Study

# Evaluation of the efficacy, safety and tolerability of tacrolimus ointment in Indian patients of moderate to severe atopic dermatitis: A multicentric, open label, phase III study

**D. G. Saple, R. G. Torsekar,[1] Vikas Pawanarkar,[2] Vijaykumar Wali,[3] G. Ravichandran,[4] U. R. Dhanalakshmi,[5] Neelesh Dongre,[6] Chetna Ballary,[6] Anish Desai[6]**

Department of Dermatology, G. T. Hospital, Grant Medical College, Mumbai; [1]Department of Skin, Rajeev Gandhi Medical College & Chhatrapati Shivaji Maharaj Hospital, Kalwa; [2]Pramila Hospital , Sneha Polyclinic & I.C.C.U., Kalwa, Thane; [3]Department of Dermatology, M. R. Medical College, Gulbarga; [4]Zubeda Hospital, Chennai; [5]B. R. Hospital, Chennai, [6]Glenmark Pharmaceuticals Limited, 801-813, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Mumbai - 400026.

**Address for correspondence:** Dr. Neelesh Dongre, Glenmark Pharmaceuticals Ltd., 801-813, Mahalaxmi Chambes, 22, Bhulabhai Desai Road, Mumbai - 400026, India.

## ABSTRACT

**Aim of study:** Tacrolimus, a topical immunomodulator, has been introduced as a new treatment for moderate to severe atopic dermatitis. The present study was conducted to evaluate the efficacy, safety and tolerability of Tacrolimus ointment in patients of atopic dermatitis in an Indian setting. **Methods:** The present study was a prospective, open, multicentric, Phase III trial.The duration of study was 5 weeks, including a 3-week active treatment period, preceded by a 1-week washout phase and followed by a 1-week follow-up phase. Patients diagnosed to be suffering from moderate to severe atopic dermatitis as per the Rajka and Langeland criteria were treated with Tacrolimus ointment 0.03% twice daily. Efficacy was assessed by modified Eczema Area Sensitivity Index (mEASI) score, patient's and physician's global assessment. Tolerability and safety was assessed by physical examination, laboratory parameters and evaluation of adverse events. **Results:** There was a statistically significant decrease in the modified Eczema Area Sensitivity Index (mEASI) score *(P<0.05)*. Patient's and Physician's global evaluation of treatment was complete resolution to very good improvement in most of the patients. The laboratory values were within normal limits. The drug was well tolerated. **Conclusions:** This study confirms the efficacy and safety of Tacrolimus ointment 0.03% in Indian patients of moderate to severe atopic dermatitis.

**Key Words:** Tacrolimus, Safety, Efficacy, Atopic dermatitis

## INTRODUCTION

Atopic dermatitis is a chronic inflammation of the skin. The condition is characterized by pruritus, xerosis and typical skin lesions. 90% of the cases develop the disease before the age of 5 yrs.[1] It is marked by exacerbations and remissions. Poor prognostic features include a family history of the condition, early disseminated infantile disease, female gender and coexisting allergic rhinitis and asthma. Genetic susceptibility, immune dysfunction and epidermal barrier dysfunction are implicated in the pathogenesis of the condition.[2]

The treatment of atopic dermatitis is aimed at

**How to cite this article:** Saple DG, Torsekar RG, Pawanarkar V, Wali V, Ravichandran G, Dhanalakshmi UR, et al. Evaluation of the efficacy, safety and tolerability of tacrolimus ointment in Indian patients of moderate to severe atopic dermatitis: A multicentric, open label, phase III study. Indian J Dermatol Venereol Leprol 2003;69:396-400.

**Received:** August, 2003. **Accepted:** November, 2003. **Source of Support:** Glenmark Pharmaceuticals Ltd., Mumbai.

increasing hydration, reducing inflammation, treating infection and eliminating antigens and irritants. Current treatment options include the use of steroids, emollients, anti-histamines, tar preparations, phototherapy and immunosuppressants. These agents are associated with a number of adverse events. Therefore, there is currently a need for a potent, safe, non-steroidal, topical treatment for atopic dermatitis.

Tacrolimus is an immunomodulatory agent developed for topical application. It is a macrolide lactone produced by Streptomyces tsukubaensis. It inhibits the T-lymphocyte activation and thus inhibits the release of inflammatory cytokines which are implicated in the pathogenesis of atopic dermatitis.[3] Topical tacrolimus ointment was approved by the US-FDA in December 2000 for the treatment of atopic dermatitis. The current study was conducted to evaluate the efficacy, safety and tolerability of Tacrolimus ointment in Indian patients of moderate to severe atopic dermatitis.

## METHODS

The present study was a prospective, multicentric, open-label, phase III study. All patients provided written informed consent before screening and enrollment in the study. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by Institutional Review Board.

Patients of both the sexes within the age group of 2-70 yrs, diagnosed with moderate to severe atopic dermatitis as per the Rajka and Langeland criteria[4] were enrolled in the study. Pregnant and lactating women, patients with known hypersensitivity to the drug, severe skin, hepatic, renal, systemic disease were excluded from the study. Duration of the study was 5 weeks, including a 3-week active treatment period, preceded by a 1-week washout phase and followed by a 1-week follow-up phase. Patients received 0.03% Tacrolimus ointment to be applied over the affected area/s twice daily as a thin film and rubbed in gently and completely, with each application separated by about 12 hours. The efficacy was evaluated by the modified eczema area sensitivity index (mEASI), physicians and patients global evaluation at follow-up visits. General clinical safety was monitored by the incidence of treatment-emergent adverse events, physical examination, and changes in clinical laboratory variables. Adverse events were monitored at baseline and throughout the study. Adverse events that occurred within 7 days of the last tacrolimus study dose were included in the safety analysis. The statistical analysis was done using the student's "t" test. *P value* $< 0.05$ was considered significant.

## RESULTS

A total of 125 patients were enrolled in 6 centers. The age of the patients was ranging from 12-69 yrs with average mean 33 yrs with mean weight 57.77 kg. 76 % of total study cases were male and mean duration of illness was 7.91 years.

Table 1 shows the changes in the mean score of erythema, oozing/crusting, excoriation, oedema/induration/papulation. At the end of 3rd and 4th week mean score of erythema had a reduction of 47.0% and 66.8% respectively from baseline. At the end of 3rd and 4th week mean score of oozing had a fall of 51.1% and 72% respectively from baseline. At the end of 3rd and 4th week mean score of excoriation had a fall of 61.5% and 79.1% respectively. At the end of 3rd and 4th week mean score of edema had a fall of 55.5% and 73.4% respectively from baseline.

Table 2 shows the changes in the mean score of scaling, lichenification, itching/pruritus. At the end of 3rd and 4th week mean score of scaling had a reduction of 61.5% and 77.1% respectively from baseline. At the end of 3rd and 4th week mean score of lichenification had a fall of 55.4% and 77.0% respectively from baseline. At the end of 3rd and 4th week mean pruritus score had a reduction

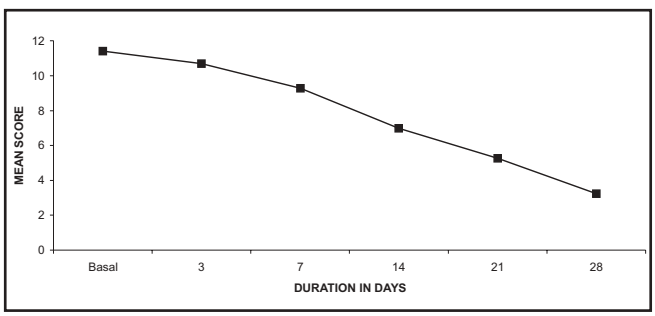
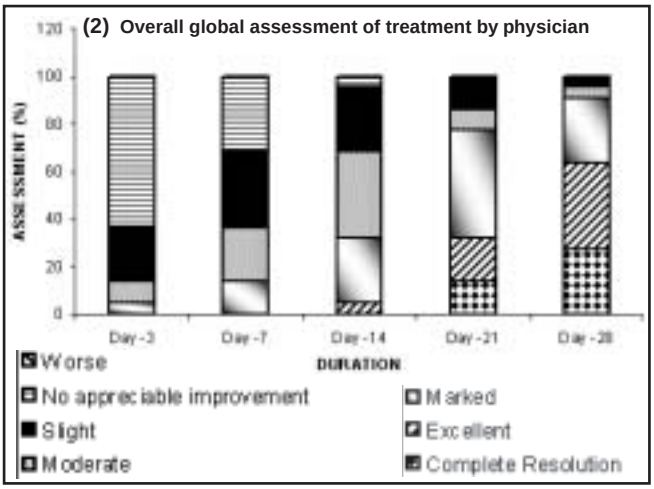
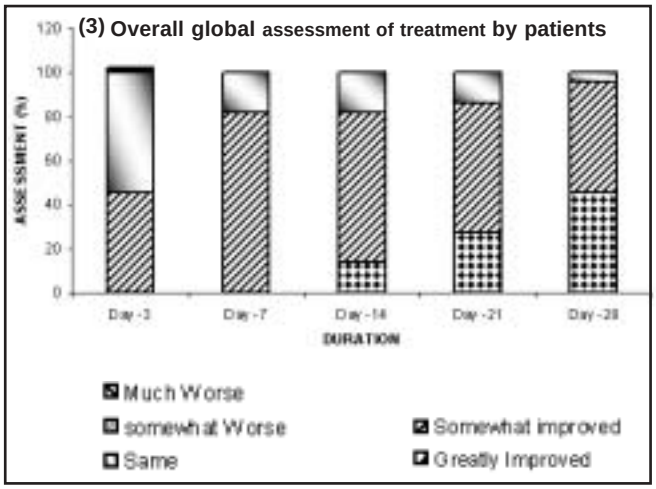



**Figure 1: The average total score after treatment**




**Figures 2 & 3: The overall global efficacy by the physician and patients. At the end of treatment 94.4% of cases showed improvement as per patients global evaluation**

**Table 1: Changes in the mean score of erythema, oozing/crusting, excoriation, oedema/induration/papulation.**

| | Erythema | Oozing/crusting | Excoriation | Oedema/Induration/Papulation |
|---|---|---|---|---|
| Duration in Days | Mean Score ($\bar{X}$ ± SD) | Mean Score ($\bar{X}$ ± SD) | Mean Score ($\bar{X}$ ± SD) | Mean Score ($\bar{X}$ ± SD) |
| Basal | 2.47 ± 0.57 | 1.71 ± 0.56 | 1.82 ± 0.58 | 1.84 ± 0.60 |
| 3 | 2.39 ± 0.60 | 1.64 ± 0.58 | 1.74 ± 0.60 | 1.76 ± 0.55 |
| 7 | 2.24 ± 0.65 | *1.38 ± 0.51 | *1.52 ± 0.54 | *1.51 ± 0.52 |
| 14 | *1.84 ± 0.57 | *1.02 ± 0.48 | *0.94 ± 0.51 | *1.12 ± 0.51 |
| 21 | *1.31 ± 0.65 | *0.83 ± 0.46 | *0.70 ± 0.44 | *0.82 ± 0.43 |
| 28 | 0.82 ± 0.47 | *0.48 ± 0.40 | *0.38 ± 0.44 | *0.49 ± 0.41 |

(By Wilcoxon Sign Rank Test). *: *P< 0.05* Significant

**Table 2: Changes in the mean score of scaling, lichenification, itching/pruritus**

| Duration In Days | Scaling Mean Score ($\bar{X}$ ± SD) | Lichenification Mean Score ($\bar{X}$ ± SD) | Itching/Pruritus Mean Score ($\bar{X}$ ± SD) |
|---|---|---|---|
| Basal | 1.92 ± 0.75 | 1.48 ± 0.53 | 2.09 ± 0.71 |
| 3 | 1.81 ± 0.71 | 1.40 ± 0.52 | 1.92 ± 0.68 |
| 7 | *1.54 ± 0.63 | *1.08 ± 0.51 | *1.63 ± 0.59 |
| 14 | *1.12 ± 0.56 | *0.88 ± 0.48 | *1.36 ± 0.58 |
| 21 | *0.74 ± 0.56 | *0.66 ± 0.43 | *0.93 ± 0.52 |
| 28 | *0.44 ± 0.43 | *0.34 ± 0.41 | *0.48 ± 0.47 |

(By Wilcoxon Sign Rank Test) *: *P< 0.05* Significant

**Table 3: Profile of adverse events**

| Events | No. of patients (n=125) | Percentage |
|---|---|---|
| Burning Sensation | 13 | 10.4 |
| Folliculitis | 03 | 2.4 |
| Pruritus | 06 | 4.8 |
| URTI | 02 | 1.6 |
| Erythema | 09 | 7.2 |
| Headache | 03 | 2.4 |
| Allergic reaction | 06 | 4.8 |
| No. of patients | 26 | 20.8 |

of 55.6% and 77.1% respectively from baseline.

Table 3 shows the profile of adverse events. 20.8% of total study cases experienced untoward effects. Out of these 10.4% of case had burning sensation followed by 4.8 % pruritus and allergic reaction, 7.2 % erythema and very few cases complained about headache and folliculitis. There was no significant change in laboratory parameters at the end of treatment.

## DISCUSSION

Tacrolimus ointment, formulated for the treatment of atopic dermatitis, is the first in a class of topical immunomodulators. It inhibits T-cell activation by inhibiting the phosphatase activity of calcineurin, which plays an essential role in the intracellular signal transduction pathway leading to the transcriptional activation of genes that encode various interleukins, granulocyte-macrophage colony stimulating factor, tumour necrosis factor alpha, and interferon gamma.[5] These inflammatory cytokines have been implicated in the pathogenesis of atopic dermatitis.[2] It also inhibits the release of mediators from skin mast cells and basophils and downregulates the expression of Fc[egr]RI on Langerhans cells. Topical tacrolimus ointment was approved by the US-FDA in December

2000 for the treatment of atopic dermatitis in patients above 2 yrs of age.

A total of 125 patients in 6 centers were included in the study. The modified eczema area sensitivity index (mEASI) score was 11.25 at baseline. The mean total score had a significant reduction at the end of 7th day i.e. 17.7% . At the end of 3rd and 4th week the reductions were 55.0% and 73.8% respectively from baseline (Figure 1). Each individual parameter showed a statistically significant improvement from the baseline *(P<0.05)*. The global assessment of response by physicians showed that 42.4% of patients showed a moderate to marked improvement in their condition by the end of 1st week of treatment (Figure 2). At the end of treatment 32% of the cases showed complete resolution whereas 36% showed an excellent improvement in their clinical signs and symptoms. Patients global assessment of response revealed that 70% showed improvement in their condition by the 1st week and 94.4% showed improvement by the end of study period (Figure 3). These findings confirm the efficacy of the drug in Indian population. Large multicentric studies in adults and children have confirmed the efficacy of the drug.[6-9]

20.8% of total study cases experienced untoward effects. These included burning sensation, pruritus and erythema. These were mild in nature and decreased with the continuation of therapy. There was no study dropout because of adverse events. There was no report of any serious adverse event. The drug was very well tolerated. No significant laboratory changes could be detected which indicates a good laboratory safety profile. Tacrolimus ointment has been extensively studied in both adults and children and found to be safe even on long term treatment.[10-12]

Tacrolimus ointment has shown to decrease the Staphylococcus aures count in lesions of atopic dermatitis.[13]Unlike topical corticosteroids, tacrolimus ointment does not interfere with collagen synthesis or cause skin atrophy and striae.[14] It does not show tachyphylaxis.[15] Systemic absorption is minimal and there is no evidence of systemic accumulation in patients treated for prolonged periods (upto three year).[16,20] It is effective and safe for application on any part of the body including face, neck, flexure areas, except on mucous membrane. [17] Comparative study with steroids showed that tacrolimus ointment 0.03% was more effective than 1% hydrocortisone acetate in treatment of moderate to severe atopic dermatitis in children.[18] Tacrolimus ointment is associated with significant quality of life benefits in patients of atopic dermatitis.[19] It has also shown good results in conditions like psoriasis, lichen planus, vitiligo, pyoderma gangrenosum and alopecia areata.[21]

In conclusion, this study confirms the efficacy and safety of tacrolimus ointment in Indian patients of moderate to severe atopic dermatitis.

## REFERENCES


1. Rudikoff D. Atopic dermatitis. Lancet 1998;351:1715-21.
2. Leung DM. Pathogenesis of atopic dermatitis. J Allergy Clin Immunology 1998;104:599-607.
3. Cheer SM. Tacrolimus ointment: A review of its therapeutic potential as a topical therapy in atopic dermatitis. Am J Clin Dermatol 2001;2:389-406.
4. Rajka G, Langeland T. Grading of severity of atopic dermatitis. Acta Derm Venerol Suppl (Stockh) 1989;144:13-4.
5. Hanifin JM. Biochemical and Immunological mechanisms in atopic dermatitis: new targets for emerging therapies. J Am Acad Dermat 1999;41:72-7.
6. Hanifin JM. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients. Part I: Efficacy. J Am Acad Dermatol 2001;44:528-38.
7. Paller A. A 12 week study of Tacrolimus ointment for the trestment of atopic dermatitis in paediatric patients J Am Acad of Dermatol 2001;44:547-57.
8. Ruzicka T. A short term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus multicentric atopic dermatitis study group. New Eng J Med 1997;377:816-21.
9. Boguniewicz M. A randomized vehicle controlled trial of Tacrolimus ointment for the treatment of atopic dermatitis in children. J Allergy Clin Immunol 1998;102:637-44.
10. Reitamo S. Safety and efficacy of 1 yr of tacrolimus ointment monotherapy in adults with atopic dermatitis. Arch Dermatol 2000;136:999-1006.
11. Soter NA. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients. Part II : Safety. J Am Acad Dermatol 2001;44:539-46.
12. Kang S. Long term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol 2001;44:558-64.
13. Remitz A. Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions. J Allergy Clin Immunol 2001;107:196-7.
14. Reitamo S. Tacrolimus ointment does not affect collagen synthesis: results of a single center randomized trial. J Invest Dermatol 1998;111:396-8.

15. Koo JYM.Tacrolimus ointment safe in extended treatment study. American Academy of Dermatology, 61st Annual Meeting: 2003. Abstract p. 22.
16. Alaiti S. Tacrolimus ointment for atopic dermatitis: A phase I study in adults and children. J Am Acad Dermatol 1998;38:69-76.
17. Makagewa H. Comparative study of tacrolimus ointment Vs alclometasone diproprionate ointment in atopic dermatitis (Face and Neck lesions). J Invest Dermat 1998;110:683.
18. Reitamo S. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. J Allergy Clin Immunol 2002;109:539-46.
19. Drake L. The impact of tacrolimus ointment on health related quality of life of adult and paediatric patients with atopic dermatitis. J Am Acad Dermatol 2001;44:S65-72.
20. Hanifin J. American Academy of Allergy, Asthma, and Immunology, 60th annual meeting. Abstract 2003. p. 244.
21. Cather JC, Abramovits W, Menter A. Cyclosporine and Tacrolimus in dermatology. Dermatol Clin 2001;19; 119-37.