A Comparative Evaluation of Efficacy of Tacrolimus and Triamcinolone Acetonide in the Management of Symptomatic Oral Lichen Planus

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Background and objectives: Oral lichen planus (OLP) is a relatively common, chronic inflammatory condition, which frequently present with burning sensation. Only symptomatic OLP requires treatment and efforts are made in a continued searching for novel therapies for symptomatic OLP. Therefore, this study was aimed to compare the efficacy of treatment with topical tacrolimus ointment with that of triamcinolone acetonide ointment in subjects with symptomatic OLP.

Materials and methods: This prospective randomized comparative study, included 30 symptomatic OLP subjects, divided into two groups as group A and group B to receive topical tacrolimus 0.03% ointment and triamcinolone acetonide 0.1% ointment application respectively, twice daily for four consecutive weeks. Burning sensation using visual analog scale (VAS), overall treatment response using Tel Aviv-San Francisco scale was recorded at every visit. The data obtained was analyzed statistically using Wilcoxon Rank Test, Mann Whitney and Fischer’s Exact Test.

Results: Subjects in both the groups showed a significant reduction in burning sensation; however, it was higher (98%) in tacrolimus group than in the triamcinolone acetonide group (72%). The overall treatment response was significantly better in tacrolimus group.

Interpretation and conclusion: Topical tacrolimus 0.03% ointment induced better initial therapeutic response than triamcinolone acetonide 0.1% ointment. However, relapses occurred in two subjects in group ‘A’ and three subjects in group ‘B’ after the cessation of the respective treatments. Nevertheless, at present topical tacrolimus may be a valuable addition to the already existing therapeutic modalities for treating subjects with OLP.

Keywords: Oral lichen planus, Tacrolimus, Triamcinolone acetonide.
Corticosteroids are the class of drug most commonly used for the treatment of OLP because of their action in suppressing cell-mediated immune activity. They can be used topically, intranasally or systemically.8 Topical corticoids effectively penetrate the squamous epithelium and have less severe side effects than systemic corticoids, due to their low systemic absorption.

Triamcinolone acetonide paste is the most widely available commercial preparation for the treatment of OLP.9

In the race to develop potent alternative immunomodulatory agents, considerable emphasis has been directed toward more selective drugs, such as macrolide lactones. One of the lead compounds of this class is tacrolimus (FK506) which is currently available worldwide for the prevention of organ transplant rejection.10, 11

It acts by inhibiting T-cell activation at 10 to 100 times lower concentration than cyclosporin. The safety profile of topical tacrolimus appears to be superior to that of high potency topical steroids when used for chronic dermatoses.11

Therefore, this study was designed to compare the efficacy of topical tacrolimus and topical triamcinolone acetonide in the management of symptomatic OLP and the data collected from this study can move us closer to implement a specific treatment plan for OLP, a dividend not only for subjects but also for dental fraternity as well.

MATERIALS AND METHODS

The study was conducted among patients attending the Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, Karnataka. The study group comprised of 30 OLP subjects of either sex in the age range of 16 to 72 years.

Inclusion Criteria

1. Patients who were physically healthy and well oriented in time, space and as a person.
2. Patients clinically and histopathologically diagnosed as suffering from oral lichen planus.
3. Patients with symptoms, i.e. pain and burning sensation, secondary to oral lichen planus.
4. Patients who agreed to take medication supplied.
5. Patients who agreed for the biopsy.

Exclusion Criteria

1. Patients suffering from any systemic diseases, like diabetes mellitus, hypertension, cardiovascular system disease, Renal dysfunction, liver disorders, etc. and patients with a history of candidiasis and anemia.
2. Patients with any other mucosal disease or any other skin disease which may be associated with oral lesions.
3. Patients on any drug therapy which may cause lichen planus like lesions.
4. Patients with findings of any physical or mental abnormality, which would interfere with or be affected by the study procedure.
5. Patients with a known allergy or contraindication to study medications.
6. Histopathological examination with atypical or lichenoid dysplastic features.

The drugs used were tacrolimus ointment (10 gm, trade name: Tacroz: Tacrolimus 0.03%. Manufacturing company: Glenmark Pharmaceuticals Ltd), triamcinolone acetonide oral paste (5 gm, trade name: Kenacort: Triamcinolone acetonide 0.1%. Manufacturing company: Ambalal Sarabhai Enterprise Ltd).

All the participants were explained the need and design of the study, the pharmacological therapy, possible adverse effects, possibility of being allocated to the groups and the need for undergoing a thorough clinical examination, biopsy and blood investigations at the start of the study. Only those patients who gave a signed informed consent on an institutionally approved document participated in the study.

Patients were numbered serially as they entered the study. However, randomized allocation for a study group was done by using thirty tokens, out of which 15 were marked ‘A’ and another 15 were marked ‘B’. Patients were randomly assigned to one of the following two groups: Group A—patients received drug ‘tacrolimus’, group B—patients received drug ‘triamcinolone acetonide’. All patients received treatment for four consecutive weeks. Patients received their first treatment on the day of the recall visit after histopathologic confirmation of the OLP. Patients were recalled at 2 week intervals for 4 weeks. At each visit, patients were reevaluated and administered the subsequent dosage. Group ‘A’ patients applied drug ‘tacrolimus’ and group ‘B’ patients applied drug ‘triamcinolone acetonide’ twice daily after food for four consecutive weeks. Clinical parameters recorded at each visit included intensity of burning sensation, size of the lesion and erythematous areas.

Intensity of the burning sensation was determined using a VAS of 0 to 10 (with 10 mm divisions, where ‘0’ is no burning sensation and ‘10’ is worst possible burning sensation). The patients were asked to mark VAS at a point which best represented the level of symptoms. The score was recorded at each subsequent visit after the administration of the drug therapy. Size of the lesion during the course of the therapy was recorded at each subsequent visit using Tel Aviv-San Francisco scale.1 Erythematous areas were determined from the baseline and at each subsequent visit, by its presence or absence, indicated by the symbols ‘+’ for presence and ‘–’ for absence.

Post-treatment follow-up involved the evaluation of the patient at the end of 6th, 8th, 10th and 12th weeks. The demographic and physical examination of data so gathered was sorted, tabulated and subjected to appropriate statistical analysis. For quantitative data, mean ± SD was used and, for categorical data, number and percentages were used and nonparametric tests were used for intra (Wilcoxon’s Sign Rank test) and intergroup (Mann Whitney test) comparisons. Categorical data were analyzed by Fisher’s exact test. For all the tests, a p-value of 0.05 or less was considered statistically significant.
RESULTS

The reduction in mean scores of burning sensation was more in tacrolimus group than that of triamcinolone acetonide group, i.e. 60 and 22% at the end of the 4th week respectively, and 98 and 72% at the end of 12th week respectively. As reduction in burning sensation was higher in group A than in group B, it was highly statistically significant (p = 0.015) (Table 1 and Fig. 1).

Improvement in the resolution of erythematous areas was observed in both the groups. At the end of 2nd week, it was statistically nonsignificant between the two groups, at the end of 4th week, it was statistically significant (0.004). After treatment, at the end of 6th week, it was highly statistically significant (0.001) and, at the end of 8th and 10th weeks, it was statistically significant (0.006, 0.04) and, at the end of 12th week again, it was nonsignificant (Table 2, Figs 2 to 4).

There was reduction in mean size of lesions in both the groups after treatment. Maximum reduction in the mean size of lesion was observed in tacrolimus group compared with triamcinolone acetonide group. At the end of 2nd week, it was statistically nonsignificant between the two groups, at the end of 4th week, it was statistically significant (0.005). After treatment, at the end of 6th, 8th and 10th weeks, it was highly statistically significant (0.01) and, at the end of 12th week again, it was statistically significant (0.002) (Table 3, Figs 3 and 4).

DISCUSSION

Lichen planus is a chronic inflammatory mucocutaneous disease that occurs in about 0.02 to 4% of the general population affecting skin and/or mucosa.12,13 The lesion has a chronic clinical course with periods of exacerbation and remission with reports of lesions persisting for up to 20 years.14,15

Although, the exact etiology of the disease is unknown, cell-mediated immunity appears to play a major role in the pathogenesis of OLP, possibly initiated by endogenous or exogenous factors in persons with a genetic predisposition.16

The treatment of symptomatic OLP represents a perplexing therapeutic challenge. Despite numerous existing remedies, there are many treatment failures.1 Multiple topical and systemic treatments for OLP have been reported to be effective, including topical and systemic corticosteroids, griseofulvin, hydroxychloroquine, dapsone, topical retinoids and topical cyclosporine; however, if OLP is resistant to these treatments, or subjects are unable to tolerate a treatment because of its adverse effects.5

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**Table 1:** Comparison of burning sensation scores before and after treatment—intra and intergroup comparisons (VAS scores)

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>Group A vs Group B**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Difference from BL</td>
<td>Reduction</td>
<td>p-value</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>BL</td>
<td>35.0 ± 22.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>33.3 ± 13.0</td>
</tr>
<tr>
<td>2nd week</td>
<td>20.8 ± 11.2</td>
<td>14.2</td>
<td>41</td>
<td>&lt; 0.01</td>
<td>30.0 ± 11.0</td>
</tr>
<tr>
<td>4th week</td>
<td>14.1 ± 9.1</td>
<td>20.9</td>
<td>60</td>
<td>&lt; 0.01</td>
<td>26.0 ± 8.7</td>
</tr>
<tr>
<td>6th week</td>
<td>07.8 ± 05.9</td>
<td>27.2</td>
<td>78</td>
<td>&lt; 0.01</td>
<td>23.5 ± 8.6</td>
</tr>
<tr>
<td>8th week</td>
<td>4.7 ± 4.5</td>
<td>30.3</td>
<td>87</td>
<td>&lt; 0.01</td>
<td>19.7 ± 9.4</td>
</tr>
<tr>
<td>10th week</td>
<td>2.4 ± 2.7</td>
<td>32.6</td>
<td>93</td>
<td>&lt; 0.01</td>
<td>14.6 ± 6.8</td>
</tr>
<tr>
<td>12th week</td>
<td>0.7 ± 1.4</td>
<td>34.3</td>
<td>98</td>
<td>&lt; 0.01</td>
<td>09.4 ± 7.7</td>
</tr>
</tbody>
</table>

S: significant; NS: not significant; HS: highly significant

*Wilcoxon’s signed rank test—intragroup comparisons; **Mann-Whitney test—intergroup comparisons
Topical tacrolimus has been reported to be effective treatment for OLP, including those forms that had been recalcitrant to treatment.

Immunosuppressive macrolide tacrolimus (FK506) exerts an activity 10 to 100 times higher than that of cyclosporin by suppressing T-cell activation by binding to cytosolic FK-binding proteins, which in turn, interferes with the calcium calmodulin-dependent phosphatase calcineurin. This ultimately results in the inhibition of cytokine gene transcription, including interleukin-2 and TNF-α. In result, this product can inhibit accumulation of inflammatory cells in OLP.5,17

Notwithstanding these various alternative treatment options, the treatment of choice remains corticoid therapy, in view of the autoimmune character of OLP, its effects on epithelial and connective tissues and its location in the oral cavity. Topical corticoids effectively penetrate the squamous epithelium and have less severe side effects than systemic corticoids, due to their low systemic absorption.2 The efficacy of triamcinolone acetonide ointment is mainly due to local anti-inflammatory properties of suppressing T-cell function. This ointment had been proven to adhere well to the oral mucosa. This can provide both transport medium of active drugs and reasonable exposure time.17

The higher reduction in VAS score seen in the tacrolimus group can be attributed to its efficacy in OLP, which is considered to have a T cell-mediated pathogenesis, may be due to its inhibitory effect on the activation and proliferation of T lymphocytes,18 while the relief seen in triamcinolone acetonide group can be attributed to its local anti-inflammatory and anti-immunological properties of suppressing T-cell function.17

The higher reduction in erythematous areas seen in the tacrolimus group can be attributed to its percutaneous penetration in damaged mucosa (40 ng/cm² per hour) which is approximately 7-fold higher than on intact mucosa.10 Rozycki TW et al (2002),5 Byrd et al (2004),19 Kaliakatsou F (2002),20 and Francine I et al (2006)11 have also reported similar results in their subjects treated with tacrolimus alone.

At the end of the treatment, with tacrolimus all 15 subjects showed 70 to 100% relief (total or partial cure) and no requirement of further treatment. In contrast, triamcinolone acetonide group four subjects showed 50% relief and 11 subjects showed 70 to 100% relief. The results showed that topical tacrolimus induced a better initial therapeutic response than triamcinolone acetonide. However, relapses occurred frequently in both groups within 3 to 9 weeks after the cessation of both the treatment.21

There have been no significant adverse effects seen locally or systemically in the present study groups, but only two subjects in group A with severe erythematous type of OLP complained of intense burning sensation on initial application that improved with 2 to 3 applications, but this did not lead to discontinuation.
of treatment. The probable reason for initial burning sensation is because of the close contact of tacrolimus to the peripheral nerve endings in the connective tissue, the erosions gradually gets epithelialized relieving symptoms.\textsuperscript{22}

The subjects who were followed up for a period of 6 months without tacrolimus application showed recurrence in two subjects, i.e. in one subject, the lesion recurred 3 months after discontinuing the treatment, and in the other subject, lesion recurred after 6 months, which suggests that there was significant relief of symptoms or controlling the symptoms. In triamcinolone acetonide group, three subjects showed relapses, two subjects reported with lesion within 2 months after discontinuing the treatment and the other subject reported with recurrence after 3 months.

From our study, it can be inferred that treatment with topical tacrolimus 0.03% ointment, applied twice daily, induced better

### Table 3: Comparison of size of the lesion as per the Tel Aviv-San Francisco scale

<table>
<thead>
<tr>
<th>Size of lesion (scores)</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>10 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1</td>
<td>3</td>
<td>7</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>13</td>
<td>−</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>13</td>
<td>−</td>
<td>8</td>
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<tr>
<td>2</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>7</td>
<td>7</td>
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<tr>
<td>3</td>
<td>−</td>
<td>−</td>
<td>1</td>
<td>−</td>
<td>8</td>
<td>−</td>
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<tr>
<td>4</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Median score</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

| p-value*                | 0.13 (NS) | 0.005 (S) | < 0.001 (HS) | < 0.001 (HS) | < 0.001 (HS) | < 0.002 (S) |

S: significant; NS: not significant; HS: highly significant; *Mann-Whitney test
initial therapeutic response than triamcinolone acetonide 0.1% ointment in subjects with symptomatic OLP. Prolonged or intermittent use of topical tacrolimus 0.03% ointment in subjects with symptomatic OLP may be useful but remains to be clearly established in large, well-designed clinical studies. Nonetheless, at present, topical tacrolimus may be a valuable addition to the already existing therapeutic modalities for treating subjects with OLP.

CONCLUSION

On the basis of the clinical examination and the statistical analysis of the data collected, the following conclusions could be drawn. Topical tacrolimus appears to be effective in the management of OLP as it produced statistically significant reduction in both the signs and symptoms of the disease, with majority of subjects showing complete cure, whereas two subjects showed relapse. Topical tacrolimus appears to be well tolerated when used on oral mucous membranes. No significant adverse effect or aggravations of the existing symptoms were noticed in any of the subjects. Only two subjects experienced side effects, but this did not limit their use of ointment. Triamcinolone acetonide also produced significant relief from symptoms (burning sensation); however, the overall treatment response by tacrolimus was significantly better than triamcinolone acetonide. The present study involved a small sample size; therefore, the promising results of this need to be confirmed by larger and comparative studies using other treatment modalities. Future research can be directed at assessing the variation in immunological markers for OLP following treatment with topical tacrolimus or with topical steroids.

REFERENCES