Clinical Study of Efficacy of Topical Tacrolimus in Various Dermatoses

Jigna Padhiyar*, Krina B. Patel**, Nayan Patel***, Kishan Ninama****, Yogesh B. Shah*****

Abstract :

Introduction : Tacrolimus is a calcineurin inhibitor. Topical tacrolimus (0.03% and 0.1%) is currently approved for the treatment of atopic dermatitis. It has been found to be an effective treatment for oral erosive lichen planus, cutaneous lichen planus, psoriasis, vitiligo, few bullous and many other inflammatory dermatoses. **Material and methods :** Total 140 patients with clinically diagnosed dermatological conditions thought to be amenable to topical tacrolimus ointment attending our department were included in this study. Almost all children (except few who were given 0.1%) were given 0.03% topical tacrolimus. 0.03% topical tacrolimus was given on all mucosal lesions. Adults with skin lesions were either given 0.03 or 0.1% as per requirement. **Results :** Topical tacrolimus is very effective in treating atopic dermatitis, oral erosive lichen planus, vitiligo, genital lichen sclerosusatrophicus and post herpes labialis depigmentation. Its efficacy in other dermatoses like – granuloma annulare, twenty nail dystrophy, alopecia areata, hand eczema etc. - needs larger study to prove its usefulness as steroid sparing agent.

Key Words: efficacy, topical tacrolimus, various dermatoses

Introduction :

The macrolide immunomodulators in clinical use are-tacrolimus (fk506), pimercrolimus (asm 981), cyclosporine and sirolimus (rapamycin) [1]. Among these, tacrolimus - a calcineurin inhibitor produced by the soil bacterium stretomycestsukubaensis was isolated in year 1984, has strong immunosuppressive activity in vivo and prevents the activation of t-lymphocytes in response to antigenic or mitogenic stimulus in vitro [2,3]. The name tacrolimus is derived by taking the 't' for tsukuba, the name of mountain where the soil sample was extracted, 'acrol' for macrolide and 'imus' for immunosuppressant [3].

Topical tacrolimus (0.03% and 0.1%) is currently approved for the treatment of atopic dermatitis (>2year of age). [1, 4] FDA has approved topical tacrolimus for continuous use of one year. Topical therapy with tacrolimus is safe and effective in paediatric and adult patient up to 4 years of continuous use. [5, 6] It has been found to be an effective treatment for oral erosive lichen planus, cutaneous lichen planus, psoriasis, vitiligo, few bullous and many other inflammatory dermatoses. These extensive arrays of disorders treated successfully with topical tacrolimus warrants further study of this drug. Contraindications include hypersensitivity to tacrolimus or any component of ointment, children < 2 yr, active skin infection at the site to be treated, netherton syndrome &erythroderma [6]. Thus present study was conducted with aims of to assess the efficacy of topical tacrolimus in various dermatoses and to assess the adverse effect profile of the drug.

* Senior Resident,
*** Assistant Professor,
***** Professor, Skin Department, GCS Medical College, Hospital & Research Centre, Ahmedabad, Gujarat, India
** Associate Professor, Skin Department, GMERS Medical College-Sola, Gujarat, India
**** Assistant Professor, Skin Department, SBKS Medical College and Research Centre, Vaghodia, Gujarat, India
Correspondence : jigna_dr12@yahoo.com

Material and methods :

Patients with clinically diagnosed dermatological conditions thought to be amenable to topical tacrolimus ointment attending a tertiary teaching institute were included in this study. Biopsy was taken when necessary. 140 patients were included in the study after counselling for the compliance and side effect profile. Patients with different dermatological disorders e.g. atopic dermatitis, vitiligo, oral and genital erosive lichen planus, granuloma annulare, genital lichen sclerosusatrophicus, alopecia areata, cicatricial alopecia, chronic eczema, hand eczema, post herpetic depigmentation, twenty nail dystrophy were included in the study. Pregnant and lactating women were excluded in the study. 41 patients were lost to follow up after 1st visit and were not included in the result.

The details of history and examination findings were recorded. A detailed lesion assessment including number of lesions (where necessary), sites of the lesions, size of the lesions were carried out at visit-1(baseline), visit -2(15 days), visit-3(30 days), visit-4(60 days), visit-5(90 days), visit-6(120 days) and visit-7(150days). Photographs were taken at each visit.All patients were observed for the recurrence of the lesion or any other unusual local skin reaction after the last visit for 7 months. Almost all children (except few who were given 0.1%) were given 0.03% topical tacrolimus. 0.03% topical tacrolimus was given on all

mucosal lesions. Adults with skin lesions were either given 0.03 or 0.1% as per requirement. Response to treatment was graded as - no improvement (<25% improvement), mild improvement (25%-50% improvement), moderate improvement (50%-75% improvement), excellent improvement (75%-90% improvement), complete improvement (90%-100% improvement). Adverse reactions were graded as mild- did not significantly interfere with patient's functioning, moderate - interfere slightly with patient functioning and severe - interfere significantly with patient functioning.

Results :

Out of 140 patients 41 patients were lost to follow up. So total 99 (male-39 and female-60) were included in the study for results.

In atopic dermatitis group (n=19), 9(47.37%) showed excellent and 10(52.63%) showed complete response. (Figure-1, 2)

In oral LP (lichen planus) group (n=21), 1(4.76%) showed no response, 2(9.52%) showed mild response, 7(33.33%) showed moderate response, 11(52.38%) showed excellent response (figure-3) and complete response was not seen in any patient.

In alopecia areata group (n=4) 1(25%) showed complete response 3(75%) (figure-4) showed mild response.

Figure-1: Atopic dermatitis in child-
(A) before treatment (B) after treatment-
complete response

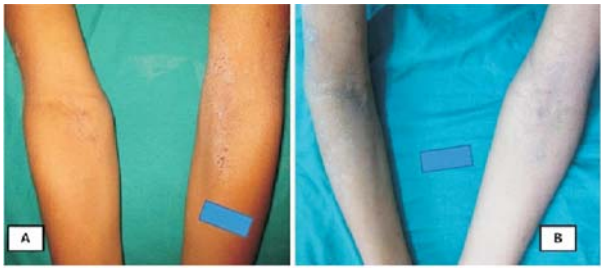

Figure-2: Atopic dermatitis in adult-
(A) before treatment (B) after treatment-
excellent response

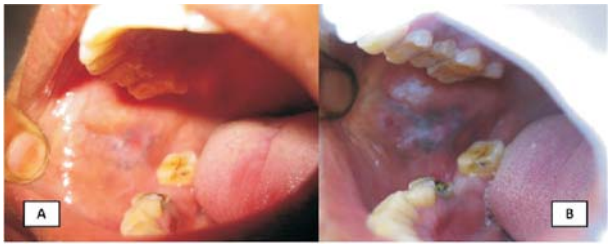

Figure-3 : Oral erosive LP-
(A) before treatment (B) after treatment-
excellent response

Figure-4: Alopecia areata-
(A) before treatment (B) after treatment-
complete response

Figure-5: Post-herpes labialis depigmentation-
(A) before treatment (B) after treatment-
complete response followed by new lesions.

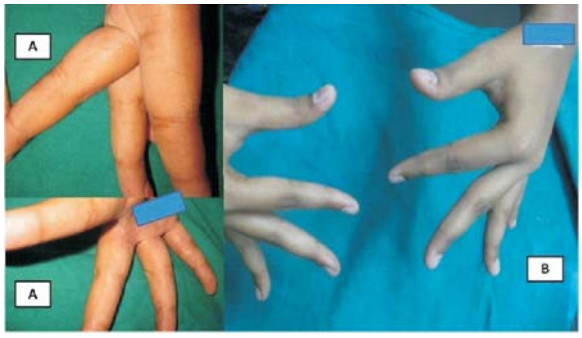

Figure-6: Pompholyx-
(A) before treatment (B) after treatment-
complete response.

In twenty nail dystrophy (n=2) both showed no improvement. None of the patient of GA (granuloma annulare) group (n=2) showed response in this study during

study period. In genital lichen sclerosus atrophicus (LSA) group (n=3), 2(66.66%) showed moderate and 1(33.33%) showed excellent response. In post herpes labialis depigmentation group (n=3), 1(33.33%) showed mild, 1(33.33%) showed excellent and 1(33.33%) showed complete response (figure-5). In pompholyx and hand eczema group (n=3) 1(33.33%) showed complete response (figure-6) and 2(66.66%) showed moderate response. In eczema other than hand eczema group (n=2) both showed mild response.

In scaring alopecia group (n=7) no showed improvement, but one patient was having associated depigmentation and depigmentation improved moderately but not scarring alopecia. In vitiligo group (n=33) who were only given topical tacrolimus (n=27), 4(14.81%) showed no, 8(29.62%) showed mild, 5(18.51%) showed moderate, 5(18.51%) showed excellent and 5(18.51%) showed complete response. In vitiligo group who did not showed any response to topical tacrolimus alone were additionally given topical steroids after study period (n=6), 1(16.66%) showed no, 3(50%) showed mild and b2(33.33%) showed moderate response.

Only 4 (3.74%) out of total 99 patients reported mild transient adverse events. In scarring alopecia group (n=7), 2(28.57%) showed adverse effect- one patient showed mild itching and other one showed pyoderma. In lichen sclerosus atrophicus group (n=3), 1(33.33%) showed mild erythema. In vitiligo group (n=33), 1(3.03%) showed acneform eruption.

Table 1: Efficacy and Safety Analysis for various Dermatoses

Group	Sample size	No response	Mild response	Moderate response	Excellent response	Complete response	Adverse reaction
Atopic dermatitis	19	-	-	-	9(47.37%)	10(52.63%)	-
Oral lp	21	1(4.76%)	2(9.52%)	7(33.33%)	11(52.38%)	-	-
Alopecia areata	4	-	3(75%)	-	-	1(25%)	-
Twenty nail dystrophy	2	2(100%)	-	-	-	-	-
Granulo-ma annulare	2	2(100%)	-	-	-	-	-
Genital LSA	3	-	-	2(66.66%)	1(33.33%)	-	Erythema in 1(33.33%)

Table 2 : Efficacy and Safety Analysis for various Dermatoses (continued...)

Group	Sample size	No response	Mild response	Moderate response	Excellent response	Complete response	Adverse reaction
Post herpetic depigmentation	3	-	1(33.33%)	-	1(33.33%)	1(33.33%)	-
Pompholix & hand eczema	3	-	-	2(66.66%)	-	1(33.33%)	-
Scaring alopecia	7	7(100%)	-	-	-	-	Pyoderm and itching in 2(28.57%)
Eczema other than hand eczema	2	-	2(100%)	-	-	-	-
Vitiligo(only given topical tacrolimus)	27	4(14.81%)	8(29.62%)	5(18.51%)	5(18.51%)	5(18.51%)	Acneform eruption in 1(3.03%)
Vitiligo (tacrolimus+ steroid)	6	1(16.66%)	3(50%)	2(33.33%)	-	-	-

Discussion :

Hanifin JM et al [7] showed that there is >90% improvement in 36.8 %(0.1% ointment) and in 27.5 %(0.03% ointment) with twice/day application for atopic dermatitis patients. My study showed >75% improvement in all patient. So, once/day application may be as effective as twice/day; though larger sample size is required to have conclusion. Similarly Schammeret [8] al showed >90% improvement in 51% of patient with 0.03% ointment twice/d application. My study showed > 90% improvement in 57.14 %(0.03% ointment) and 50 %(0.1% ointment) of patients. So we can say that once/d application may be as effective as twice/day.

As compare to study by Jain S. Et al [9] my study did not show any response in GA, may be due to application used once daily only.

Though number of patient was few in my study, results were comparable to study by Schilieman et al [10] for hand eczema group of patients.

Total response rate and duration for response in present study for vitiligo group were comparable to study by XuAE et al [11]. My study also showed greater response in lesions on head and neck as in Xu AE et al. Response rate in vulgaris group was comparable to study by Udompataikul M et al [12], but response in segmental and acrofacialis group was less in my study compared to same.

As compare to Hodgson TA et al[13] and Vente C. et al[14] my study did not showed complete improvement in any patient of oral erosive LP group, may be because, in present study only 0.03% topical tacrolimus was used and that also only once/day. Even mean duration of partial response was also higher in my study. Relapse rate was comparable to study by Vente C et al.

As compare to other study by BöhmM Et al[15](n=6) and Luesley DM et al[16](n=16) in my study for genital LSA group no patient showed complete response, may be because, in present study 0.03% once daily was used and that also for lesser duration. Further study with larger sample size is required.

Anecdotal reports of efficacy of topical tacrolimus in lichen planopilaris by Blazek C et al [17] is there. In my study two patient of scarring alopecia were diagnosed as LPP (lichen planopilaris). Both of them did not showed any response to 0.1% tacrolimus at 5 month.

Anecdotal reports of efficacy of topical tacrolimus in cutaneous resistant lupus erythematosus by Lampropoulos CE et al [18]. In my study one patient was having scarring alopecia due to DLE but did not improve with 0.1% at 5 month. This again can be due to once/d application of medicine and shorter duration of treatment.

References :

1. Lin AN. Topical calcineurin inhibitors. In: Wolverton SE, editors. Comprehensive dermatologic drug therapy, 2nd ed. China: Elsevier; 2007.p.671-89.
2. Kino T, Hatanaka H, Hashimoto M, Nishiyama M, Goto T, Okuhara M, Kohsaka M, Aoki H, Imanaka H. "FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physio-chemical and biological characteristics."J Antibiot (Tokyo) 1987; 40(9):1249–55.
3. Sehgal VN, Srivastava G, Dogra S. Tacrolimus in dermatology-pharmacokinetics, mechanism of action, drug interactions, dosages, and side effects: part-I. Skinmed.2008; 7:27-30.
4. Bornhovd E, Burgdorf W, Wollenberg A. Macrolactumimmunomodulators for topical treatment of inflammatory skin diseases. J Am AcadDermatol 2001; 45:736-43.
5. Gupta AK, Adamiak A, Chow M. Tacrolimus: a review of its use for the management of dermatoses. J Eur Acad Dermatol Venereol 2006; 16:100-114.
6. Hanifin JM et al. Tacrolimus in atopic dermatitis: long term efficacy and safety. J AM Acad Dermatol. 2005; 53(2 suppl2):S186-94.
7. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E. Tacrolimus ointment for the treatment of atopic dermatitis in adults patients: Part I, efficacy. J Am AcadDermatol 2001; 44(1 Suppl):S28-38.
8. Schachner LA, Lamerson C, Sheehan MP et al. Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from randomized, double-blind, vehicle controlled study. Paediatrics 2005; 116:e334-e342.
9. Jain S, Stephens CJ. Successful treatment of disseminated granuloma annulare with topical tacrolimus. Br J Dermatol 2004; 150:1042-3.
10. Schliemann S, Kelterer D, Bauer A, et al. Tacrolimus ointment in the treatment of occupationally induced chronic hand dermatitis. Contact Dermatitis 2008; 58(5):299-306.
11. Xu AE, Zhang DM, Wei XD, Huang B, Lu LJ. Efficacy and safety of tarcrolimus cream 0.1% in the treatment of vitiligo. Int J Dermatol. 2009 Jan; 48(1):86-90.
12. Udompataikul M, Boonsupthip P, Siriwattanagate R.Effectiveness of 0.1% topical tacrolimus in adult and children patients with vitiligo. J Dermatol. 2011; 38(6):536-40.
13. Hodgson TA, Sahani N, Kaliakatsou F et al. Long –term efficacy and safety of topical tacrolimus in the management of ulcerative/erosive oral lichen planus. Eur J Dermatol. 2003; 13(5):466-70.
14. Vente C, Reich K, Rupprecht R, Neumann C. Erosive mucosal lichen planus: response to topical treatment with tacrolimus. Br J Dermatol 1999; 140:338-42.
15. Böhm M, Frieling U, Luger TA, Bonsmann G. Successful treatment of anogenital lichen sclerosus with topical tacrolimus. Arch Dermatol. 2003; 139:922-924.
16. Luesley DM, Downey GP. Topical tacrolimus in the management of lichen sclerosus. BJOG 2006; 113:832-834.
17. Blazek C, Megahed M. Lichen planopilaris. Successful treatment with tacrolimus. Hautarzt. 2008; 59(11):874-7.
18. Lampropoulos CE, Sangle S, Harrison P et al.topicaltacrolimus therapy of resistant cutaneous lesions in lupus eryhtematosus: a possible alternative. Rheumatology (Oxford) 2004; 43(11):1383-5.