Review Article

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Medical Management of Oral Lichen Planus: A Systematic Review

Dentistry Section

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ABSTRACT

Introduction: Oral Lichen Planus (OLP) is a chronic inflammatory, T-cell-mediated autoimmune oral mucosal disease with unclear aetiology. The clinical management of OLP poses considerable difficulties to the oral physician.

Aim: The aim was to assess the efficacy of any form of intervention used to medically manage OLP.

Materials and Methods: We searched and analysed the following databases (from January 1990 to December 2014):- Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE.

All Randomised Controlled Trials (RCTs) for the medical management of OLP which compared active treatment with placebo or between active treatments were considered in this systematic review. Participants of any age, gender or race having symptomatic OLP (including mixed forms), unconnected to any identifiable cause (e.g. lichenoid drug reactions) and confirmed by histopathology have been included. Interventions of all types, including topical treatments or systemic drugs of variable dosage, duration & frequency of delivery have been considered. All the trials identified were appraised by five review authors and the data for all the trials were synthesised using specifically designed data extraction form. Binary data has been presented as risk ratios (RR) with 95% confidence intervals (CI) and continuous data as mean differences (MD) with 95% CIs.

Results: A total of 35 RCTs were included in this systematic review on medical management of OLP. No strong evidence suggesting superiority of any specific intervention in reducing pain and clinical signs of OLP were shown by the RCTs included here.

Conclusion: Future RCTs on a larger scale, adopting standardized outcome assessing parameters should be considered.

Keywords: Autoimmune disease, Interventions, Randomised controlled trials (RCTs), Treatment of oral lichen planus (OLP)

INTRODUCTION

Oral Lichen Planus (OLP) is generally accepted as a chronic and T-cell-mediated autoimmune disease with unclear aetiology [1]. There is substantial fluctuation in disease activity within an individual patient and there are also variations between patients with regard to both the desire for, and response to, various treatments [2]. The management of OLP is challenging. Currently, treatment for OLP is focused mainly to eliminate mucosal erythema, ulcerations and alleviate symptoms of disease during periods of activity and, if possible, increase the periods of disease quiescence. Various treatment regimens have been tried to improve the lesions and reduce the associated pain, but a cure for OLP has not yet been found because of its recalcitrant nature & lack of an apparent cause. Many other systematic reviews suggest the use of topical corticosteroids or topical calcineurin inhibitors.

Hence the purpose of the present systematic review was to evaluate the efficacy & safety of interventions in the treatment of OLP.

MATERIALS AND METHODS

The study design chosen was randomised control trials. All participants of any age, gender or race having symptomatic OLP (including mixed forms), unconnected to any identifiable cause (e.g. lichenoid drug reactions) and confirmed by histopathology were included. All types of interventions, including topical treatments or oral medications of variable dosage, duration & frequency of delivery were considered.

Trials of different doses of the same intervention, comparison trials between different interventions, intervention versus placebo trials, intervention versus 'no treatment' trials, and cross-over studies were included.

The primary outcomes that were registered include

(a) Pain reduction using a Visual Analogue Scale (VAS) rated by participants (e.g. 0 to 10).

(b) Physician Global Assessment,

(c) Ordinal & Nominal scales of self-assessment.

(d) Oral Mucositis Assessment Scale.

The secondary outcomes that were registered include

(a) Clinical presentation of the disease in terms of extension and severity (degree of erosion, erythema and reticulation).

(b) Reduction in severity of flares.

(c) Reduction in number of flares.

(d) Relapse rate when medications were stopped or reduced.

The outcomes, wherever possible, were recorded either in the short-term (less than six months) or long-term (six months or more) from the beginning of treatment.

For the identification of studies included or considered for this review, we searched and analysed the databases [Table/Fig-1] from January 1990 to December 2014. The search was limited to English literature. In addition to searching databases, we also used supplementary approaches to identify studies, such as hand searching of journals and checking reference lists. The search items that were used are given in [Table/Fig-2]. Eligibility assessments of all the studies available were performed independently in an unblind standardized manner by three reviewers. All studies meeting the inclusion criteria underwent data extraction performed by five review authors, using a specially designed form [Table/Fig-3].

The review authors independently assessed the risk of bias of the included trials. The full text papers were assessed independently

Information Sources
Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE EMBASE Journal of Oral Surgery Oral Medicine Oral Pathology Oral Radiology Oral Diseases Journal of Oral Pathology and Medicine The American Journal of the Medical Sciences Journal of American Academy of Dermatology International Journal of Oral & Maxillofacial Surgery British Journal of Dermatology

[Table/Fig-1]: Information sources.

Search items
Lichen planus Oral lichen planus Randomised trials oral lichen planus Placebo trial oral lichen planus Drug therapy oral lichen planus Steroids oral lichen planus Calcineurin inhibitors oral lichen planus Aloe vera oral lichen planus Curcuminoids oral lichen planus

[Table/Fig-2]: Search items.

Data items
SOURCE: Study title, author names, year & the journal **STUDY DESIGN:** Total study duration, Random sequence generation, Allocation sequence concealment, Blinding. **PARTICIPANTS:** Total number, Setting, Inclusion criteria, Age & Sex, **INTERVENTIONS:** Total number of intervention groups, For each intervention and comparison group of interest:- • Specific intervention; • Intervention details (type, dose, duration and frequency) **OUTCOMES:** Type of Outcome, Unit of Measurement for each type of outcome **RESULTS:** Number of participants allocated to each intervention group; For each outcome of interest: • Sample size • Missing participants; • Summary data for each intervention group; • Post treatment relapse. **MISCELLANEOUS:** Key conclusions, Miscellaneous comments.

[Table/Fig-3]: Data items.

and unblinded by all authors and any disagreement was resolved through discussion and consensus. Common markers of validity used for randomized trials:

1. Random sequence generation.
2. Allocation sequence concealment.
3. Blinding of participants, health care providers, data collectors & outcome adjudicators.
4. Incomplete outcome data.
5. Selective reporting.

Studies were graded into the following categories:

1. Low risk of bias.
2. High risk of bias.
3. Unclear risk of bias.

For binary outcomes, risk ratios (RR) with 95% confidence intervals (CI) are presented and for continuous data, mean differences (MD) with 95% CIs are presented.

RESULTS

The database search identified 220 papers initially. Fifty-one full text papers were retrieved, of which 35 were included [3-37].

Study Characteristics

All the included studies were randomised control trials [Table/Fig-4]. Total numbers of participants included in the trials were 2120, with a mean of 60 participants per study. All included studies were performed in secondary care. One study [14] was a multicentre study. The diagnosis of OLP was confirmed clinically in all studies and histologically in all but one [20].

Multiple therapies were considered. Of the 35 included trials, 12 trials [3,17-19,21,24-26,30,32,33,37] compared an active intervention with placebo. Two active treatments were compared in 16 trials [4-7,13-16,20,22,23,28,29,31,34,35]. In seven studies [8-10,12,27,36] same intervention was compared in different arms/ different concentrations.

Twenty-nine trials used steroid as an active intervention, of which, topical steroids were used in twenty-one trials [4-10,14-16,19,20, 22,23,27-29,31,34-36]. Three trials [8,10,36] compared the same steroid in different forms, one study [27] the same steroid in different concentrations, three studies [4,9,20] made a comparison between different steroids and one trial [19] the same steroid with or without an antimycotic drug. In one study [18] all the participants received a systemic steroid, and in another study [28] the experimental intervention was compared with intralesional steroid. Of the 29 trials using steroid as an active intervention, clobetasol was used in nine trials [4,7,10,11,19,22,23,27,35], triamcinolone in ten trials [4,5,13-16,20,28,31,36], flucinolone in two trials [6,8], dexamethasone in two trials [29,34], prednisolone in one trial [18], fluticasone in one trial [9] & betamethasone in two trials [9,20]. Systemic prednisolone was used in one trial [18].

Local calcineurin inhibitors were employed in 12 trials. Topical tacrolimus was used in four trials [13,22,23,35], topical pimecrolimus in four trials [15,17,24,33], topical cyclosporine in four trials [3,5,14,16].

Other treatments included: aloe vera in three trials [21,30,31], hyaluronic acid [26], curcuminoids as adjunctive treatment to prednisone [18], Bacillus Calmette-Guerin polysaccharide nucleic acid [28], topical retinoic acid [6], topical thalidomide [29], lycopene [32], topical isotretinoin [12], ignatia [25] & MuGard [37].

OUTCOMES

Primary

In this review, all included studies assessed pain as the primary outcome. But, all these studies used different parameters to assess pain.

Pain was reported as a continuous outcome using visual analogue scales (VAS) of different lengths in all trials, except five trials [3,17,22,20,35]. Eisen measured global symptom scores on an ordinal scale of 0 to 3 [3]. Passeron used a visual scale of 0 to 4 [17], Corrocher used an ordinal scale of 0 to 3 [22]. Sonthalia measured pain on a nominal scale [35]. Sieg and Laeijendecker measured only the areas of ulceration & not stated anything about the pain score [5,13].

Secondary

Clinical response was measured by eleven trials [6-10,14-16,21,27,30,31] using the clinical grading by Thongprasom 1992 consisting of a six-point ordinal scale, four trials [17,19,22,24] used a different clinical grading scale with scores 1 to 4. Tel Aviv San Francisco scale was used in one trial [32]. Erythema was measured on a 0-3 scale and size of target erosion in mm in one study [33] and Net Clinical Score was used in another study [35]. The erosive area was measured in mm^2 using a calibrated dental probe in one trial

Study (first author, year)	No. of patients & interventions	Outcomes	Duration
Eisen 1990	n=8 -Cyclosporin n=8 -placebo	global score, mean erosion score, mean pain score	8 weeks
Rodstrom 1994	n=20-0.05% clobetasol propionate ointment n=20-0.1% triamcinolone acetonide ointment	VAS score & 4 point clinical score	9 weeks
Sieg 1995	n=6-Cyclosporin solution n=7-Triamcinolone acetonide oral paste	Clinical extent of lesion-score 1-7	6 weeks
Buajeeb 1997	n=18- 0.1% flucinoloneacetonide paste n=15- 0.05% retinoic acid paste	VAS score Thongprasom clinical grading	4 weeks
Sardella 1998	n=14-clobetasol ointment n=11- mesalazine gel.	VAS score	4 weeks
Buajeeb 2000	Group A:-(n=18) - fluocinoloneacetonide in an oral base 0.1%, Group B(n=15)- fluocinoloneacetonide gel 0.1% no. 1 (with carbopol 934, 1%) Group C(n=15)- fluocinoloneacetonide gel 0.1% no. 2 (with carbopol 940, 0.5%).	VAS score Thongprasom clinical grading	4 weeks
Hegarty 2002	Sequence 1(n=22): Patients initially received fluticasone propionate spray(50 µg aqueous solution) +washout period +betamethasone sodium phosphate mouthrinse(0.5 mg tablet dissolved in 10 mL water). Sequence 2(n=22): Patients initially received betamethasone sodium phosphate mouth rinse+ washout period+ fluticasone propionate spray.	VAS & McGill Pain questionnaire Oral Health Impact Profile (OHIP 14) & the Oral Health Quality of Life index (OHQoL-16) Grid in mm.	6 weeks
Campisi 2004	Group A(n=20)- clobetasol propionate in microspheres 0.025% Group B (n=30)- clobetasol propionate 0.025% in a dispersion of a lipophilic ointment in a hydrophilic phase	VAS score Thongprasom clinical grading Clinical resolution index Compliance	2 months
Conrotto 2006	n=20-0.025% clobetasol propionate ointment n=20-1.5% ciclosporin ointment	VAS score Thongprasom clinical grading	2 months
Scardina 2006	n=35- 0.18% topical isotretinoin n=35-0.05% topical isotretinoin	VAS score 3 point clinical score	3 months
Yoke 2006	n=71- triamcinolone acetonide paste n=68-cyclosporine solution	VAS score Thongprasom clinical grading	8 weeks
Laeijendecker 2006	group I(n=20)- tacrolimus 0.1% ointment , group II(n=20)- triamcinolone acetonide 0.1% in hypromellose 20% ointment	Ordinal scale for clinical score	6 weeks
Gorouhi 2007	n=20-Pimecrolimus 1% cream n=20-Triamcinolone 0.1% cream	VAS Oral Health Impact Profile	2 months
Passeron 2007	n=6-Pimecrolimus 1% cream n=6-vehicle	VAS Clinical surface area measured	4 weeks
Thongprasom 2007	n=6-cyclosporin solution n=7-tiamcinolone acetonide 0.1% in orabase	VAS score Thongprasom clinical grading	8 weeks
Chainani-Wu 2007	n=16-curcuminoid capsules n=17-placebo	VAS Change in symptom scale Modified Oral Mucositis	7 weeks
Lodi 2007	n=18-clobetasol propionate gel + miconazole gel n=17- clobetasol propionate gel+ placebo	VAS Extension of the lesion	6weeks
Malhotra 2008	n=25-Betamethasone 5mg orally N=24-Triamcinolone Acetonide 0.1% paste	Objective & subjective response	6 months
Choonhakaran 2008	N=27-Aloe vera gel n=27-Placebo	VAS score Thongprasom clinical grading	8 weeks
Corrocher 2008	n=16-Tacrolimus 0.1% ointment n=16-Clobetasol 0.05% ointment	4 point scale for pain & burning sensation 4 point scale for mucosal surface extension	4 weeks
Radfar 2008	n=15-Tacrolimus 0.1% ointment n=15-Clobetasol 0.05% ointment	VAS Complete response	6 weeks
Volz 2008	n=10-Pimecrolimus 1% cream n=10-vehicle	VAS 4 point scale for surface area	30 days
Mousavi 2009	n=15-Ignatia n=15-Placebo	VAS Transparent grid for ulcer area	4 months
Nolan 2009	n=62-0.2% Hyaluronic acid gel n=62-placebo gel.	VAS score Thongprasom clinical grading Oral function ability	28 days
Carbone 2009	n=18-Clobetasol 0.025% n=17-Clobetasol 0.05%	VAS score Thongprasom clinical grading	2 months
Xiong 2009	n=31- BCG-PSN intralesional n=25- intralesional TA	VAS Clinical area using calibrated dental probe	2 weeks
Wu 2010	n=37- thalidomide 1% paste n=32-dexamethasone 0.043% paste n=32	VAS Erosive area	3 weeks
Salazar-Sanchez 2010	n=32-aloe vera n=32-placebo	VAS score Thongprasom clinical grading OHIP-49 HAD scale	12 weeks
Mansourian 2011	n=23- Aloe vera mouth wash n=23-triamcinolone acetonide paste	VAS score Thongprasom clinical grading	4 weeks
Sawaarn 2011	n=15- lycopene capsule n=15- placebo	VAS Tel Aviv Fransisco scale	8 weeks
McCaughey 2011	n=10-1% pimecrolimus cream n=11-placebo	VAS Investigator's Global Assessment	6 weeks
Fu 2012	n=20-Amlexanox paste n=18-dexamethasone paste	VAS Size of lesion	7 days
Sonthalia 2012	n=20- clobetasol propionate 0.05% ointment n=20-tacrolimus 0.1% ointment	Net clinical score	8 weeks
Lee 2013	n=20-0.4% TA mouth rinse n=20-TA injection 0.5 ml	VAS OHIP-14	6 weeks
Velez 2014	n=10-MuGuard 5ml n=10-saline bicarbonate control	VAS Oral Mucositis Assessment Scale	14 days

[Table/Fig-4]: Characteristics of included studies.

[34]. Yet another study [37] employed Oral Mucositis Assessment Scale. Eleven other trials [3-5,12,13,18,23,25,26,28,29] used their own clinical sign score. No objective symptoms were recorded in one trial [12].

RISK OF BIAS WITHIN STUDIES

The risk of bias for each included study was analysed using a standard approach independently by the authors [Table/Fig-5].

	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Eisen 1990	+	?	+	+	+
Rodstrom 1994	?	?	+	_	_
Seig 1995	?	?	+	+	_
Buajeeb 1997	_	_	?	+	+
Sardella 1998	+	?	+	+	+
Buajeeb 2000	?	?	_	_	_
Hegarty 2002	+	+	+	_	+
Campisi 2004	+	?	+	_	+
Conrotto 2006	+	+	+	?	+
Scardina 2006	?	?	+	+	+
Yoke 2006	+	+	?	+	+
Laeijendecker 2006	+	?	?	+	?
Gorouhi 2007	+	+	+	+	?
Passeron 2007	+	?	?	+	+
Thongaprasom 2007	?	?	_	_	_
Chainani-Wu 2007	+	?	+	+	_
Lodi 2007	+	+	+	_	+
Malhotra 2008	+	+	_	_	+
Choonhakaran 2008	+	+	+	+	+
Corrocher 2008	+	+	+	+	+
Radfar 2008	+	+	+	+	+
Volz 2008	+	+	+	+	+
Mousavi 2009	+	?	+	+	+
Nolan 2009	?	?	+	_	+
Carbone 2009	+	+	+	_	+
Xiong 2009	+	?	+	_	+
Wu 2010	+	+	+	_	+
Salazar-Sanchez 2010	+	+	+	_	+
Mansourian 2011	+	+	+	+	+
Saawarn 2011	?	?	+	+	+
McCaughey 2011	+	+	+	+	+
Fu 2012	+	+	+	_	+
Sonthalia 2012	+	+	+	_	+
Lee 2013	+	?	+	_	+
Velez 2014	_	+	+	+	+

[Table/Fig-5]: Assessment of risk of bias.

STUDY DESIGN

Randomisation

Of the 35 RCTs, the randomisation methods used by some studies [3,7,9,20,21,28-30] was random number tables, by few others [10,14,15,18,36] was block randomisation, and an automated system of assigning randomisation numbers was followed by few other trials [19,22-25,27,31,34,35]. Passeron used draw lots method [17]. McCaughey used R-statistical package to achieve randomisation [33]. Rest of the RCTs have not mentioned the randomization method.

Allocation

Allocation concealment was stated in 18 studies [3,9,13-17,19-21,23,24,26,27,29,30,35,37]

Blinding

In 20 trials [3,4,6,14,17-19,21-26,27,29-33,35,37] patients and outcome assessors were both blinded, five trials [5,9,10,15,36] reported that only assessors were blind and one [28] that only patients were blind. In the other studies, both patients and outcome assessors were unblind or no clear information was provided.

Incomplete Outcome Data

In 11trials [5-8,12,21,22,31,32,35,37] all patients enrolled completed the study, in other 10 trials [4,9,16,20,23,26,28,29,34,36] the rate of drop-outs was less than 10%, in 5 trials [3,10,19,27,30] the rate of drop-outs was between 10% & 20% and one study [35] had more than 20% drop-outs and an another study [25] does not specify about drop-outs.

Six studies [14,15,17,18,24,33] performed intention-to-treat (ITT) analyses. Of these, except Yoke and Gorouhi, the rest enrolled only erosive oral lichen planus [14,15]. Number-needed-to-treat (NNT) analysis was performed by Velez et al., [37].

EFFECTS OF INTERVENTIONS

Active Intervention vs Placebo

Twelve trials compared an active intervention with placebo: cyclosporine [3], clobetasol & miconazole [19], curcuminoids as an adjunct to prednisone [18], pimecrolimus [17,24,33], aloe vera [21,30], hyaluronic acid [26], ignatia [25], lycopene [32] & MuGard [37]. There was no evidence of difference in mean pain score after treatment between active intervention & placebo in three trials [18,19,30]. A statistically significant reduction in mean pain score favouring the active intervention was seen in the remaining nine trials [3,17,21,24-26,32,33,37].

All the studies comparing an active treatment with placebo included clinical aspect among the outcomes considered. Few studies [3,17,21,24-26,33,37] found a statistically significant difference in clinical improvement favouring their respective active interventions when compared to placebo. No statistically significant clinical improvement in the intervention groups when compared to placebo was noted by few other studies [18,19,30]. Sawaarn has recorded the overall treatment response and not the clinical area [32].

Nine studies [3,17-19,21,24,30,33,37] comparing an active treatment with placebo included data on adverse effects among the outcomes considered. When present, adverse effects were more common in the treatment group compared with placebo group, but the difference was not statistically significant in any of the studies.

Steroid vs Steroid

Three trials compared the same steroid in different forms. The comparisons were: flucinoloneacetonide in an oral base 0.1% vs flucinoloneacetonide gel no.1 and the same orabase with flucinoloneacetonide gel no.2 [8], clobetasol (0.025%) in microspheres with clobetasol ointment (0.025%) [10], triamcinolone acetonide in mouth rinse vs intralesional triamcinolone acetonide injection [36]; two studies compared different steroids in different arms topical fluticasone propionate spray and betamethasone sodium phosphate mouthrinse [9]; betamethasone OMP and triamcinolone acetonide paste [20]; one trial [4] compared different steroids in the same arm (clobetasolorabase ointment and triamcinoloneacetonide ointment); one study [27] used the same steroid clobetasol ointment in different concentrations (0.05% vs 0.025%). Among these studies, [4,8,9,27,36] did not present any significant difference in pain reduction. However, lower pain scores in the group that used microsphere formulation [10] & better response in betamethasone group [20] were shown.

All the trials in this group, except Rodstrom, Malhotra and Lee adopted Thongprasom's clinical grading criteria [4,20,36]. Hegarty reported that fluticasone propionate spray was statistically significantly better than betamethasone sodium phosphate mouthrinse in reducing lesion surface area [9]. None of the remaining trials in this group found a difference between the steroids compared.

Significantly more adverse effects were reported in the clobetasol ointment group [4], fluticasone spray group [9], betamethasone OMP group [20], triamcinoloneacetonide mouth rinse group [36]. Campisi [10] reported similar frequency of adverse effects in both the formulations of clobetasol. Data on adverse effects was not available from Buajeeb [8]. Carbone noted no adverse effects in either group [27].

Steroids vs Calcineurin inhibitors

Eight studies compared the effects of a topical steroid (clobetasol or triamcinolone) with a topical calcineurin inhibitor (cyclosporin, tacrolimus or pimecrolimus) - triamcinolone and cyclosporine [5,14,16], triamcinolone and tacrolimus [13], triamcinolone and pimecrolimus [15] clobetasol and tacrolimus [22,23,35].

Pain was included among the outcomes considered by all but two studies [5,13]. All the trials in this group except two [22,35] reported VAS values for pain at the end of the study. Results favouring tacrolimus were seen in two studies [22,35]. Four studies [14-16,23] showed no difference between the interventions for the outcome of pain.

All the studies comparing steroid with a calcineurin inhibitor included clinical aspect among the outcomes considered, either area of ulceration, mean clinical scores in each group or number of participants showing clinical improvement per group. A statistically significant reduction in the mean area of ulceration was seen in the triamcinolone group [14]. Two studies [13,22] found a benefit favouring calcineurin inhibitor when compared to topical corticosteroid. Sieg, Thongprasom, Radfar, Gorouhi, Sonthalia found no statistically significant difference in the clinical response between steroid & calcineurin inhibitor [5,15,16,23,35].

Yoke and Thongprasom found a significantly greater frequency of adverse effects in the cyclosporin group [14,16]. Radfar has not clearly specified about the adverse effects [23]. The other trials in this group found no statistically significant difference in the frequency of adverse effects in each intervention group. None of the trials under this group reported clinical remission on follow up.

From these studies of 'head to head' comparisons there is no consistent evidence of a class effect of topical steroids compared to calcineurin inhibitors.

Other Treatment Comparisons

One study compared topical flucinoloneacetonide (0.1%) in an oral base with topical retinoic acid (0.05%) in an oral base [6] and found that both the pain scores & the clinical scores of lesions showed improvement in the flucinoloneacetonide group. Different concentrations of topical isotretinoin were compared [12] and the higher concentrations of the intervention were found to be more effective in reducing the symptoms as well as in clearing the lesions. Some studies: topical clobetasol compared with topical mesalazine [7]; intralesional injection of Bacillus Calmette- Guerin polysaccharide nucleic acid (BCG-PSN) compared with intralesional injection of triamcinolone acetonide [28]; thalidomide paste with dexamethasone paste [29]; topical triamcinolone with topical aloe vera [31]; amlexanox paste with dexamethasone paste [34] found no statistically significant differences in either pain reduction or clinical improvement between the two treatments.

DISCUSSION

In the present systematic review on medical management of OLP, we have included 35 RCTs. All the trials that were included here used different interventions, comparisons, dosages, vehicles, times of application and different ways of measuring the common outcomes such as pain and clinical symptoms.

There were 12 studies which compared a range of nine different active treatments with placebo. Not all the trials using steroids showed evidence that these treatments were better than placebo in reducing pain and the lesional size of OLP. The evidence that cyclosporin may be effective in reducing pain and clinical signs of OLP is weak as one study [3] is at unclear risk of bias. There was weak evidence from two trials [21,30] that aloe vera gel may be associated with a reduction in pain, but it was not possible to pool the pain data from these trials. Of the three trials of pimecrolimus showing evidence that this treatment is better than placebo in reducing pain and improving the clinical lesions of OLP, one was at unclear risk [17]; another had a very short period of follow up of 30 days [24] and yet another [33] had no post-treatment follow up. There was weak evidence from the trials using hyaluronic acid [26] and ignatia [25], at unclear and high risk of bias, respectively that these treatments may be effective in reducing pain and clinical signs of OLP. The study using lycopene [32] showed significant reduction in pain from OLP when compared to placebo, but did not record the clinical area, however, is at unclear risk. Velez saw significant reductions in all outcome measures in the MuGuard treated group [37]. But, several limitations of the trial [37] such as high risk of bias, short span of study, lack of head-to-head comparison with the frequently used steroids and calcineurin inhibitors in OLP management makes MuGuard use debatable.

Nine trials compared different steroid treatments. One study [10] showed microspheres and another trial [20] showed betamethasone to be efficient in reducing pain. Lesional surface area reduction favouring spray was seen in one trial [9]. However, all the three trials were at high risk. The remaining studies in this group showed no difference statistically.

There were eight trials that compared steroids with calcineurin inhibitors, each evaluating a different pair of intervention. Only two trials [22,35] favoured tacrolimus in terms of pain reduction. Of these two trials, one [35] is at high risk of bias and the results from the other [22] should be interpreted with caution as it is the only study with significant difference. In terms of clinical improvement, one trial [13] favoured the calcineurin inhibitor and the other [14] steroid, however, both at unclear risk of bias.

Seven trials comparing two active interventions (excluding steroids and calcineurin inhibitors) did not show evidence that any of these interventions may be effective in reducing pain and clinical signs of OLP, except for two trials [6,12]. However, these two trials were at high and unclear risk of bias respectively.

LIMITATION

Limitations of the several included RCTs such as small sample size, lack of consistent outcome measures employed to assess treatment efficacy, short treatment duration, absent or short follow up data, absence of quality-of-life questionnaire, publication bias make their results unreliable.

Overall, the evidence is not sufficiently robust to determine the effectiveness of any specific palliative treatment for symptomatic OLP. Even after including many more studies in the present systematic review when compared with the Cochrane review updates (Thongprasom 2011 and Cheng 2012), the conclusions of our study results are similar to that obtained by them.

Future studies of well-designed RCTs for the medical management of OLP unresponsive to first-line treatment with topical steroids and head-to-head comparison with treatments that are currently in use should be undertaken. The trials should also adopt standard parameters, long-term follow up, along with sufficient detailing of relapse rate and adverse effects.

CONCLUSION

Taking into consideration only RCTs, an attempt was made to set forth therapeutic indications, using evidence based medicine analysis. Though, topical corticosteroids and calcineurin inhibitors are the most common drugs used for treatment of symptomatic OLP,

from the trials included here, the evidence suggesting superiority of either in reducing pain and clinical signs of OLP are weak.

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