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Topical Tacrolimus in the Treatment of Symptomatic Oral Lichen Planus - A Systematic Review

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Abstract: *Background and Aim: Tacrolimus (FK506) is an immunomodulatory agent which is used topically for the treatment of Oral Lichen Planus.There is variation in the concentration of topical tacrolimus used, frequency and duration of the treatment among different authors. Also, vast literature wherein tacrolimus is compared with other therapeutic modalities is available. The aim of this systematic review is to evaluate the efficiency of Tacrolimus in the treatment of symptomatic Oral Lichen Planus.*
Methods: A systematic literature search was conducted until December 2018 using PubMed, Scopus, Cochrane library,Science Direct and Google scholar databases to identify human clinical trials with topical tacrolimus as one of the interventionsand published in English. Studies for which complete electronic data was available on internet was included in the study. Quality assessment was done based on recommendation of CONSORT statement and 'Cochrane Hand Book'.
Results: A total of 409 articles were initially identified. From these only those articles which fulfilled the inclusion and exclusion criteria were chosen. Finally, a total of 15 articles were included in the study. After quality assessment it was found that 4 articles had low risk of bias, 6 had moderate risk of bias and 5 studies had high risk of bias.
Conclusion:The existing evidence proves with no doubt that topical 0.1% and 0.03% tacrolimus are effective in the treatment of lichen planus. More studies that have a low risk of bias and long term follow up may be required to standardise the protocol for usage of topical tacrolimus for treating oral lichen planus.
Key words:*Oral Lichen Planus, Topical Tacrolimus, Oral Lesions, Treatment, Burning sensation.*

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I. Introduction

Lichen planus is a chronic inflammatory autoimmune vesiculo-bullous disease affecting skin and mucous membrane. In addition to skin, mucous membrane of oral cavity and genitalia, this muco-cutaneous disorder of stratified squamous epithelium also affects nails and scalp. The mucosal counterpart of cutaneous lichen planusinvolving oral cavity is called Oral Lichen Planus.[1-3]This papulo-squamous disease is usually found among middle aged adults between 3rd and 6th decade of life with female predilection having a female to male ratio of 1.4:1. Due to the ability to develop into malignancy, erosive lichen planus is listed as a potentially malignant disorder of the oral cavity.[3-5]The etiology of lichen planus is notclearly understood till date. Stress, Hepatitis C infection,etc. are proposed as possible etiologic factors. It is chronic in occurrence and autoimmune in pathogenesis with periods of exacerbations and remission.[6]

The treatment of lichen planus is aimed at minimising the pain, preventing new lesions, preventing malignancy and maintaining good oral hygiene. There are variety of treatment modalities available for lichen planus, which includes drug therapy, CO_2 LASER, PUVA therapy, cryotherapy and surgery. Drug therapy can be through systemic or local route. The various groups of drugs used for the therapy include corticosteroids, immunosuppressives, immunomodulators and retinoids.[1]

Tacrolimus (FK506) is an immunomodulatory agent belonging to the macrolide family. It is synthesised by Japanese soil fungus *Streptomyces tsukubaensis*.[7] (Thomson et al., 2004) It induces an inhibition of phosphatase activity of calcineurin which causes suppression of various cytokines such as interleukins, granulocyte-monocyte colony-stimulating factor, tumour necrosis factor-α and interferon-γ. Thus lymphocytes, monocytes and neutrophils are suppressed. Tacrolimus is like cyclosporine in its action of inhibiting the activation and proliferation of T lymphocytes; but tacrolimus is a preferred drug for its better efficacy.[8-10] Both systemic and topical forms of tacrolimus is available. Topical form of tacrolimus as a 0.1%

ointment or 0.1% cream is preferred in dermatological disorders as there is least systemic absorption and hence more safety profile.[11]Adverse effects if any, would mostly be seen about the area of application. Infections and flu-like symptoms are the systemic adverse effects reported with topical tacrolimus application.[9]

There is plenty of literature on the efficiency of topical Tacrolimus in the treatment Lichen Planus. Many authors have reported adverse reactions following the usage of this drug. Also, the concentration of the drug and the vehicle used for delivering the drug is highly variable in the existing literature. This necessitates a systematic review of the existing studies. Hence, the aim of this systematic review is to evaluate the efficiency of Tacrolimus in the treatment of symptomatic Oral Lichen Planus.

II. Materials and Methods

2.1 Search Strategies

Search strategies used were the electronic data base PubMed [Mesh], Cochrane library, Science Direct and Google scholar. The key words used were 'Tacrolimus' and 'Oral Lichen Planus'. The article search had been done to find literature until December 2018.

2.2. Inclusion Criteria:

1. Human Clinical Trials wherein tacrolimus was compared with any other therapeutic modality or placebo
2. Studies in which Lichen Planus was confirmed clinically and histopathologically.
3. Articles for which complete electronic data is available on the internet.

2.3. Exclusion Criteria:

1. Literature reviews, Case reports, case series, in-vitro studies andAnimal studies.
2. Studies in which tacrolimus is combined with any another pharmacological agent used for treating LP.
3. Articles which are not in English language.
4. Articles for which complete electronic data is not available on the internet.

2.4. Data Extraction:

The articles were assessed by two independent examiners. Each article was scrutinized for author information and publication year, sample size, the dosage and form of tacrolimus used, the intervention used for comparison, follow-up, adverse effects and bias.

2.5. Quality assessment:

Quality assessment was done based on recommendation of CONSORT statement and 'Cochrane Hand Book'.There are six parameters that were taken into consideration while quality of the studies were assessed. Each article was scrutinized to see the following details

- If there was a systematic way for sequence generation?
- If steps were adopted for allocation concealment?
- If the examiner or patients were blinded?
- If the authors had addressed the issue of incomplete outcome data if any?
- If the article was free of selective outcome reporting?
- How many observers were involved in the study and if the authors had taken steps to avoid the bias in case there were more than one observers?

A study is considered to have a low risk bias if it was found to answer positively for all the above mentioned questions. If it was found to answer positively for atleast 3 questions, it was categorized to be having moderate risk bias. If the answers weren't positive for atleast 3 questions, it was categorized as to be having high risk bias.

III. Results

A total of 409 articles were identified. From these only those articles which fit into the inclusion and exclusion criteria were chosen. The list was narrowed down to 16 articles. However, one of the 16 articles, was further eliminated from the study based on the joint decision of the examiners as the parameters used for outcome reporting were non-satisfactory. Thus, a total of 15 articles were finally included in the study.

3.1. General Characteristics of the Articles included in the Review

The data extracted from the article is tabulated in table 1.Out of the 15 articles included in this review, 10 were randomized controlled trials and 5 were non-randomized. The total number of patients in the study ranged between 27 and 200.In all of the studies, patients with histopathologically confirmed disease only were included. However in the study by Singh et al. (2017) even clinical cases of lichen planus which were found to be chronic inflammation on histopathological examination were included. 7 studies did not specify which type

of lichen plans was being treated. Erosive, atrophic, ulcerative and reticular variants of lichen planus were specified in the other studies. Sample population in 12 of the studies was predominantly female and in 3 studies it was predominantly male.The comparison of tacrolimus was made with topical triamcinolone acetonide in 7 of the studies, with topical clobetasol propionate in 5 studies, topical Pimecrolimus in 2 studies, oral mometasone furoate, Oral dapsone, Topical retinoid, Oral methotrexate, combination of antimicrobials and placebo in 1 study each. In 1 study intra-lesional triamcinolone combined with topical flucinolone was compared with topical tacrolimus. 0.1% concentration of Tacrolimus was used in 13 studies; whereas 0.03% was used in 2 studies. Except for 2 studies in which the follow up period was not mentioned, all the other studies had a follow up period between 2 weeks to 12 months. All the studies employed clinical scoring parameters to evaluate the disease during and after the treatment. But, only 10 studies evaluated the subjective relief of pain and burning sensation of the patient. In 13 studies, atleast some degree of side-effects due to tacrolimus was reported. Two articles contained unclear information on adverse effects of the drug.

3.2. Quality of included Studies:

After the careful analysis of quality, it was found that 4 articles had low risk of bias, 6 had moderate risk of bias and 5 studies had high risk of bias. However these 5 studies were also included in this review to ensure completion of reporting of the available relevant data. The results of quality analysis is tabulated in table 2. Figure 1 shows the graphical representation of bias encountered in the review.

IV. Discussion

Tacrolimus is an immunomodulatory agent which was found to be more effective than cyclosporine. The small molecule of tacrolimus penetrates into the mucosa and it was approved as a safe treatment modality for atopic dermatitis[12] Multiple case reports have suggested that tacrolimus is effective in treating lichenplanus which is non-responsive to corticosteroids.[13]This systematic review includes 15 studies in which topical tacrolimus was compared with various other pharmacological agents and placebo. There was variation in the dosage, form, and vehicle used for tacrolimus between the different groups. The comparison had been made with steroids and other immune-modulators. However, only one study compared tacrolimus with placebo. There was a great variation in the parameters that was used in the assessment of disease. All the studies tested the clinical appearance of the lesion and used it as criteria for defining treatment response. However, symptomatic relief of the patient was not assessed in all the studies. There is diversity in the results among the different studies. This may be because of the variability in the drug's concentration, frequency of administration, and parameters used for outcome reporting.

3.3. Efficiency of tacrolimus when compared with other pharmacological agents.

3.3.1. Topical Triamcenolone Acetonide

In the study by Laeijendecker et al. (2006), the initial results were better in the tacrolimus group. There was only temporary side effects, and it was more common in the group that used 0.1% tacrolimus than in the group that used 0.1% triamcinolone. However, after three to nine weeks from the time of discontinuation of the therapy, recurrence was noted in 72% of the patients in the tacrolimus group. This was lower than that in the triamcinolone group, wherein the recurrence rate was 78%. The study by Revanappa et al. (2012) and Singh et. al (2017) revealed that there is a statistically significant improvement in the group that used 0.1% tacrolimus when compared to the group that used 0.1% triamcinolone acetonide. In the study by Swarna et al. (2011) 0.03% tacrolimus was found to be more effective than 0.1% triamcinolone acetonide in reducing the burning sensation and the size of the lesion. There was a recurrence of the lesion in both groups. In tacrolimus group, recurrence occurred in fewer patients and it happened 3-6 months after the discontinuation of the drug in contrast to the triamcinolone group wherein the recurrence occurred after 2-3 months. The findings of Sivaraman et al. (2016) was contradictory to the findings of Swarna et al (2011). The study showed that 0.1% triamcinolone is more effective than 0.03% tacrolimus. The authors proposed that this result may be because of the reduced concentration of tacrolimus used.[12,14-17]

The study by Azizi et al. (2007) and Siponen et al. (2017) showed that there is no statistically significant difference between the efficacy of tacrolimus and triamcinolone acetonide. However, in the study by Siponen et al. (2017), the VAS values increased during the six months follow-up period in the triamcinolone acetonide group whereas it remained stable in the tacrolimus group. The authors also reported that the incidence of adverse reactions, such as burning sensation, was more common in the tacrolimus group when compared to the triamcinolone group.[18,19]

Out of the 4 studies that revealed better results in the tacrolimus group, 2 studies had a high risk bias and 2 studies had a moderate risk of bias. One of the two studies that reported similar efficiency for the two drugs had a high risk bias and the other one moderate risk of bias. The study that found triamcinolone to be

better than tacrolimus had a high risk bias. Thus, the reliability of the evidence from these studies is less. Further studies are required to arrive at a reliable conclusion.

3.3.2. Topical Clobetasol Propionate

Rafdar et al. (2008) compared the efficiency of 0.05% clobetasol and 0.1% tacrolimus. The results revealed that there is no statistically significant difference between the efficacies of the two drugs. There was less recurrence of the lesion in the tacrolimus group when compared to the clobetasol group. These findings are in contrast to the findings of Corrocher et al. (2008) and Hettiarachi et al.(2016). According to these studies, tacrolimus was found to be more efficient than clobetasol. In the study by Corrocher at al (2008), though there was initial worsening of the burning sensation in the tacrolimus group, it resolved in 4-5 days of the commencement of the treatment. Thus, the authors concluded that topical tacrolimus is better than high potency topical steroids for management of symptomatic lichen planus. In the study by Sonthalia et al. (2012) though initially clobetasol gave better results over the first two weeks, in the subsequent visits, tacrolimus was found to be better than clobetasol. However, the results were not statistically significant. Similarly, the study by Sivaraman et al. (2016) showed that 0.05% clobetasol propionate is better than tacrolimus. [17,20-23]

The study that showed better results with clobetasol had a high risk of bias and the study which revealed equal efficacy for both the drugs had a moderate risk of bias. Among the three studies that reported better results with tacrolimus, two had a low risk for bias and one study had a moderate risk of bias. Hence, based on the evidence, it is to be concluded that 0.1% tacrolimus is more effective than 0.05% clobetasol for treating lichen planus.

3.3.3. Intralesional steroid injections

Shah et al. (2014) compared 0.1% topical tacrolimus with intra-lesional triamcinolone acetonide injection. In cases wherein 75% resolution did not occur with the first injection, a second round of injection was also administrated. In addition to this, 0.1% topical flucinolone acetonide was applied by the patients in the group. At the end of the treatment, there is statistically significant improvement in the triamcinolone group when compared to topical tacrolimus group. 26% of the patients did not respond to topical tacrolimus in this study, whereas all the patients responded well to intralesional steroid injections. All the patients in the tacrolimus group showed relapse of the disease whereas only 10% of the patients in the triamcinolone group showed relapse. Thus the authors concluded that intralesional triamcinolone combined with topical flucinolone is more efficient in treating lichen planus. This study had a high risk bias.[24]

3.3.4. Topical Pimecrolimus

Arduino et al. (2013) compared the efficacy of 0.1% pimecrolimus and 0.1% tacrolimus. Both the drugs were found to be effective against lichen planus. There was no statistically significant difference between the two groups. In the study, a quick response was attained between the two groups within 2 weeks of commencement of the therapy. However, there was marked recurrence of the lesion 6 months after the discontinuation of the therapy. Hence the authors concluded that though, pimecrolimus and tacrolimus have similar efficacy, a significantly better stability is achieved with pimecrolimus. In the study by Vohra et al. (2015), pimecrolimus was found to be slightly better than tacrolimus.However, this difference was not statistically significant. Except for mild burning sensation and dysguisea, no major side effects were encountered in either of the groups. The burning sensation was more prevalent in the tacrolimus group. Since both these studies had a low risk of bias, the level of evidence substantiates that both drugs have similar efficacy against lichen planus.[25,26]

3.3.5. Mometasone Furoate

Chappidi et. al (2017) compared the efficiency of 0.1% tacrolimus and 0.1% mometasone furoate for the management of erosive and ulcerative lichen planus. All the patients in the tacrolimus group responded to the treatment. However, 2 out of the total 15 patients in momentasone group were unresponsive. Ulceration, erythema, size of the lesion and VAS scores showed statistically significant improvement in tacrolimus group when compared to the mometasone group. The post-treatment recurrence of the disease after 8 weeks was higher in the mometasone group when compared to tacrolimus. Though major side-effects were not encountered, side-effects such as transient burning sensation, dryness of mouth and transient alteration of taste was found to be more prevalent in the tacrolimus group. This study had a moderate risk of bias.[27]

3.3.6. Oral Dapsone

In the study by Singh et al. (2017) a group of 10 patients were administrated systemic 100 mg dapsone with iron and folic acid tablets. Oral dapsone was found to be more efficacious than 0.1% tacrolimus. However, the post-treatment symptom and sign scores were comparable between dapsone and tacrolimus. Although no major side effect was encountered with both agents, mild tingling sensation was encountered with topical

tacrolimus. There was no recurrence of the disease in the dapsone group, whereas there was a 30% recurrence in the tacrolimus group. There was a moderate risk of bias for this study.[15]

3.3.7. Oral Methotrexate

Shah et al. (2014) compared 2.5mg oral Methotraxate/week with 0.1% topical tacrolimus. Both the medications were found to be equally efficient in the management of Oral Lichen Planus. Hair fall was the side-effect noted with methotrexate whereas burning sensation and local irritation were encountered with tacrolimus. Relapse occurred in both the groups. The study had a high risk bias.[24]

3.3.8. Topical Retinoids

Singh et al. (2017) provided one of the study groups with topical retinoid. Though the percentage improvement of signs and symptoms was higher in the tacrolimus group, the difference was not statistically significant. In this study, only 30% of patients each, in retinoid and tacrolimus groups experienced complete remission of the disease. 30% of the patients in tacrolimus group and 10% of patients in retinoid group experienced the recurrence of the disease within three to four weeks after the discontinuation of the medication. This study also had a moderate risk of bias.[15]

3.3.9. Antimicrobial agents

In the study by Shah et al. (2014), topical 0.1% tacrolimus was compared with a combination of antimicrobials. The antimicrobials included, 0.12% chlorohexidine hydrochloride mouth wash, 0.15% benzydamine hydrochloride and 400mg oral metronidazole. Tacrolimus was found to be effective in reducing the severity of the disease; but, none of the patients responded to antimicrobials. This study had a high risk bias.[24]

3.3.10. Placebo

In the study by Siponen et al. (2017), Orabase paste was used as placebo. 0.1% Tacrolimus was found to be effective in decreasing the disease severity whereas the clinical score of the lesion was found to be increasing in the placebo group. This is the only study whrein a comparison is made with placebo. It may be due to the ethical issues associated with placebo controlled trials.[19]

3.4. Side effects

The most common side effects reported with tacrolimus include burning sensation, transient alteration in the taste sensation, headache and patchy hyperpigmentation.[12,13]There may be initial worsening of the burning sensation for the first 2 days of the commencement of topical tacrolimus application whichmay be because of the erosive nature of the lesion. Swarna et al. (2011) suggested that, the burning sensation may be due to the close contact of the drug to nerve endings in the connective tissue. Once, the re-epithelialisation sets in, the burning sensation also resolves. This burning sensation rarely warrants the discontinuation of the treatment and would resolve in four to five days from the commencement of the treatment. Besides this, sialorrhoea, and dryness of mouth were also reported as side effects of topical tacrolimus.[16,21,25,27]

In none of the studies, clinically significant blood levels of tacrolimus could be detected. Unlike topical steroids, topical tacrolimus did not lead to the development of candidiasis. Thus, it has to be inferred that, apart from the initial burning sensation, tacrolimus has no major side effect and is well tolerated by the patients.

Recurrence was encountered in some studies. Hittiachari et al. (2016) suggested that in the patients who has the remission of the lesion in 4-8 weeks of therapy, maintenance of therapy for another 1-2 months is desired to avoid recurrence.[22]

3.5. Limitations

There were few limitations that we encountered in this systematic review. The chief one is the compromised methodological quality of the studies that were included. Very few studies had a low risk of bias and hence to ensure the completion, other studies also had to be included in this review. Another major problem is the heterogeneity of the included studies. The studies varied much in the concentration of topical tacrolimus, frequency of usage, and treatment duration. Hence, we could not standardise the results. Also, there was variation in the parameters used for measuring the outcome. It could have contributed to the difference in the results between different studies. None of the studies mentioned the sample size calculation and the power of the study. Another major setback was the lack of long-term follow-up. Out of the 15 studies we had included in here only 4 studies had atleast 6 months post-treatment follow-up period. It is essential to have atleast 6 months follow up to test recurrence. Systemic tacrolimus is associated with the development of malignancies. This is because of the increased immunosuppressive properties of the drug. When administered as a topical medication, the systemic absorption is less and the blood concentrations are usually well within the safe-limit and sometimes undetected in serum. However, there are few case reports of squamous cell carcinoma developing at the intra-

oral site wherein topical tacrolimus was applied for treating lichen planus.[28,29] Though the link between oral cancer and tacrolimus are not established with suggestions that the carcinoma could have developed from lichen planus itself, a long term follow up for five to ten years would be required to analyse such changes.

V. Conclusion

The existing evidence proves with no doubt that topical 0.1% and 0.03% tacrolimus are effective in the treatment of symptomatic Oral Lichen Planus. Due to the heterogeneity of the studies, we could not derive a standard protocol for the usage of this drug for Oral Lichen Planus. More studies that have a low risk of bias and long term follow up may be required to standardise the protocol for the usage of topical tacrolimus. However, considering the possibilities for post-treatment recurrence, long-term maintenance therapy and follow-up may be required to ensure complete remission of the disease.

Ethical Statement: Ethical committee approval was not required as this is a review of existing literature.

Conflict of Interest: None

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APPENDIX-A

Author & Year	Groups and sample	Concentration of topical tacrolimus; Mode of usage; frequency	Comparison group(s)	Type of OLP	Post treatment Follow-up	Outcome analysis parameters	Study outcome
Laeijendecker et al. 2006	Group 1=20 Group 2=20	0.1% ointment 4 times daily for 6 weeks	Traincenolone acetonide 0.1% in hypromellose 20% ointment 4 times daily for 6 weeks	NS	3 months	CS	Comparatively better improvement in tacrolimus group
Azizi et al 2007	Group 1=30 Group 2=30	0.1% ointment 4 times daily for 4 weeks	Adcorlyl ointment (triamcinolone in orabase) 4 times daily for 4 weeks	Erosive and Atrophic LP	Unclear	CS VAS	Significant reduction in the disease. No significant difference in the severity score and lesion score between two groups. Pain was significantly less in tacrolimus group.
Rafdar et al. 2007	Group 1=15 Group 2=15	0.1% ointment 4 times daily for 2 weeks followed by thrice daily for 2 weeks and twice daily for 2 weeks	Clobetasol 0.05% ointment 4 times daily for 2 week followed by thrice daily for 2 weeks and twice daily for 2 weeks	Erosive/Ulcerative LP	9 months	CS VAS	Significant reduction in the disease. No significant difference in the profiles of change in mean sizes and VAS scores between the two groups
Corrocher et al. 2008	Group 1=16 Group 2=16	0.1% ointment 4 times daily for 4 weeks	Clobetasol propionate 0.05% ointment 4 times daily for 4 weeks	NS	2 weeks	CS	Median pain, burning sensation and mucosal extension were significantly lower in tacrolimus.

Swarna et al. 2011	Group 1=15 Group 2=15	0.03% ointment twice daily for four weeks	Topical triamcinolone 0.1% oral paste twice daily for four weeks	NS	8 weeks	CS VAS	Comparatively better improvement in burning sensation and area of lesion in tacrolimus group. Erythematous areas showed similar improvement in both groups.
Revanappa et al. 2012	Group 1=30 Group 2=30	0.1% in orabase vehicle thrice daily for two weeks	Triamcinolone acetonide 0.1% in orabase thrice daily for two weeks	NS	4 weeks	CS VAS	VAS score and CS showed statistically significant improvement in tacrolimus group than in the control group at the end of 4th week.
Sonthalia et al 2012	Group 1=20 Group 2=20	0.1% ointment twice daily for eight weeks	Topical clobetasol propionate 0.05% ointment twice daily for eight weeks	NS	12 weeks	CS	CS in tacrolimus group was lower than clobetasol at the end of the study. No statistically significant differences between the groups in follow up visits.
Arduino et al. 2013	Group 1=15 Group 2=15	0.1% ointment in hydroxyethyl cellulose adhesive gel twice daily for 8 weeks	Topical pimecrolimus 1% cream mixed with hydroxyethyl cellulose adhesisve medium twice daily for 8 weeks	Atrophic/Erosive LP	6 month	CS VAS	Significant reduction in the disease. No significant difference between the two groups in the reduction of signs and symptoms.

Shah et al. 2014	Group 1=50 Group 2=50 Group 3=50 Group 4=50	0.1% ointment 2-3 times per day for 6 months	1. 0.12% chlorohexidine hydrochloride mouth wash (m/w), 0.15% benzydamine hydrochloride m/w, oral metronidazole 400mg thrice daily for 14 days 2. oral Methotraxate 2.5mg/week for 6 months 3. Intra-lesional triamcinolone acetonide injection (TA) 1ml (40mg/ml); one injection followed by second one after 2 weeks depending upon the response of the lesion. 0.1% topical flucinolone acetonide ointment (FA) was applied 2-3 times per day for 6 months.	Reticular,Erythematous/atrophic and erosive LP	1 month for chlorhexidine group; 12 months for all other groups.	CS VAS	Better result in triamcinolone group. Except in the chlorhexidine group, all other groups showed statistically significant improvement. There is no significant difference in the efficiency of tacrolimus and methotrexate.
Vohra et al 2015	Group 1=20 Group 2=20	0.1% ointment twice daily 8 weeks	Pimecrolimus 0.1% cream twice daily 8 weeks	Reticular, Erosive and Ulcerative LP	4 weeks	CS	Comparatively more reduction in pimecrolimus group. But the result was not statistically significant.
Hettiarachchi et al. 2016	Group 1=34 Group 2=34	0.1% cream twice daily for 3 weeks	Topical clobetasol propionate 0.05% cream twice daily for 3 weeks	NS	5 weeks	CS VAS	More significant reduction in the symptoms in tacrolimus group.
Sivaraman et al. 2016	Group 1=10 Group 2= 10 Group 3=10	0.03% ointment in orabase 4 times daily for 6 weeks	1. Topical triamcenole acetonide 0.1% ointment 4 times daily for 6 weeks 2. Topical clobetasol propionate 0.05% 4 times daily for 6 weeks	Reticular and Erosive LP	3 months	CS	Clobetasol group showed better result than traimcenolone and tacrolimus groups. The order of effectiveness is as follows. Clobetasol 0.05%> Triamcenolone 0.1% >Tacrolimus 0.03%
Siponen et al. 2017	Group 1 =11 Group 2=7 Group 3=9	0.1% ointment 3 times daily for 6-9 weeks	1. Topical Triamcenolone paste 0.1% 3 times daily for 6-9 weeks 2. Placebo(Orabase paste) 3 times daily for 6-9 weeks	NS	6 months	CS VAS	Triamcenolone and tacrolimus were found to be better than placebo. Tacrolimus showed a long term pain reduction without candidiasis.

Chappidi et al. 2017	Group 1=15 Group 2=15	0.1% ointment twice daily for 6 weeks	Topical 0.1% mometasone furoate ointment twice daily for 6 weeks	Erosive and ulcerative LP	8 weeks	CS VAS	Comparatively significant improvement in tacrolimus group in ulceration, erythema, size of the lesion and VAS scores.
Singh et al 2017	Group 1=10 Group 2=10 Group 3=10 Group 4=10	0.1% twice daily for 3 months	1. Topical Triamcenolone acetonide 0.1% twice daily for 3 months 2. Oral dapsone 100 mg twice daily with iron and folic acid tablets for 3 months 3. Topical retinoid twice daily for 3 months	Reticular, Erosive, Atrophic, Plaque Like LP	Not clear	Clinical Scoring (Sign score & symptom score)	Dapsone was found to be better than the other modalities. 0.1% tacrolimus, 0.1% triamcinolone and topical retinoid were found to have the same degree of effect.

NS- Not Specified; LP- Lichen Planus; CS- Clinical Scoring; VAS-Visual Analogue Scale.
Table 1: Summery of the studies included in the review

APPENDIX B

Sl.No	Authors	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed?	Free of Selective Outcome Reporting	Observer related bias Addressed?	Degree of Bias
1.	Laeijendecker et al.	×	×	×	✓	✓	×	High Risk Bias
2.	Azizi et al	×	×	×	✓	×	×	High Risk Bias
3.	Radfar et al	✓	✓	✓	×	✓	×	Moderate Risk Bias
4.	Corrocher et al	✓	✓	✓	✓	✓	✓	Low Risk Bias
5.	Swarna et al.	✓	×	×	✓	✓	×	Moderate Risk Bias
6.	Revanappa et al.	×	×	×	✓	✓	×	High Risk Bias
7.	Sonthalia et al.	✓	✓	✓	×	✓	×	Moderate Risk Bias
8.	Arduino et al.	✓	✓	✓	✓	✓	✓	Low Risk Bias
9.	Shah et al.	×	×	×	✓	✓	×	High Risk Bias
10.	Vohra et al	✓	✓	✓	✓	✓	✓	Low Risk Bias
11.	Hettiarachchi et al.	✓	✓	✓	✓	✓	✓	Low Risk Bias
12.	Sivaraman et al.	✓	×	×	✓	×	×	High Risk Bias
13.	Siponen et al.	✓	✓	✓	×	✓	×	Moderate Risk Bias
14.	Chappidi et al	×	×	✓	✓	✓	×	Moderate Risk Bias
15.	Singh et al	✓	×	×	✓	✓	×	Moderate Risk Bias

Table 2: Critical Analysis of studies included in the review

APPENDIX C

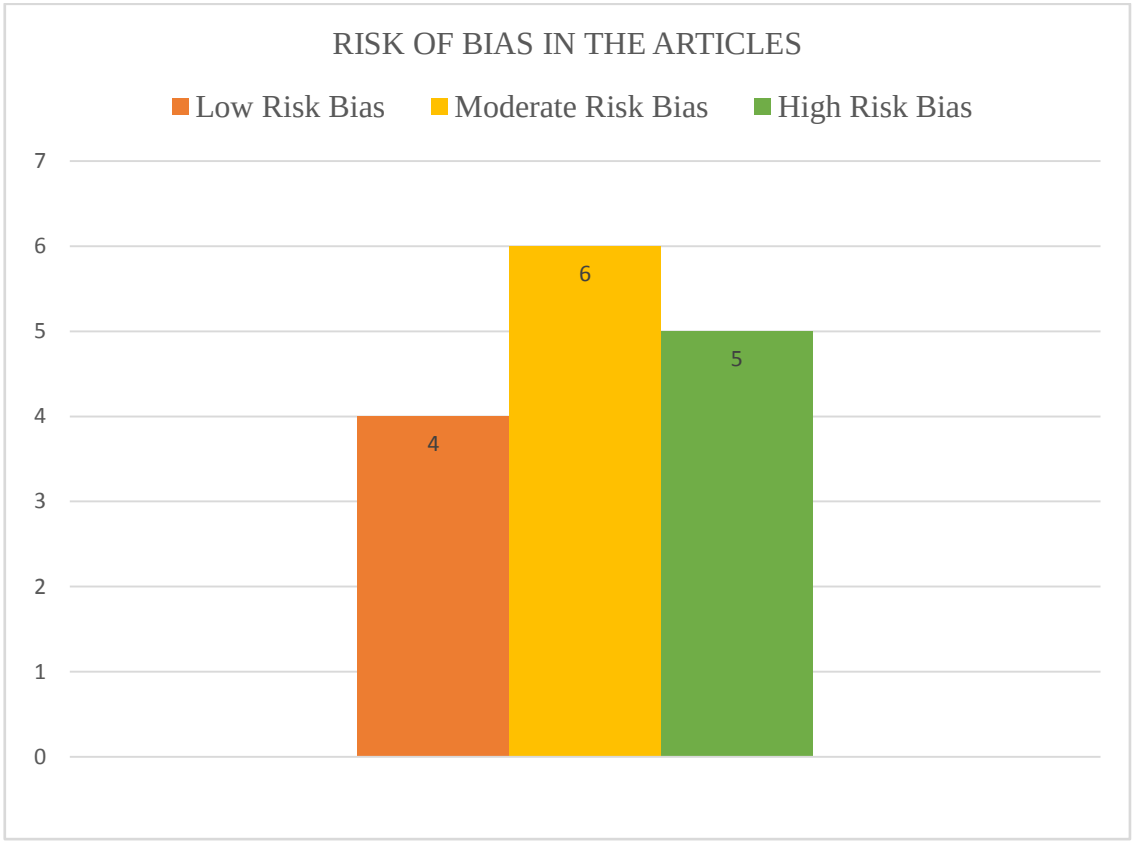

Figure 1: Bar graph representing bias in the studies

Dr. Sosa George. "Topical Tacrolimus in the Treatment of Symptomatic Oral Lichen Planus - A Systematic Review." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 12, 2019, pp 07-17.