatory properties. Since 1993 it has been used systemically to prevent rejection of liver and kidney transplants. The development of tacrolimus ointment was collectively supported by nonclinical pharmacology and toxicology-safety studies.[2] The mechanism of action of tacrolimus relevant in the pathogenesis of inflammatory skin disorders provided a rationale for topical application in patients with atopic dermatitis. Tacrolimus ointment 0.03% is generally well-tolerated, only mild to moderate and transient burning, pruritus and erythema at the application site have been reported.[3] It has no atrophogenic property[4] and does not increase the risk of cutaneous bacterial, viral or fungal infection in patients with atopic dermatitis.[5]

Nothing stronger than 1% hydrocortisone acetate preparation is practically safe in long-term use. Topical hydrocortisone failed to attain desirable efficacy during short-term use[6-7]. Clobetasone butyrate is a low potency corticosteroid with topical anti-inflammatory activity greater than hydrocortisone acetate 1%.[6-7] It has no detectable effect on plasma cortisol levels when used without occlusion in normal amounts (8 to 150g/week) for 1-2 weeks[8-9] and in animal model it caused slight cutaneous atrophy when applied under occlusion for seven weeks.[7] Therefore, short-term concomitant use of clobetasone butyrate cream 0.05% and tacrolimus ointment 0.03% is justifiable when augmented therapeutic response with a wide margin of safety is desired.

Patients and methods

Study design This comparative, multicenter, open, randomized, parallel-group study was designed to asses the efficacy and safety of 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream alone and their combination for the treatment of atopic dermatitis in older children. The study was performed at 3 centers in Dhaka during the period from October 2004 to February 2005. The study consisted of a screening visit within 7 days before the baseline visit (week 0). After baseline visit the patients were evaluated 2 weeks apart (weeks 2 and 4) during treatment and 2 weeks after treatment (weeks 6).

Patient selection and randomization Patients aged 7 to 15 years (older children) of either sex with a diagnosis of AD on the basis of the criteria of Hanifin and Rajka[10] were eligible for the screening visit. The severity of AD was graded according to the criteria of Rajka and Langeland.[11] Only

patients with an AD severity grading of moderate to severe and disease involvement of at least 5% but not more than 50% of the total body surface area (BSA) were recruited in the study. Patients having a serious skin disease other than AD that required treatment, patients with a history of eczema herpeticum, patients who had received topical treatment for AD within 2 weeks and/or systemic drug for AD within 4 weeks before the study and the patient or parents who refused to give consent were excluded. Patients were stratified by age and disease severity and randomized in parallel group (1:1:1) to receive a commercial preparation of 0.03% tacrolimus ointment alone, 0.05% clobetasone butyrate cream alone or both.

Treatment All patients who consented to participate in the study were assigned to treatment groups according to the study protocol (**Figure 1**). A thin layer of ointment and/or cream was applied twice daily to areas of actively diseased skin. All other topical and systemic drugs used in AD were prohibited, only bath oil and nonmedicated emollients were allowed. Inhaled or intranasal corticosteroids, if being used, were limited to 1mg/day.

Assessment At baseline and all fortnightly follow-up visits the patients were examined for erythema, edema-induration-papulation, excoriations and lichenification graded on a four point scale i.e. 0, absent; 1, mild; 2, moderate and 3, severe and estimated the percentage of the total BSA affected by AD (0%-100%) for 4 body region (head and neck, upper limbs, trunk and lower limbs) was also estimated. Patients assessed the intensity of itching experienced during previous 24 hours using a 10 cm visual analogue scale with 0 cm indicating 'no itch' and 10 cm indicating 'severe intractable itch". These assessments were used to calculate the modified eczema area and severity index (mEASI), the variant of EASI developed by Hanifin *et al*.[12] The following steps were carried out: (1) The affected BSA (0%-100%) was graded on an affected area score of 0 to 6; (2) the individual rating for erythema, edema-induration-papulation, excoriations and lichenification (0-3 for each of the 4 symptoms) were summed for each body region; (3) the sum for the individual symptoms (maximum=12) was multiplied by the affected area score (maximum=6), for a maximum of 72; (4) for 7 to 15 years old children, the head and neck subtotal was multiplied by 0.1, the upper limb subtotal by 0.2, the trunk subtotal by 0.3 and lower limb subtotal by 0.4; (5) all components were summed to get EASI (maximum=72); (6) the patients assessment of itching was converted to an ordinal scale of 0 to 3 and multiplied by the total affected area score (0-6), for a maximum itching score of 18. The EASI was summed with the itching score to get mEASI (maximum=72+18=90). Affected BSA and mEASI were assessed and compared to the baseline scores. Investigators also assessed the overall clinical response. "Cleared" indicated improvement of 100%, "excellent" indicated improvement of 90% to 99%, "marked" indicated improvement of 75% to 89%,"moderate" indicated improvement of 50% to 74%,"slight" indicated improvement of 30% to 49%, and "no" indicated improvement of 0% to 29%.

End point (EP) analysis EP1= No. of patients with 75% or more decrease in mEASI at the end of treatment/ No. of

patients included at week 0 (including all patients lost to follow-up) x 100.

EP2= No. of patients with 75% or more decrease in mEASI at the end of follow-up/ No. of patients with 75% or more decrease in mEASI at the end of treatment x 100.

Statistical Analysis The Pearson chi-square, the Yate's corrected chi-square test (when appropriate), Independent t test and paired t test were applied to assess the differences in proportions for statistical significance. Confidence interval (CI) was used for measure of dispersion.

Results

Patients From October 2004 to February 2005, the study required 6 months for its successful completion. A total of 45 patients (15 in each group) having clinical diagnosis of moderate to severe AD were needed. A total of 57 patients who met the enrollment criteria were approached. Three patients lost during treatment, of them two received 0.03% tacrolimus ointment and one received 0.05% clobetasone butyrate. Another dropout observed at the end of follow-up who received combination regimens. Demographic and baseline characteristics of the patients are presented in **Table 1**. Among three treatment groups there were no significant differences in age, gender, socioeconomic status, duration of current episode of disease, site of involvement, affected body surface area and disease severity (mEASI).

Efficacy All the treatment groups showed significant improvement throughout the treatment period. After 2 weeks of treatment median improvement as assessed with percentage decrease in mEASI and in the size of the affected BSA were nearly three times large in the 0.05% clobetasone butyrate and combination regimen group as in the 0.03% tacrolimus ointment group (**Figure 2**). At the end of 4 weeks patients had a median improvement of 81.9% in mEASI and 40% in the size of affected BSA with 0.03% tacrolimus ointment (arm A), 95.1% in mEASI and 66.7% in the size of affected BSA with 0.05% clobetasone butyrate (arm B) and 98.7% in mEASI and 83.3% in the size of affected BSA with combination regimen (arm C). The improvement among three treatment groups % reduction in mEASI showed significant difference between arm C and arm A [mean difference (95% CI) = 19.0 (10.5-27.6), p=0.00], arm B and arm A [mean difference (95% CI) = 12.5 (2.4-22.7), P=0.018] but no significant difference observed between arm C and arm B [mean difference (95% CI) = 6.5 (-2.0-15.1), p=0.128]. In accordance with mEASI, % reduction in the size of the affected BSA showed significant difference between arm C and arm A [mean difference (95% CI) = 42.6 (28.5-56.7), p=0.00] , arm B and arm A [mean difference (95% CI) = 26.7 (8.1-45.3), p=0.007] and no significant difference between arm C and arm B [mean difference (95% CI) = 15.9 (-1.3-33.0), p=0.069].

After 2 weeks drug restriction i.e. at the end of 6 weeks patient had a median increase of 6.3% in mEASI and 11.1% in the size of affected BSA with 0.03% tacrolimus ointment, 20.6% in mEASI and 33.3% in the size of affected BSA with 0.05% clobetasone butyrate and 7.9% in mEASI and 23.6% in the size of affected BSA with combination regimen. Therefore findings of

Table 1 Demographic and baseline characteristics of the patients (older children) with Atopic Dermatitis (AD).

Characteristics	*Arm A* n (%)	*Arm B* *n (%)*	*Arm C* *n (%)*	*Total* *n (%)*	*Test statistics*
Age group					
07 – 09 years	6 (40.0)	3 (20.0)	7 (46.7)	16 (35.6)	$\chi^2 = 7.550$
10 – 12 years	5 (33.3)	9 (60.0)	3 (20.0)	17 (37.8)	df: 16
13 – 15 years	4 (26.7)	3 (20.0)	5 (33.3)	12 (26.7)	$p = 0.961$
(Mean ± SD)	*10.5 ± 2.5*	*10.7 ± 1.8*	*10.5 ± 2.7*	*10.5 ± 2.3*	
Sex					$\chi^2 = 3.420$
Male	6 (40.0)	11 (73.3)	8 (53.3)	25 (55.6)	df: 2
Female	9 (60.0)	4 (26.7)	7 (46.7)	20 (44.4)	$p = 0.181$
Socioeconomic status					
Higher	4 (26.7)	2 (13.3)	3 (20.0)	9 (20.0)	$\chi^2 = 2.392$
Upper Middle	6 (40.0)	5 (33.3)	5 (33.3)	16 (35.6)	df: 6
Lower Middle	3 (20.0)	3 (20.0)	4 (26.7)	10 (22.2)	$p = 0.880$
Poor	2 (13.3)	5 (33.3)	3 (20.0)	10 (22.2)	
Current episode of AD					
< 6 month duration	10 (66.7)	9 (60.0)	11 (73.3)	30 (66.7)	$\chi^2 = 7.147$
> 6 month duration	5 (33.3)	6 (40.0)	4 (26.7)	15 (33.3)	df:14
Duration (Mean ± SD)	*5.8 ± 3.1*	*6.7 ± 3.2*	*5.7 ± 3.2*	*6.1 ± 3.1*	$p = 0.917$
Site of Involvement					
Head and Neck	7 (46.7)	6 (40.0)	11 (73.3)	24 (53.3)	$p = 0.153$
Upper Limb	14 (93.3)	15 (100.0)	13 (86.7)	42 (93.3)	$p = 0.343$
Trunk	12 (80.0)	13 (86.7)	12 (80.0)	37 (82.2)	$p = 0.859$
Lower Limb	12 (80.0)	11 (73.3)	10 (66.7)	33 (73.3)	= 0.711
Baseline BSA (%)					
18 – 24	7 (46.7)	6 (40.0)	9 (60.0)	22 (48.9)	$\chi^2 = 10.350$
25 – 30	7 (46.7)	8 (53.3)	4 (26.7)	19 (42.2)	df: 14
31 – 36	1 (6.7)	1 (6.7)	2 (13.3)	4 (8.9)	$p = 0.736$
(Mean ± SD)	*25.2 ± 5.0*	*25.4± 4.8*	*24.9 ± 5.0*	*25.2 ± 4.8*	
Baseline mEASI					
<11	2 (13.3)	4 (26.7)	4 (26.7)	10 (22.2)	$\chi^2 = 10.350$
11 – 21	11 (73.3)	9 (60.0)	10 (66.7)	30 (66.7)	df: 14
> 21	2 (13.3)	2 (13.3)	1 (6.7)	5 (11.1)	$p = 0.736$
(Mean ± SD)	*14.8 ± 4.3*	*15.6 ± 5.3*	*14.4 ± 5.7*	*14.9 ± 5.0*	
Total	15 (100.0)	15 (100.0)	15 (100.0)	45 (100.0)	

percentage increase in mEASI were similar in combination regimen and 0.03% tacrolimus ointment group (95% CI of the difference; -0.9%-8.0%, p=0.111) but both significantly differed with 0.05% clobetasone butyrate treatment group (arm C

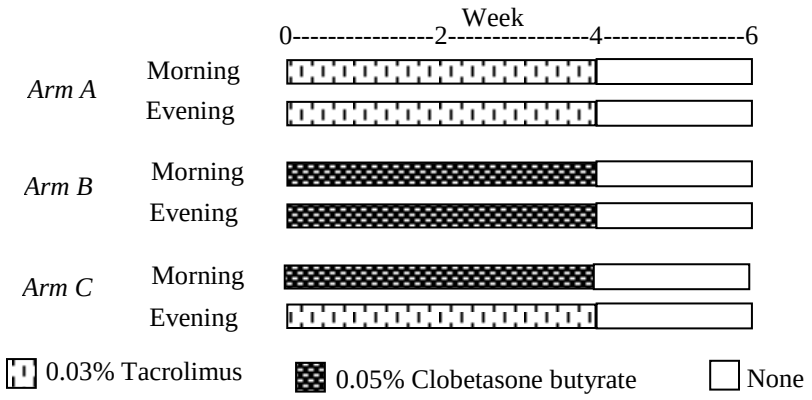

Figure 1 Treatment assignment in different arms (**Arm A** 0.03% tacrolimus twice-daily application, **Arm B** 0.05% clobetasone butyrate twice-daily application, and **Arm C** 0.05% clobetasone butyrate in the morning and 0.03% tacrolimus in the evening).

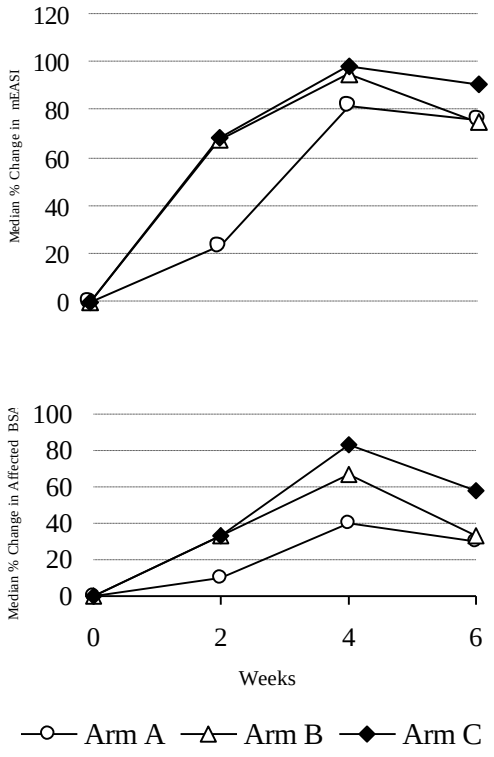

Figure 2: Median % Changes in the mEASI and affected body surface area (BSA) during treatment and two weeks after end of treatment.

vs. arm B: 95% CI of the Difference; 4.5%-24.8%, *P*=0.007, arm A vs. arm B: 95% CI of the Difference; 8.6%-27.9%, *P*=0.001). On the other hand percentage increase in the size of affected BSA showed no significant difference between 0.05% clobetasone butyrate and combination regimen group (95% CI of the difference; -4.9%-21.9%, *p*=0.205) but both significantly differed with 0.03% tacrolimus ointment group (arm B vs. arm A: 95% CI of the difference; 9.4%-30.8%, *p*=0.001, arm C vs. arm A: 95% CI of the difference; 1.1%-22.2%, *p*=0.032) [**Figure 2**].

Investigator's evaluations Investigator's evaluation carried on all 45 patients (intent-to-treat population). Only 13.3% patients who received 0.03% tacrolimus ointment experienced excellent improvement and clearance by the end of the treatment compared with 66.7% patients who received 0.05% clobetasone butyrate and 93.3% patients who received combination regimens. Marked to moderate improvement was observed for 73.3%, 66.7% and 6.7% of patients who received 0.03% tacrolimus, 0.05% clobetasone butyrate and combination regimen respectively. At the end of follow-up excellent improvement and

clearance was observed in 6.7% of patients of 0.03% tacrolimus group and 0.05% clobetasone butyrate group respectively, and in 60.0% patients who received combination regimens. Marked to moderate improvement was observed for 73.3%, 60.0% and 33.3% of patients who received 0.03% tacrolimus, 0.05% clobetasone butyrate and combination regimen respectively. Slight improvement was observed in 6.7% patients who received 0.03% tacrolimus ointment and 13.3% patients who received 0.05% clobetasone butyrate ointment, in the later group 13.3% experienced no improvement by the end of the follow-up (**Figure 3**). Investigator's evaluations that made at the end of treatment remained unchanged at the end of follow-up for 76.9%, 7.1% and 50.0% of patients who received 0.03% tacrolimus, 0.05% clobetasone butyrate and combination regimen respectively.

End Point Analysis EP1 rate was 53.3% and EP2 rate was 87.5% for 0.03% tacrolimus group, on the other hand EP1 rate was 73.3% and EP2 rate was 63.6% for 0.05% clobetasone butyrate group. In combination regimen EP1 rate was 93.3% and EP2 rate was 85.7%. Overall efficacy was in favor of combination regimen.

Adverse Effects Skin burning was the most common event to show a significant high incidence in the 0.03% tacrolimus treatment group than in the 0.05% clobetasone butyrate group (7/15 vs. 1/15, p=0.010) and in the combination regimen group (7/15 vs.2/15, p=0.042). More itching was reported by 20.0%, 13.3% and 6.7% of patients who received 0.03% tacrolimus, 0.05% clobetasone butyrate and combination regimen respectively without showing any significant differences (X^2=1.154, df: 2, p=0.562). During treatment period 2 of the 3 dropout cases reported skin burning, both of them were in 0.03% tacrolimus group but the reason of withdrawn was unknown. Otherwise none had to discontinue treatment for these adverse events. Two patients experienced fever, one from 0.05% clobetasone butyrate group and another from combination regimen group; this event did not suggest a relationship with treatment regimens.

Discussion

The sample populations were randomly selected and distributed with no significant difference between three treatment groups irrespective of demographic and baseline characteristics. Therefore patients in three treatment arms were balanced and most of the confounding factors were eliminated.

Results of this preliminary study are encouraging. The rate of response of 0.03% tacrolimus ointment at the end of 4 weeks treatment are nearly similar to the rate observed in other studies.[14-16] and the observed therapeutic effectiveness of 0.05% clobetasone butyrate is also in agreement with previous relevant studies.[6-9] During first half of the treatment clobetasone butyrate showed greater improvement than tacrolimus but at the end of treatment no significant difference was observed between two treatment groups.

Despite showing similar efficacy disease flare-up at the end of follow-up was more significant in the patients those treated with 0.05% clobetasone butyrate cream. The minimal relapse seen in 0.03% tacrolimus treated patient may be associated with noncrticosteroidal immunomodulatory

effects of the drug. In atopic dermatitis allergen in contact with immunoglobulin E (IgE) form allergen-IgE complex that bind to high-affinity IgE receptor (FcεRI) exists on the Langerhan's cells, the dendritic antigen presenting cells of the of the skin. The genetic contribution may involve the beta (β) subunit of Fc epsilon RI gene (FcεRI- β) localized to chromosome 11q 12-13.[13] Tacrolimus is known to decrease the Fc epsilon RI expression on these dendritic antigen presenting cells,[17] thus down regulate the T cell activation in response to triggering antigen. Experimental evidence also suggests that tacrolimus binds to an intracellular protein FKBP-12, found in T-lymphocytes. This binding phenomenon inhibits the ability of calcineurin to activate the promoter region of the gene for IL-2, IL-3, IL-4, IL-5, interferon gamma, tumor necrosis factor alpha, and granulocyte macrophage colony-stimulating factor, all of which participate in the early immune response and play a role in the pathogenesis of atopic dermatitis.[18]

In this clinical trial we did not try to investigate the mechanism of action of tacrolimus rather we attempted to evaluate the efficacy and safety of tacrolimus alone or combination with clobetasone butyrate in the management of atopic dermatitis. The combination regimen have shown significant efficacy and safety compared with 0.03% tacrolimus ointment and 0.05% clobetasone butyrate cream alone. The overall therapeutic response was in favor of combination regimen except moderate disease flare-up at the end of follow-up.

Topical corticosteroids are very effective in the short term treatment of AD as the drug suppress the inflammation by vasoconstrictive and glucocorticoid activities in the acute stage of the disease. Topical tacrolimus modulates inflammatory responses in the skin by inhibiting T-cell activation and cytokine production and has a good safety profile for long-term control of AD. Transient skin burning that produce by tacrolimus in first days of treatment may have suppressed by anti-inflammatory activities of topical corticosteroids when combination regimen used. Topical corticosteroids up-regulate the expression of FcεRI; in contrast, tacrolimus down-regulates its expression. Perhaps dual therapy may minimize the potential adverse effects of both treatment alone and may potentially improve overall responses. The greater efficacy of the 0.03% tacrolimus ointment was apparent after 2 weeks of treatment. Before that the changes in severity of the disease was minimal. At the end of treatment 0.03% tacrolimus ointment showed nearly similar therapeutic effectiveness as observed with 0.05% clobetasone butyrate. This fact suggest that equal therapeutic response might be attained by replacing 0.05% clobetasone butyrate cream with 0.03% tacrolimus ointment after 2 weeks of treatment. It would be of interest to assess prospectively.

Conclusion

The overall therapeutic effectiveness and safety were significantly in favor of Combination regimen. Clinical trials are needed using more steroid sparing combination regimens.

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