

TOPICAL TACROLIMUS, TRIAMCINOLONE ACETONIDE AND PLACEBO IN ORAL LICHEN PLANUS: A PILOT RANDOMIZED CONTROLLED TRIAL

Running title: Tacrolimus, triamcinolone acetonide and placebo in OLP.

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M Siponen ^{1,2,3}, L Huuskonen¹, S Kallio-Pulkkinen¹, P Nieminen⁴, T Salo ^{1,2,5,6}.

¹*Institute of Dentistry, University of Oulu, Finland (until 2013)*

²*Cancer and Translational Medicine Research Unit, University of Oulu, Finland*

³*Department of Oral and Maxillofacial Diseases, Kuopio University Hospital, Finland*

⁴*Medical Informatics and Statistics Research Group, University of Oulu, Finland*

⁵*Department of Oral and Maxillofacial Diseases, University of Helsinki, Finland*

⁶*Medical Research Center, Oulu University Hospital, Finland*

Corresponding author:

Maria Siponen

Cancer and Translational Medicine Research Unit,

Faculty of Medicine,

90014 University of Oulu,

Finland

Email: maria.siponen@kuh.fi, mariasiponen@yahoo.com

Fax: +358 8 344 084

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Abstract

Objective To carry out a double-blind RCT to compare the effectiveness of topical tacrolimus (TAC), triamcinolone acetonide (TRI) and placebo (PLA) in symptomatic OLP.

Subjects and methods A clinical score (CS, range 0-130) was developed to measure the clinical signs and symptoms of OLP. Twenty-seven OLP patients with a CS of ≥ 20 were randomly allocated to receive 0.1% TAC ointment (n=11), 0.1% TRI paste (n=7) or Orabase® paste as PLA (n=9) for 3 weeks. If the CS dropped $\geq 20\%$ (interpreted as response), the patients continued the same medication for another 3 weeks. If the CS dropped $< 20\%$ or increased (non-response), the patients were switched to TAC for 6 weeks. A 6-month follow-up period ensued. The primary outcome variable was the change in CS from baseline to week 3. In primary outcome analysis, CS values between the treatment arms were compared.

Results TAC and TRI were more effective ($p=0.012$ and 0.031 , respectively) than PLA in reducing the CS at week 3. No difference in the efficacy was noted between TAC and TRI ($p=0.997$).

Conclusions This pilot RCT provides evidence for the effectiveness of TAC and TRI over PLA in the management of OLP.

Introduction

Oral lichen planus (OLP) is a chronic immune-mediated mucosal disease that affects about 1-2% of the population (McCartan and Healy, 2008). The majority of patients suffer from intermittent symptoms (Eisen, 2002, Ingafou et al., 2006). There is no curative treatment for OLP. Therapy is aimed at alleviation of the symptoms and consists generally of topical corticosteroids (Thongprasom et al., 2013). However, some patients are not responsive to this therapy.

Tacrolimus (TAC) is a macrolide derived from the bacteria *Streptomyces tsukubaensis* that is used systemically as an immunosuppressive agent in organ transplant patients (Fung and Starzl, 1995). Tacrolimus ointment (Protopic®, Astellas Pharma, Tokyo, Japan) is indicated for use in atopic dermatitis (AD) (Cury Martins et al., 2015). Off-label use of topical TAC in the treatment of severe, erosive OLP was reported as open-label case reports or series with favorable results since 1999 (Lener et al., 2001, Vente et al., 1999, Rozycki et al., 2002, Morrison et al., 2002, Kaliakatsou et al., 2002, Hodgson et al., 2003, Narayan, 2003). Since the current trial was designed and commenced (2004), a few double-blind randomized controlled studies (RCTs) comparing topical corticosteroids with TAC have shown equal (Radfar et al., 2008, Sonthalia and Singal, 2012), better (Corrocher et al., 2008) or worse (Sivaraman et al., 2016) efficacy of TAC compared to corticosteroids. Of note, no studies comparing topical TAC to placebo in OLP have been published.

This study was therefore set up to compare for the first time the effectiveness of topical 0.1% TAC and 0.1% triamcinolone acetonide (TRI) to placebo (PLA) in symptomatic OLP.

Patients and methods

Study design and participants

This investigator-initiated study was designed as a multi-center, double-blind (first 3-6 weeks), placebo-controlled parallel RCT with an initial trial period of 6-9 weeks and a follow-up period of 6 months.

For measuring the OLP status, we developed a clinical score (CS) that was modified from a method of assessment described by Setterfield et al. (Setterfield et al., 1998, Siponen and Salo, 2008) (Appendix). Briefly, the

score takes into account the clinical features and the size of the OLP lesions, as well as subjective symptoms of the patient. The numeric values of different clinical presentations (1= white, 2=predominantly white, 4=predominantly red, 6=ulcerative or bullous) were chosen to reflect the increasing severity of clinical presentation and to better distinguish the often symptomatic forms (atrophic, ulcerative) of OLP from the less severe and often asymptomatic ones (reticular, papular, plaque-like). The severity of symptoms was measured using a visual analogue scale (VAS). The inter-rater reliability of CS was studied by assessing 17 OLP patients during the same day by four clinicians.

When designing the study, a sample size was calculated. We postulated that if the CS dropped a minimum of 10%, 20% or 25% with PLA, TRI and TAC, respectively, it would mean clinically significant improvement. A decrease of this size with a two tailed p-value of 0.05 and power of .80 would require a total sample size of 36. Allowing for a non-adherence rate of 10%, we prepared the randomization lists for 40 patients.

The diagnosis of OLP was made based on clinical and histopathological features (Pindborg et al., 1997). Clinical features required for OLP diagnosis were symmetrical distribution of the lesions and the presence of white striae or reticulations as part of the clinical appearance. Patients with lesions that were suspected to be lichenoid were not included. Most patients (n=25) had at least one previous oral mucosal biopsy, for the rest the histopathological diagnosis was sought from the first research protocol biopsy.

Patients were recruited either by letter sent to persons who had visited the Department of Diagnostics and Oral Medicine, Institute of Dentistry, University of Oulu or Oulu University Hospital for their OLP, or by informing new referral patients about the study in the abovementioned institutions and at the Department of Oral and Maxillofacial Diseases at Kuopio University Hospital. The inclusion criteria were a diagnosis of symptomatic OLP, CS \geq 20 (including VAS > 0), age over 18 and a washout period of 2 weeks. The exclusion criteria were pregnancy or current nursing, allergy to tacrolimus, other macrolides or other substances used in the study medications, hepatic insufficiency, and use of medications that could have significant interactions with tacrolimus, including cyclosporin, erythromycin, rifamycin, posaconazole, itraconazole, ketoconazole, fluconazole, voriconazole, rifampicin, phenytoin and dabigatran. Patients were given information about the study orally and in written form and informed consent was signed by the participants.

All participants were tested for oral candidiasis and treated, if indicated, for at least two weeks before starting the intervention. Additional culture specimens were taken also later during the study if candidiasis was suspected. As a safety procedure, blood tests consisting of serum alanine transaminase, serum creatinine and blood count were done for every patient at baseline and at weeks 3, 6 and 9 if relevant. If the patient received TAC, blood levels of TAC were monitored. Blood pressure and heart rate were recorded at the beginning. A biopsy was taken from oral lesional tissue before the intervention. If the patient had dental or periodontal problems needing treatment, he/she was advised to have these treated before commencing the study.

Study interventions

The patients were randomly assigned to one of the three treatment arms: group 1 received 0.1% TAC ointment (Protopic®, Astellas Pharma), group 2 received 0.1 % TRI paste (Kenacort-T®, Bristol-Myers Squibb, New York City, USA/Kenacort-A®Orabase®, Dermapharm, Grünwald, Germany) and group 3 received PLA paste (Orabase® paste, ConvaTec, Deeside, UK). Computer-generated randomization lists and allocation sequences were prepared by an independent statistician (Ahti Niinimaa, PhD). Two blocks were created: for participants 1-14 and 15-40. Allocation concealment was ensured by keeping the randomization lists in the care of one of the investigators (TS) who was not involved in the clinical part of the study. Independent pharmacists dispensed the study medications into identical, sequentially numbered containers according to randomization lists.

The patients were advised to apply the medication thinly to oral mucosal lesions three times daily. The patients were seen at least weeks 3, 6 (and 9 if relevant) during the first study period. During the visits, the CS was recorded, clinical photographs were taken and the study medications were weighed. Patients were asked to record VAS scores at home twice daily (morning and evening) during the first 6-9 weeks of the study and once a week (on the same day of the week) after that until the follow-up visit at 6 months. Regarding the VAS score, participants were instructed to make a vertical mark along a horizontal 10 cm line, with the left end representing no discomfort, and the right end representing the worst imaginable discomfort caused by OLP.

After three weeks, the *treatment response* was assessed. If the CS had dropped at least 20% from the baseline, it was considered an adequate treatment response, and the patient continued to use the same

intervention for another three weeks. If the CS dropped < 20%, remained unchanged or increased, the treatment response was considered inadequate, and the intervention was switched to 0.1% TAC, and used for 6 weeks thereafter. A biopsy was taken from the same area of the oral mucosa as the first biopsy after the first 3 weeks if there was an adequate treatment response, and after 6 weeks if the intervention was switched to TAC. After this initial phase of either 6 or 9 weeks of intervention, those patients that used TAC in the end were advised to use it sporadically during the next 6 months only if needed. Those patients that used PLA or TRI in the end, were advised to use the topical corticosteroid preparation intermittently if needed. At the 6-month follow-up visit, the CS was recorded. After that the participants were treated and followed according to usual clinical practices.

Study oversight

The study plan was approved by The Regional Ethics Committee of the Northern Ostrobothnia Hospital District in Oulu (103/2002). The Research Ethics Committee of the Northern Savo Hospital District in Kuopio was informed of the approval subsequently. Approval to use study medications was granted from the Finnish Medicines Agency (91/2003). The trial was registered at Clinical.trials.gov, identifier: NCT01544842. The research was conducted in accordance with ethical principles stated in the World Medical Association Declaration of Helsinki.

Study outcomes

The primary outcome variable was the change in CS from baseline to week 3, and the primary aim was to study the differences between the treatment arms. Secondary outcomes variables were: 1) the changes in CS from baseline to week 6 (and 9 if relevant) and to 6 months; 2) the changes in VAS scores measured *at visits* and *at home* from baseline to weeks 3 and 6 (and 9 if relevant), and to 6 months; 3) the changes in VAS scores measured *at home* from start of follow-up to weeks 1-8, 9-16 and 17-24.

Statistical methods

The statistical analyses were performed using IBM SPSS Statistics version 22 for Windows. G*Power and SamplePower 3.0 software were used for sample size and power calculations (Cohen, 1988).

The inter-rater reliability of the CS measurements was estimated with intraclass correlation coefficient (ICC). Pearson correlation coefficient was used to measure the correlation between clinical signs (1A and 1B of CS) and subjective symptoms (VAS).

The statistical significance of changes in the CS and VAS values in the different treatment arms over time was examined with repeated measures t-test. The differences in the CS and VAS values between the intervention groups over time were estimated with analysis of variance (ANOVA) and pairwise differences were investigated with Tukey's test.

Differences in the *treatment responses* between the intervention groups at week 3 were calculated with cross-tabulation, and statistical significance of the differences was estimated with chi-square test with exact p-values. Probability values of < 0.05 were considered statistically significant. Missing values (5%) were replaced with the nearest neighbor method. Primary analysis was carried out according to the intention-to-treat principle.

Results

Patient flow and characteristics

The patient flow and baseline clinical and demographic data of the intervention groups are presented in Figure 1, Table 1 and supplementary tables 1, 2. The baseline mean values for CS and VAS were comparable between the intervention groups: CS was 28.55 (SD 7.20), 31.71 (SD 10.70) and 26.11 (SD 7.30), and the VAS score was 3.64 (SD 1.29), 3.71 (SD 2.21) and 3.78 (SD 2.17) in the TAC, TRI and PLA groups, respectively. For meaningful analyses, the TRI group was divided into two: those with a treatment response and those who showed no response. The respective baseline mean values for these groups were 34.50 (SD 12.66) and 28.00 (SD 8.18) for CS and 4.25 (SD 2.50) and 3.00 (SD 2.00) for VAS.

During the period from June 2004 to December 2014, a total of 27 patients were enrolled (14 in Oulu and 13 in Kuopio) for the study. The first participant visit was July 2nd, 2004 and last visit was February 26th, 2015.

The study was completed before the target sample size was met due to lack of financial resources and collaborators. Because of this, the actual power of the study was .70.

Clinical score (CS) reliability and validity

The inter-rater reliability of CS was strong, as the ICC of the CS assessments between the four clinicians was 0.96. The Pearson correlation coefficient between clinical signs (1A + 1B of the CS) and symptoms (VAS) in the study done with 17 patients was 0.180, representing very weak correlation.

Primary outcome analysis

All the participants were included in the primary analysis.

The development of CS values from baseline to week 3, 6 (and 9 if relevant) in the intervention groups is shown in Figure 2a. At week 3, TAC and TRI groups showed better efficacy ($p=0.012$ and 0.031 , respectively) than placebo in reducing the CS. There was no difference in the efficacy between TAC and TRI ($p=0.997$). The mean decrease in CS from baseline to week 3 was 10.5 (95% CI 4.77 to 16.32; 37%; $p=0.002$) in the TAC group ($n=11$) and 10.3 (95% CI 4.02 to 16.55; 32%; $p=0.007$) in the TRI group ($n=7$). In the TRI group that responded to intervention ($n=4$), and that did not respond to intervention ($n=3$), the mean decrease in CS was 14 (95% CI 3.05 to 24.95; 41%; $p=0.027$) and 5.3 (95% CI 1.54 to 9.13; 19%; $p=0.026$), respectively. The CS increased 0.22 (95% CI -5.64 to 5.20; 0.8%; $p=0.927$) in the PLA group.

When looking at the *response to intervention* ($\geq 20\%$ decrease in CS from baseline) at week 3 in different treatment arms, both TAC ($p=0.005$) and TRI ($p=0.019$) were more effective than PLA in producing a treatment response (Table 2). There was no difference in the efficacy between TAC and TRI groups ($p > 0.999$).

Pre-intervention anti-mycotic treatment had no effect on the CS at week 3 ($p=0.872$).

Secondary outcomes

Secondary outcomes of this study are presented in Figure 2 (b, c, d) and supplementary tables 3 and 4. Some secondary outcome analyses could not be performed for all the participants. Because of the small sample size, especially in the TRI group that was divided into responders and non-responders to treatment at week 3, statistical significance cannot be noted while a clear effect is seen in many of the outcome measures.

At week 6, the mean CS values decreased further from the baseline in the TAC group, and in the TRI and PLA groups who were switched to TAC. In the group that used TRI for 6 weeks, the mean CS increased from week 3 to 6, but remained still below the baseline value. Of note, the mean VAS values measured at visits and at home remained at the 3-week level in this group at week 6. The mean CS values from baseline to 6 months decreased in the group that was advised to use TAC sporadically if needed (n=18) and in the group that was advised to use topical corticosteroid intermittently if needed (n=5).

In general, the mean VAS values measured *at visits* decreased 44-71% from baseline to week 3 and 6 in the TAC and TRI groups. In the PLA group, the mean VAS values remained almost the same from baseline to week 3, but decreased after switching to TAC (Figure 2b). However, at week 3, the differences in the VAS values between the intervention groups were not statistically significant. The mean VAS values from baseline to 6 months decreased by over 50% in both groups (tacrolimus and topical corticosteroid).

The mean VAS values measured *at home* from baseline to week 1 decreased most in the TRI group that responded to treatment and in the PLA group. However, at weeks 2 and 3 the mean VAS values in the PLA group did not show further decrease (Figure 2c). At week 3, the differences in VAS scores among the treatment arms were not statistically significant. From week 3 to 4 (after switching to TAC) the mean VAS values increased in the PLA group, but after that decreased and remained below the week 4 values. In the other groups, the mean VAS values showed a steady decrease until week 4, after which the values remained in almost the same level except for an increase at weeks 8 and 9 in the TRI group that switched to TAC. The mean VAS values during the 6-month follow-up period remained in about the same level than in the start of the follow-up in the group that was advised to use TAC, and increased considerably in the group that was advised to use topical corticosteroid.

Safety

Adverse effects reported by the participants and the results of safety measures are presented in supplementary file. No serious side effects were encountered during the study.

Discussion

Our findings indicate that 0.1% TAC ointment and 0.1% TRI paste are both more effective than PLA in alleviating signs and symptoms of OLP, measured by reduction in the CS. The efficacy of topical TAC compared to PLA is shown for the first time in OLP. Interestingly, TRI and even PLA seemed to be more effective than TAC in reducing the discomfort measured by VAS at week 1. TAC seemed to maintain the symptoms at a lower level during the 6-month follow-up.

Among the strengths of the present RCT is its design and the fact that it was performed without the support or interference of pharmaceutical companies. On the other hand, one of the weaknesses of this study was that we were not able to accrue the pre-specified number of patients, which reduced the power of the study. Therefore it is considered a pilot study. In addition, analyses of some of the patient assessed VAS scores during the follow-up period were hampered by missing data. Furthermore, with such a long enrollment period, recalibration of the CS would have been adequate. Unfortunately, we were unable to repeat the calibration.

The diagnosis of OLP was made combining the characteristic clinical features of OLP with a histopathological finding compatible with OLP. Most of the patients used systemic medication which could have produced a lichenoid reaction of the oral mucosa. However, there was no indication in their history that the lesions were drug-induced. In general, many OLP patients do use some form of systemic medication due to the typical age range of the disease. Two patients had a positive patch test to mercury, which suggests that their oral disease could have been a lichenoid contact lesion in relation to amalgam fillings. However, these patients did not have amalgam fillings in contact with the oral lesions.

Considering that topical corticosteroids are the first-line therapy for symptomatic OLP, it is surprising that only a few studies have evaluated their effectiveness against placebo (Voute et al., 1993, Carbone et al., 1999, Cilurzo et al., 2010, Kazancioglu and Erisen, 2015, Tyldesley and Harding, 1977). In fact, a Cochrane review from 2011

identified no RCTs that compared corticosteroids with placebo in patients with symptomatic OLP (Thongprasom et al., 2011). Clinical trials comparing tacrolimus with corticosteroids in OLP are also scarce (Corrocher et al., 2008, Radfar et al., 2008, Sonthalia and Singal, 2012, Azizi and Lawaf, 2007, Revanappa et al., 2012, Sivaraman et al., 2016, Laeijendecker et al., 2006). Some of the above mentioned studies were not performed as double blind (Revanappa et al., 2012, Laeijendecker et al., 2006, Azizi and Lawaf, 2007, Carbone et al., 1999), thereby lowering the level of evidence they provide. We have not identified any previous studies comparing TAC with PLA in OLP.

Evaluation and comparison of the results of the published intervention studies in OLP is difficult due to heterogeneous reporting (Lopez-Jornet and Camacho-Alonso, 2010). A crucial question is how to reliably measure the outcome of intervention. Different OLP scoring systems have been developed (Escudier et al., 2007, Chainani-Wu et al., 2008, Lopez-Jornet and Camacho-Alonso, 2010), but a validated, universally-accepted outcome measure for OLP is still lacking (Wang and van der Waal, 2015). It has been proposed that quality-of-life measures could be used to evaluate the outcome of interventions in OLP (Wang and van der Waal, 2015).

We found that in our CS developed for this study, the inter-rater reliability was strong. There was a weak correlation between the clinical signs and symptoms reported by the patients, which is a common phenomenon in OLP. VAS (one component of the present CS) has been shown to be a valid instrument for symptom measurement (Flaherty, 1996, Miller and Ferris, 1993). In addition, the expected decrease in CS in the active intervention groups versus placebo group provides support for the validity of this score. Therefore we believe that CS accurately represents the overall progression of OLP.

The present study suggests that TAC may not predispose patients to secondary candidiasis like topical corticosteroids, and this finding is in line with previous studies (Sonthalia and Singal, 2012, Olivier et al., 2002). However, one trial found no difference in the incidence of candidiasis between topical corticosteroid and tacrolimus users (Corrocher et al., 2008) and in some study protocols preventive anti-mycotics were used (Lozada-Nur and Sroussi, 2006, Radfar et al., 2008, Hettiarachchi et al., 2016). Of note, many studies did not report the incidence of secondary oral candidiasis, a complication that is often associated with OLP (Laeijendecker et al., 2006, Azizi and Lawaf, 2007).

In the present study, TAC was associated with more local patient-reported adverse effects than TRI, the most common being burning sensation and increased sensitivity of the oral mucosa to hot, cold and spicy food or

drink. Others have also reported initial worsening of burning in TAC users (Corrocher et al., 2008, Laeijendecker et al., 2006). We observed systemic absorption of TAC in two patients, one of whom had therapeutic levels of the drug at 6-month follow-up. Minimal systemic absorption is noted after topical application of TAC on the skin in patients with atopic dermatitis (Undre et al., 2009). After mucosal application, a proportion of the patients will have detectable levels of TAC in the blood, but these are typically well below therapeutic levels of 5-20ng/L (Hodgson et al., 2003, Morrison et al., 2002). However, it would be prudent to monitor TAC levels if it is used in OLP.

In 2005 the FDA issued a "black box" warning concerning the use of topical tacrolimus (Food and Drug Administration, 2006). Based on a small number of case reports, animal studies, and on the knowledge of how this class of drugs works, it was suggested that there might be an increased risk of lymphoma and skin cancer in patients treated with topical calcineurin inhibitors (TCI), including tacrolimus ointment (Ormerod, 2005). Later the European Medicines Agency (EMA) and the manufacturer (Astellas Pharma) adjusted recommendations for topical TAC use in AD, stating among other things that the drug should be used as a second-line option, and only intermittently (not continuously on long-term basis). They did not recommend topical TAC use in immunocompromised individuals, or applying it to lesions that are considered potentially malignant or premalignant. However, to date there is no causal evidence that topical TCIs cause malignancy when used for AD (Cury Martins et al., 2015, Chia and Tey, 2015, Legendre et al., 2015). There have been safety concerns also related to TAC use in OLP, as a few case reports describe oral squamous cell carcinoma (SCC) developing after use of topical tacrolimus (Mattsson et al., 2010, Becker et al., 2006, Morita et al., 2016). Although at the moment no firm evidence links topical TAC to oral SCC (Lopez-Jornet P et al., 2010, Ribero et al., 2015), it seems advisable that TAC is used for short periods only in cases not responsive to topical corticosteroids.

In conclusion, this pilot study suggests that topical 0.1% TRI and 0.1% TAC are more effective than PLA in reducing the CS in OLP. Although TRI, and even PLA, seemed more effective in reducing patient-assessed discomfort during the first week of treatment, TAC showed a tendency to provide a better long-term pain reduction without candidiasis. Topical tacrolimus may be considered as an alternative drug in the management of symptomatic OLP not responsive to conventional treatment.

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Supporting information:

Appendix: Clinical score of oral lichen planus.

The clinical score (1A+1B+2) consists of measurement of signs (size and type of lesions, 1A and 1B) and subjective symptoms measured by VAS (2).

Supplementary table 1. Basic characteristics of the patients.

Supplementary table 2. Duration of the study medication for each participant (first 6-9 weeks).

Supplementary table 3. Secondary outcomes during the first 6-9 weeks of the study.

Supplementary table 4. Secondary outcomes during the 6-month follow-up period.

Supplementary file. Adverse effects reported by the patients and results of safety measures.

Figure legends:

Figure 1. Participant flow diagram.

Figure 2. Change in clinical score (CS) and visual analogue scale (VAS) values over time.

A. Mean CS at baseline and weeks 3, 6 and 9 in different intervention groups.

2 patients that received tacrolimus (TAC) continued to use it up to 9 weeks (no response at 3 weeks), but the 9 week CS is not included in the figure.

1 patient responded to placebo (PLA) and continued to use it for 6 weeks (6 week CS not included in the figure).

B. Mean VAS (*measured at visits*) values at baseline and weeks 3, 6 and 9 in different intervention groups.

C. Mean VAS (*measured at home*) values at baseline and weeks 1-9 in different intervention groups.

D. Mean VAS (*measured at home*) values during the 6-month follow-up period in the intervention groups that were advised to use either tacrolimus (TAC) or topical corticosteroid preparation after the first study period if needed (start of follow-up values represent mean VAS values obtained at last study visit of the first study period).

In the TRI group, follow-up information was available for 3 patients (no follow-up forms n=2, lost to follow-up n=1).

VAS values after 24 weeks were available only for 3 participants in total, so they were not included in the figure.

Table 1. Baseline characteristics of the intervention groups.

Characteristic	Tacrolimus (n=11)	Triamcinolone (n=7)	Placebo (n=9)
Age – years			
Mean (SD)	60(±9)	51(±12)	58(±10)
Range	41-71	37-66	38-69
Sex – no. (%)			
Male	1 (9)	0 (0)	3 (33)
Female	10 (91)	7 (100)	6 (67)
Smoking - no. (%)	2 (18)	0 (0)	0 (0)
Cutaneous lichen planus – no. (%)	3 (27)	0 (0)	3 (33)
Medical history – no. (%)*			
Hypertension	5 (45)	1 (14)	2 (22)
Hypothyroidism	2 (18)	1 (14)	1 (11)
Asthma	1 (9)	2 (29)	1 (11)
Osteoarthritis	3 (27)	0 (0)	1 (11)
Hypercholesterolemia	2 (18)	1 (14)	1 (11)
Depression	2 (18)	1 (14)	1 (11)
Allergies*	8 (73)	5 (71)	4 (44)
Clinical features of OLP			
Reticular-atrophic	3 (27)	2 (29)	5 (56)
Reticular-atrophic-ulcerative	4 (36)	4 (57)	1 (11)
Reticular-atrophic-ulcerative-plaque like	3 (27)	0 (0)	2 (22)
Reticular-atrophic-plaque like	1 (9)	0 (0)	1 (11)
Reticular-plaque like	0 (0)	1 (14)	0 (0)
Localization of OLP			
Buccal mucosa and gingiva	4 (36)	3 (43)	2 (22)
Buccal mucosa, gingiva, tongue, floor of mouth	2 (18)	2 (29)	1 (11)
Buccal mucosa, gingiva, tongue	2 (18)	0 (0)	2 (22)
Buccal mucosa, gingiva, lip	1 (9)	0 (0)	2 (22)
Buccal mucosa, gingiva, tongue, palate	1 (9)	1 (14)	0 (0)
Buccal mucosa, gingiva, tongue, floor of mouth, palate	0 (0)	1 (14)	0 (0)
Buccal mucosa, gingiva, palate	0 (0)	0 (0)	1 (11)
Buccal mucosa, gingiva, floor of mouth	0 (0)	0 (0)	1 (11)
Buccal mucosa, floor of mouth, palate, lip	1 (9)	0 (0)	0 (0)

*Complete medical histories and list of allergies are available as Supporting information

Table 2. Response to intervention at week 3 in different treatment arms.

Treatment arm	Change in clinical score at week 3			Total
	≥ 20% reduction (response)	< 20% reduction (non-response)	Increase (non-response)	
Tacrolimus	7 (63.6%)	4 (36.4%)	0 (0%)	11 (100%)
Triamcinolone	4 (57.1%)	3 (42.9%)	0 (0%)	7 (100%)
Placebo	1 (11.1%)	2 (22.1%)	6 (66.7%)	9 (100%)
Total	12	9	6	27 (100%)

Exact p-value of chi-square test = 0.004