Expert Opinion

Topical immunomodulators for management of oral mucosal conditions, a systematic review; part I: calcineurin inhibitors

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Importance of the field: Topical immunomodulators have been used for the management of oral mucosal diseases. Topical immunomodulating preparations may have utility in local management of oral disease which is resistant to topical steroids and oral findings of an immunologic-mediated systemic disease with primary or persisting, oral mucosal involvement.

Areas covered in this review: This paper is the first part of a systematic review of topical immunomodulators for the management of various oral indications focused on calcineurin inhibitors. The literature search revealed that data are available for cyclosporine, tacrolimus and pimecrolimus. In addition to the review of scientific evidence, this paper presents the potential market, the mechanism of action, the competitive environment and future development options.

What the reader will gain: The reader will find weighted conclusions for the topical use of the calcineurin inhibitors in the management of oral diseases.

Take home message: Topical calcineurin inhibitors may be useful as a second-line treatment in several oral diseases, particularly oral lichen planus.

Keywords: calcineurin inhibitors, cyclosporine, evidence-based, mechanism, mucosal, oral, pimecrolimus, tacrolimus, topical

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1. Background

Oral mucosal diseases are common and variable. Due to the accessibility of the oral mucosa, topical treatment is practical and commonly used. When a mucosal condition has an immunologic pathogenesis, treatment with topical immunomudolators may be appropriate. Current clinical practice uses topical steroids applications as the first choice in topical therapy, but in the case of limited response or side effects, other immunomodulators may be considered [1,2]. The purpose of this review is to assess immunomodulating medications that have been studied for topical application in the management of oral mucosal conditions. In Part I, we review the calcineurin inhibitors and in Part II additional agents are reviewed.

1.1 Methods

In order to identify all existing topical calcineurin inhibitors, a literature search was conducted in PubMed from 1948 (as early as PubMed database allows) to April 2010. The search terms used were topical, oral, mouth, tongue, mouthwash, 'calcineurin inhibitor' and a list of known immunomodulators: cyclosporine, tacrolimus and pimecrolimus. The search was limited to human subjects and studies published in English in peer-reviewed journals which are ranked using an impact

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factor. Publication types included were meta-analyses, reviews, randomized controlled trials (RCT), nonrandomized studies, cohort studies, case studies and opinion papers. Publications presenting original data on topical calcineurin inhibitors for the treatment of oral mucosal diseases were reviewed. The meta-analyses and reviews were used to identify studies that should be added to the review, including studies of other immunomodulators. Non-English publications and animal studies were excluded. Non-systematic reviews are not reported separately.

Study descriptors such as type of study, blinding, presence of control group, scale validity and samples size were used to assign quality scores to the included literature. The development of recommendations was based on the findings using a well-recognized system for grading the recommendation [3]. Briefly, The Oxford University Center of Evidence Based Medicine (CEBM) 'Levels of Evidence' document sets out one approach to systematizing this process for different question types. In our review, the scale pertinent to 'therapy/prevention' was used. It defined the levels of evidence and the grades of recommendation. Three researchers extracted the data from the original papers that were retrieved.

2. Medical need

The potential utility of topical immunomodulating medications for immune-mediated oral mucosal conditions is significant as a number of local epithelial lesions, oral manifestations of immunologic diseases, and oral complications of systemic treatment that modifies the oral epithelium or oral immunology may be candidates for topical therapy. The conditions represent a wide variety of mucosal changes.

Topical therapies may allow increased concentration of medication for the management of local oral disease with limited or no systemic effects. Oral manifestations may be the primary site of symptoms or may persist despite systemic therapy that has effectively controlled signs and symptoms at other sites. Local applications may enhance local effects and yield improved control without the need to increase dose or frequency of systemic treatment. Topical calcineurin inhibitors are recognized as effective therapy for some indications, second only to topical steroids [4].

3. Existing treatment

The flowchart of studies included is tabulated according to the CEBM ranking (**Table 1**).

3.1 Cyclosporine

Cyclosporine A (CsA) was first used in the 1970s to prevent organ allograft rejection among transplant recipients and has been shown to dramatically improve the long-term survival of transplanted organs [5].

Topical CsA was assessed in the treatment of oral lichen planus (OLP) (**Table 2**) and graft-versus-host disease (GvHD) [6-26]. It was suggested for the treatment of oral pemphigus [27,28], oral aphthae [19], pemphigoid [28] and plasma cell mucositis [29]. One systematic review that included topical CsA for the treatment of OLP was identified [30].

3.1.1 Oral lichen planus

CsA was assessed in five RCTs for the treatment of OLP: one was a comparison to placebo [12] and four RCTs compared CsA to topical steroids (triamcinolone acetonide or clobetasol) [6-9]. Compared to placebo, CsA showed improvement in erythema, erosion, reticulation and pain in a portion of the patients [12]. However, the sample size in this study was small (eight patients in the CsA and eight in the control group). Of the four additional studies, a total of 100 patients were treated in the CsA arm compared to 104 treated with topical steroids. Variables to assess response to treatment varied; this included Thongprasom clinical scale, lesion size, Asian Lichen Planus Group Scale, patient's report of pain and other study-specific scales. In these studies, CsA was prepared to a concentration of 15 – 100 mg/ml and administered three times daily and patients were followed for 6 – 8 weeks. Two of the RCTs suggested comparable effect of CsA to topical steroids and two of the RCTs suggested topical steroids to be more effective than CsA [6-9]. In one of these later studies, although objective clinical improvement was better with clobetasol compared to cyclosporine, the patient's subjective description of symptomatic improvement with cyclosporine and clobetasol was similar [8].

In a nonrandomized controlled pilot trial, systemic sulodexide was compared to topical CsA. Intramuscular sulodexide (600 units) was administered followed by oral doses of sulodexide (250 units twice daily) for 1 month and oral CsA rinse (100 mg/ml three times daily for 3 min) was administered for 1 month. At 5 months follow-up, there was comparable pain relief for CsA and sulodexide; however, more rapid healing was noted with sulodexide [13]. An additional nonrandomized controlled study compared CsA (100 mg/ml, 5 ml, 5 min, once a day) to placebo for a period of 4 weeks. All experimental sites (in seven patients) exhibited enhanced healing and decreased pain scores whereas control sites (in seven patients) demonstrated minimal change [15]. A third nonrandomized controlled study compared CsA 16 mg of a bioadhesive gel (concentration unclear) three times a day to placebo during a 10 weeks course. Cyclosporine appeared to be very effective in 9 out of 10 patients in the treatment group whereas no effect was noticed in the 10 control patients [26].

There are nine additional case series reports describing CsA for the treatment of OLP comprising a total of 62 patients [10,14,16,17,19-23]. Treatment consisted of an oral rinse (100mg/ml) two to four times a day in six studies [10,16,17,19-21], an oral cream (5 mg/ml) four times a day in a single trial [22] and a topical hydrophilic formulation (100 mg/g formulation) [14]. Results were ambivalent. In a series of six patients, erosions and lesions cleared in two patients and marked improvement was observed in two [19].

Table 1. Schematic steps in the literature search and review.

		Cyclosporine	Tacrolimus	Pimecrolimus
Total publications retrieved at literature search		36	41	12
Publications about systemic treatment		-5	0	0
Case reports		-5	-20	-4
CEBM score for therapy/prevention				
1a	Systematic reviews (with homogeneity) of RCT	0	0	0
1b	RCT	5	4	4
2a	Systematic reviews (with homogeneity) of cohort studies	0	0	0
2b	Individual cohort study (including low quality RCT; e.g., < 80% follow-up)	0	0	0
2c	Outcomes research; ecological studies	0	0	0
3a	Systematic review (with homogeneity) of case-control studies	1*	1*	1*
3b	Individual case-control study	3	0	0
4	Case series (and poor quality cohort and case-control studies)	11	13	0
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	6	3	3

*Excluding Zakrzewska *et al.* [93] which does not refer to cyclosporine, tacrolimus or pimecrolimus.
CEBM: Center of Evidence Based Medicine; RCT: Randomized controlled trial.

However, overall improvement in disease severity was moderate (rated as 24% by patients) [10] and 50 – 100% of cases which reported in the remaining case series studies were unchanged or worsened [14,16,17,20-22].

One case series report focused on the gingival involvement of lichen planus in the form of desquamative gingivitis [23]. Six patients rinsed with 5 ml oral cyclosporine solution (100 mg/ml) once a day for 5 min. Five patients reported complete alleviation of gingival and mucosal discomfort within 2 – 4 weeks of commencing therapy, although five patients continued to have painful lesions of the tongue. In contrast to the symptomatic relief in the gingivae, signs of desquamative gingivitis remained and no patient had complete resolution of all involved areas.

Three case reports, describing a total of four patients, were published with successful results reported with topical CsA [18,24,25].

A systematic review that assessed topical cyclosporine was identified [30]. It concluded that there is little evidence that cyclosporine is more effective than steroids for the treatment of OLP and scarce evidence regarding the benefits of topical cyclosporine for the management of other immunologically-mediated oral mucosal disorders [30]. Additional reviews pointed out the inconsistent results of the studies [31-33].

3.1.2 GvHD

Two case series assessed the efficacy of CsA for the treatment of oral GvHD [10,11]. In the first report, 11 patients were instructed to rinse their mouths with 5 ml (100 mg/ml three times a day). At a mean follow-up time of 11 weeks, signs and symptoms improved by > 50% in 7 out of 11 patients [11]. In the second report, four patients were enrolled and used topical CsA in a bioadhesive base four times a day. When examined after 4 weeks of treatment, total ulcer area was reduced in 86% [10]. The difference between the response rate of OLP patients and GvHD patients to topical CsA treatment suggests that these two entities may show different responses.

3.1.3 Pemphigus and mucous membrane pemphigoid

One case series of three patients and one case report documented the response of pemphigus vulgaris to topical CsA [27,28]. Both reports used a total daily dose of 1500 mg as a mouth-rinse. Results were mixed in the case series and included exacerbation, partial healing and complete healing [28]. The case report showed that topical CsA successfully treated pemphigus vulgaris that had persisted for 23 years despite numerous previous local and systemic treatments [27].

Pemphigoid patients were reported to benefit from topical CsA [28]. In three patients, a dose of 1500 mg/d was used as a mouth-rinse. At 8 weeks follow-up, erosions and pain were significantly improved and erythema was moderately improved.

3.1.4 RAS

Eight patients with recurrent aphthous stomatitis (RAS) were treated with topical CsA (500 mg rinse, three times a day) [19]. At 8 weeks follow-up, four of eight patients reported smaller, less painful and fewer nascent ulcerations. Two of these four patients remained free of RAS after discontinuing CsA at 7 months follow-up, while four patients had no response.

3.1.5 Plasma cell mucositis

A patient with plasma cell mucositis was successfully treated with topical CsA concomitantly with systemic prednisolone [29]. For topical application, a swab soaked with 5 ml CsA solution was used for 15 min twice daily. In the second week of treatment, CsA use was reduced and was applied every alternate day.

Table 2. Cyclosporine: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation CsA (M/G/OB)	Dose CsA	Dose control	Study arm (no. of pts.)	Control arm (no. of pts.)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Adverse effects
Eisen *et al.* (1990) [12]	OLP	RCT	M	100 mg/ml, 5 ml, for 5 min, × 3/d	Placebo, 5 ml, for 5 min, × 3/d	8	8	Erythema Erosion Reticulation Pain	Y	
Thongprasom *et al.* (2007) [6]	OLP	RCT	M	100 mg/ml, × 3/d	Triamcinolone acetonide 0.1%, × 3/d	6	7	Thongprasom scale Lesion's size Asian lichen planus Group grade	Good as control	Transient burning sensation, gastrointestinal discomfort, breast tenderness, dizziness, itching, swelling lips and petechial hemorrhages
Yoke *et al.* (2006) [7]	OLP	RCT	M	100 mg/ml, × 3/d	Triamcinolone acetonide 0.1%, × 3/d	68	71	Erythema Reticulation Ulceration Pain Burning sensation	Good as control	Transient burning sensation, local swelling and itching of the lip lesion, gastrointestinal upsets
Conrotto *et al.* (2006) [8]	OLP	RCT	G*	CsA 1.5%, × 2/d	Clobetasole priopionate 0.025%, × 2/d	20	19	Thongprasom scale Pain	N‡	Dyspepsia
Sieg *et al.* (1995) [9]	OLP	RCT	M	100 mg/ml for 5 min, × 3/d	Triamcinolone acetonide 1 mg/g × 3/d	6	7	Reticulation Erosion Erythema	N	Precipitation of waxy particles during 'swishing' the oily CsA solution
Femiano *et al.* (2003) [13]	OLP	CT	M	100 mg/ml, 1 ml, for 3 min, × 3/d	Sulodexide 600 units IM and 250 units PO, × 2/d	10	10	Pain Healing time	Good as control	None
Harpenau *et al.* (1995) [15]	OLP	CT	M	100 mg/ml, 5 ml, for 5 min, × 1/d	Placebo, 5 ml, for 5 min, × 1/d	7	7	Surface involved Discomfort score Blood levels	Y	None
Gaeta *et al.* (1994) [26]	OLP	CT	G	16 mg gel, × 3/d	Placebo, × 3/d	10	10	Surface involved Histological and immunofluorescence response	Y	None

*Cyclosporine was dissolved in an adhesive medium mainly composed of hydroxyethyl cellulose gel. CsA volume: study-scoop.

‡Clobetasol more effective; however, symptomatic control is similar.

CsA: Cyclosporine A; CT: Controlled trial; G: Gel; M: Mouthwash; N: No; No.: Number; OB: Oral base; OLP: Oral lichen planus; pts: Patients; RCT: Randomized controlled trial; VAS: Visual analog scale; Y: Yes.

3.2 Tacrolimus

Tacrolimus was first isolated in 1984 from a Japanese soil fungus. It is an immunosuppressant used systemically for the prevention of organ transplant rejection [34]. Tacrolimus ointment has shown benefit in atopic dermatitis [35].

The use of tacrolimus in a topical formulation has been reported for the management of a number of immune-mediated disorders including: OLP (**Table 3**) [36-58], oral lichenoid reactions [38], oral manifestations of GvHD [59-64], pemphigoid [65,66], Crohn's disease [67], pemphigus [68,69], psoriasis [70], desquamative gingivitis [71] and pyostomatitis vegetans (**Table 3**) [72].

One systematic review of calcineurin inhibitors in oral medicine included topical tacrolimus for the treatment of OLP [30]. It was stated in the review that there were very limited data on the potential use of tacrolimus in other oral mucosal conditions.

3.2.1 OLP

In an RCT, 32 OLP patients were randomized to tacrolimus (0.1%) or clobetasol (0.05%) ointment treatment applied four times daily for 4 weeks. At the end of treatment, symptoms improved in both groups although symptom scores (pain severity, burning sensation, mucosal lesion extension) were lower in the tacrolimus compared to clobetasol group. Nine patients in the tacrolimus group experienced initial worsening of symptoms, which resolved in less than a week. No severe adverse events were reported in either group [53].

One RCT included 30 patients with symptomatic OLP [36]. A total of 15 patients were treated with tacrolimus ointment (0.1%) and 15 with clobetasol ointment (0.05%). Initially treatment was conducted four times a day, with gradually decreasing doses per day over a 6 week period. The mean lesion size was shown to be reduced by 82% in the tacrolimus group after 6 weeks and pain reduction measured by visual analog scale (VAS) decreased by 44%. The results did not differ statistically between groups.

In another RCT [37], tacrolimus ointment (0.1%) was compared to triamcinolone acetonide (0.1%) applied four times a day to treat symptomatic OLP in a total of 40 patients. Topical tacrolimus resulted in a significantly better therapeutic response than triamcinolone after 6 weeks of treatment by objective clinical measure. However, relapse occurred in both groups within 3 – 9 weeks of cessation of treatment in 72 and 78% of the patients, respectively. Some burning or stinging sensation was noted in erosive lesions for 10 – 30 min after application of the ointments.

Treatment of symptomatic OLP lesions with topical tacrolimus was reported in a number of case series [38-45,54,55].

In all but one of the reports, a local ointment was used, most commonly 0.1% and applied twice or thrice daily; in one study, a mouthwash was used. In one of the studies, tacrolimus ointment was prescribed to seven patients for 14 days with evaluation was done at day 28. OLP lesions decreased in size and pain decreased [38]. In another study, 21 of 23 patients reported symptomatic improvement within 6 weeks. Length of treatment differed and the longest was 43 months. In all, 6 patients remained asymptomatic after cessation of therapy while the other 15 (65%) patients required maintenance therapy to prevent relapses. High plasma levels of tacrolimus were seen in 1 patient and moderate levels in 11 patients. This study showed that the majority of patients required long-term therapy to remain in remission [40]. Fifty patients, refractory to corticosteroid treatment, were evaluated after 8 weeks of tacrolimus treatment. In all, 14% achieved complete resolution and 80% had a partial resolution. Moderate adverse effects occurred, with 16% of the patients reporting a burning sensation and 8% reporting taste change. Moderately elevated plasma levels of tacrolimus gradually decreased. The mean total treatment period was 19.8 months. Tacrolimus was shown to be an effective means of controlling the symptoms of erosive or ulcerative OLP, without serious side effects over the treatment period (mean of 19.8 months) [41]. In six patients, treated for 3 months, erosions changed from severe to mild as judged by lesion number and size and patient reported symptoms. Five of the six patients had undetectable tacrolimus plasma levels. It was concluded that tacrolimus is effective and well tolerated but tacrolimus plasma, levels should be monitored [43]. In 17 patients treated for 8 weeks, a mean decrease of 73% occurred in the area of ulceration and 54% reduction in Oral Health Impact Profile (OHIP 14) score. Mild adverse effects were burning sensation, tingling, slight nausea, mild headache and constipation. Thirteen of the seventeen patients had a relapse within 2 – 15 weeks after cessation of topical tacrolimus [44]. Thirty-seven patients were treated with 0.03 or 0.1% tacrolimus. Symptoms improved within 1 month; however, four or five of the nine patients who discontinued use experienced a flare of symptoms. Of the 37 patients, 28 continued treatment on a long time basis (mean 1.3 years; range 49 days – 2.7 years). Initial adverse effects of topical tacrolimus were burning and tingling sensations [39]. In one study, 13 patients participated and were given 0.03, 0.1 or 0.3% tacrolimus with 11 responding to treatment, and three with complete response [45]. In four patients with recalcitrant erosive OLP, 4 weeks of tacrolimus ointment treatment caused improvement in all patients. Cessation led to relapse within weeks [55]. Heat shock protein 70 levels in biopsies from OLP lesions in 11 patients were measured before and after 8 weeks of tacrolimus treatment with no significant changes found [54].

A mouthwash with tacrolimus (0.1 mg/100 ml in distilled water) was used in a case series four times daily for 6 months by 10 patients with chronic erosive OLP, refractory to other treatments. The lesions had been present with a mean duration of 3.6 years (6 months – 7 years) before tacrolimus treatment. Eight patients completed the study. Of these, one had no improvement and seven improved gradually within the 6 months, both in surface area of erosions and in reported pain. No serious side effects were noted and tacrolimus was not detected in plasma. By 6 months after end of therapy,

Table 3. Tacrolimus: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation tacrolimus	Dose tacrolimus	Dose control	Study arm (no. of pts.)	Control arm (no. of pts.)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Adverse effects
Corrocher *et al.* (2008) [53]	OLP	RCT	Ointment	0.1% × 4 times a day for 4 weeks	Clobetasol 0.05%	16	16	Lesion extension Pain severity Burning sensation	Y	56.3% tacrolimus pts. experienced initial worsened burning sensation first 2 days
Radfar *et al.* (2008) [36]	OLP	RCT	Ointment	0.1% × 4 times a day and decreasing number of doses for 6 weeks	Clobetasol 0.05%	15	15	Lesion size Pain (VAS)	Good as control	One tacrolimus pt. quit treatment because of burning sensation
Laeijendecker *et al.* (2006) [37]	OLP	RCT	Ointment	0.1% × 4 following for 6 weeks	Triamcinolone acetonide 0.1%	20	20	Clinical appearance	Y	Temporary burning or stinging sensation in 40% on tacrolimus and 15% on corticosteroid
Corrocher *et al.* (2006) [71]	DG	RCT	Ointment	0.1% × 0.1 time/day for 4 weeks	Clobetasol proprionate 0.5%	12	12	Clinical appearance	Y	50% of tacrolimus pts. had mild oral burning sensation. 50% of clobetasol pts. reported mild mouth dryness

CT: Controlled trial; DG: Desquamative gingivitis; N: No; No.: Number; OLP: Oral lichen planus; pts: Patients; RCT: Randomized controlled trial; VAS: Visual analog scale; Y: Yes.

all patients had relapsed and were placed on corticosteroids to which they responded well. It was concluded that a low concentration of tacrolimus oral rinse may result in effective palliation [42].

Eleven patients with symptomatic OLP, some of them refractory to corticosteroids, were described in case reports [46-52,56-58].

The patients were treated with tacrolimus (0.1% twice daily), which resulted in lesions that were resolved, decreased, or less symptomatic or asymptomatic during treatment. In one patient, the positive result remained several months after cessation of the drug. Two patients developed oral mucosal staining which disappeared within months after cessation of the drug. In one case, long time follow-up after cessation of the drug showed recurrent lesions once or twice per month but these were controlled after a single dose of tacrolimus [52]. All case reports described partial or complete remission. In most cases, a continuous low dose treatment was needed to maintain improvement. Two cases of suspected causal relationship between long term topical use of tacrolimus and the development of squamous cell carcinoma were reported [57,58].

A systematic review, published in 2009, assessed topical tacrolimus treatment for OLP [30]. It was concluded that current evidence suggests that topical tacrolimus may be of benefit (at least in the short term) in the treatment of OLP that has not responded to topical corticosteroids. Additional reviews support the potential future use of tacrolimus in patients resistant to topical corticosteroids [73-75].

3.2.2 Oral lichenoid reactions

In one of the case series assessing tacrolimus (0.1%) for OLP [38], three patients with oral lichenoid reactions were included. Treatment was continued for 14 days and evaluation at day 28. Lesions and related pain decreased to approximately a third of pretreatment levels.

3.2.3 GvHD

In a case series, three patients with erosive chronic GvHD of the oral cavity who received treatment with extracorporal photopheresis also received topical tacrolimus for 2 months. The addition of tacrolimus appeared to be beneficial when compared to a patient who did not receive tacrolimus [59].

Six children (6 – 16 years) with oral GvHD were treated twice daily with tacrolimus ointment (0.1%). Tacrolimus was applied to gauze which was left in place for 15 min. Complete remission of GvHD was achieved in two patients, good partial response in two and partial response in two patients. Systemic absorption occurred in four of six patients in this study as evidenced by plasma levels of up to 5.6 ng/ml [60].

In case reports [61-64], eight patients with chronic GvHD were treated with tacrolimus ointment (0.1%) twice or thrice a day for 2 – 3 months. The oral lesions improved in all cases within weeks. In one patient, who also received systemic tacrolimus, plasma levels increased dramatically when local treatment was added and decreased after cessation of systemic treatment and lowered local dose. The authors hypothesize that damage to the mucosal barrier may lead to increased absorption [62].

3.2.4 Mucous membrane pemphigoid

Two case reports examined tacrolimus ointment (0.1%) twice or thrice a day in three patients with oral pemphigoid. The oral lesions resolved to a great extent and did not reoccur after several months [65,66]. All three patients had received other medications to treat the condition with little improvement prior to use of tacrolimus.

3.2.5 Pemphigus

Topical tacrolimus ointment (0.1%) twice daily for 4 weeks was prescribed to a patient with recalcitrant labial pemphigus vulgaris persisting for 15 months. The lesion resolved with local tacrolimus in combination with mycophenolate mofetil (1 g) twice daily [68]. Tacrolimus was not associated with adverse reactions and there was no sign of systemic absorption. After 9 months of mycophenolate mofetil alone, systemic tacrolimus was added and remission was again achieved. One patient with paraneoplastic pemphigus, refractory to other treatments, was put on three 5-min oral rinses a day of a suspension of tacrolimus (0.03%) for 2 weeks at each relapse with good response [69].

3.2.6 Psoriasis

Improvement in psoriatic lip lesions was achieved by tacrolimus ointment (0.1%) twice daily applied for 2 weeks in two patients [70].

3.2.7 Crohn's disease

Eight patient children (5 – 18 years old) with Crohn's disease treated with topical tacrolimus (0.5 mg/g in orabase) twice daily resulted in promising results, with healing of the lesions in seven patients within 1 – 6 months [67]. The authors suggested that gradual cessation of the drug may be useful as two patients had rebound worsening after tacrolimus was reduced quickly.

3.2.8 Desquamative gingivitis

In an RCT including 24 patients with dequamative gingivitis, 12 patients were randomized to tacrolimus (0.1%) and 12 patients to clobetasol proprionate ointment (0.5%) applied once daily for 4 weeks [71]. In the tacrolimus group, remission of erythema and/or desquamation was achieved in 11 (91.7%) of 12 patients at 4 and 6 weeks, and at 8 weeks, 9 (75%) of the 12 patients remained in remission, while none of the patients in the clobetasol group achieved remission at any time point ($p < 0.001$) [71]. Tacrolimus plasma concentrations were undetectable. Six patients in both groups experienced adverse effects with mild oral burning in the tacrolimus group and mild mouth dryness in the clobetasol group.

3.2.9 *Pyostomatitis vegetans*

The oral lesions in a patient with ulcerative colitis and pyostomatitis vegetans improved with short term tacrolimus ointment (0.1%) applied twice a day. As the patient's colitis was controlled by other medication, no recurrence of stomatitis was seen [72].

3.3 Pimecrolimus

Pimecrolimus is a calcineurin inhibitor similar to cyclosporine and tacrolimus. Topical pimecrolimus may suppress disease activity in atopic dermatitis and psoriasis due to its anti-inflammatory activity [76]. The use of pimecrolimus in a topical formulation was reported on the treatment of OLP (**Table 4**) [76-83]. One systematic review of calcineurin inhibitors included topical pimecrolimus for the treatment of OLP [30], which identified very limited data on the potential use of pimecrolimus in other oral mucosal conditions.

3.3.1 *Oral lichen planus*

The efficacy, relative safety and tolerability of pimecrolimus cream (1%) in the treatment of erosive OLP were evaluated in an RCT with 20 patients. In the treatment group of 10 patients, pimecrolimus cream was applied twice daily to oral lesions for 4 weeks. The control group used a placebo cream. Photographs were analyzed for areas of ulceration, erythema and reticulation. Discomfort was scored using a VAS scale and blood samples were analyzed. The experimental group showed a statistically significant decrease in ulceration, erythema and VAS score. Blood levels were within the normal range [83].

Pimecrolimus cream (1%) was compared to the vehicle in an RCT of a total of 20 patients with erosive OLP [77]. The medications were applied twice daily for 30 days. Erosions cleared completely in seven of ten patients in the pimecrolimus group and in two of the ten patients in the vehicle group. Pain was significantly reduced in the pimecrolimus group compared to the vehicle group. A further 30 days of pimecrolimus application led to resolution in the three patients who did not respond to pimecrolimus the first 30 days. No severe adverse events were reported. In five patients, blood levels of pimecrolimus were detected, but remained below 4 ng/ml.

Pimecrolimus cream (1%) was compared to triamcinolone acetonide paste (0.1%) in a RCT [78]. Eighteen and seventeen patients respectively, completed the study. The medications were applied four times a day for 2 months. Evaluation of pain, quality of life by OHIP and objective clinical evaluation was conducted at 2 months. Both groups showed improvement in all measures with no significant differences between groups. Two patients in the pimecrolimus group felt a burning sensation early in treatment.

Further, pimecrolimus cream (1%) was compared to a vehicle in a RCT treating six patients per group twice daily for 4 weeks [82]. In the placebo group, mean score was 4.67 on day 0 versus 3.33 on day 28 ($p = 0.22$). In the pimecrolimus group, mean score was 6.83 on day 0 versus 3.33 on day 28 ($p = 0.04$). Blood levels of pimecrolimus were above a threshold, and mean value was 2.84 ng/ml (range 0 – 6.19 ng/ml). Pimecrolimus cream was well tolerated and only transient burning sensations were reported by some subjects. The patients in the pimecrolimus group, whose condition improved, had relapsed when assessed 1 month after treatment, suggesting prophylaxis should be considered. The finding of systemic levels of pimecrolimus necessitates a long-term study.

In six patients, described in four case reports, pimecrolimus was applied for 3 – 6 months for OLP [76,79-81]. In one case, the pimecrolimus treatment was preceded by tacrolimus treatment for 3 months. The oral lesions resolved in these cases.

A systematic review, published in 2009, assessing topical pimecrolimus treatment for OLP was identified [30]. It was concluded that topical pimecrolimus may be of benefit (at least in the short term) in the treatment of OLP that has not responded to topical corticosteroids. Additional reviews supported the potential future use of pimocrolimus in patients resistant to topical corticosteroids [73-75].

4. Market review

The indications that will be listed for each of the topical immunomudolators reviewed above reflect the market that may benefit from such treatment. OLP affects 0.1 – 2.2% of the population [84], RAS affects 0.89% of the population [85] and oral mucositis affects up to 100% of patients treated with head and neck radiotherapy [86]. Other immune-mediated mucosal lesions included above are less common.

5. Current research goals

This review focuses on evidence derived from trials with high-quality study design that includes most studies in patient OLP and fewer studies in oral cGvHD. Continuing research of currently available systemic medications for topical use and development of new molecular topical therapies are indicated. Development of improved vehicles to increase contact time, convenience and provide sustained release medications may increase utility of these approaches to mucosal diseases.

6. Scientific rationale

Each of the agents reviewed modulate the immune response as presented in the 'mechanism of action' section below. Some of the agents have additional mechanism of actions. However, this is beyond the scope of this review.

6.1 Mechanism of action

6.1.1 *Cyclosporine*

CsA is a lipophilic cyclic polypeptide derived from fungal extracts that selectively inhibits transcription of cytokines, including IL- 2 and has effects on T-cell lymphocyte function.

Table 4. Pimecrolimus: list of controlled studies.

Reference	Indication	Study design (RCT/CT)	Preparation pimecrolimus	Dose pimecrolimus	Dose control	Study arm (No. of pts)	Control arm (No. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Adverse effects
Swift *et al.* (2005) [83]	OLP	RCT	Cream	1% twice daily for 4 weeks	Vehicle	10	10	• Clinical appearance • Discomfort (VAS) • Blood values	Partial	One pt. reported slight burning sensation
Volz *et al.* (2008) [77]	OLP	RCT	Cream	1% twice daily for 30 days	Vehicle	10	10	• Clinical appearance • Pain (VAS)	Y	40% of pimecrolimus pts. had burning sensation after application. 50% had detectable, but low, pimecrolimus blood levels
Gorouhi *et al.* (2007) [78]	OLP	RCT	Cream	1% four times daily for 2 months	Triamcinolone acetonide 0.1%	18	17	• Clinical appearance • Pain (VAS) • OHIP	Good as control	10% pimecrolimus pts. had transient burning sensation during first week
Passeron *et al.* (2007) [82]	OLP	RCT	Cream	1% twice daily for 4 weeks	Vehicle	6	6	• Clinical appearance • Size • Pain (VAS)	Partial	30% pimecrolimus pts. had transient burning sensation the first day. Blood levels of pimecrolimus were detected in all 6 pts.

CT: Controlled trial; N: No; OHIP: Oral health impact profile; OLP: Oral lichen planus; RCT: Randomized controlled trial; pts: Patients; VAS: Visual analog scale; Y: Yes.

CsA binds cyclophilins (cytoplasmic proteins present in most cells), forming a complex that competitively binds to and inhibits calcineurin (a calcium- and calmodulin-dependent phosphatase) [5,87]. This inhibits translocation of a family of nuclear transcription factors (NF-AT). CsA exerts its immunosuppressive effects primarily by inhibiting T-helper cell activation and also by inhibiting the release of pro-inflammatory cytokines [88]. The result is reduced transcriptional activation of early cytokine genes for several pro-inflammatory cytokines, including IL-2, IL-3, IL-4, CD40 L, GM-CSF, TNF-a and IFN-γ [87]. CsA has no direct effects on differentiation or proliferation of B cells, but inhibits T cell-dependent B-cell responses and probably also inhibits T-suppressor and T-cytotoxic cells [89].

6.1.2 *Tacrolimus*

Tacrolimus is a calcineurin inhibitor immunosuppressant, which inhibits T-helper lymphocyte activation. Calcineurin is a calcium-dependant protein phosphatase responsible for immune response [34]. Tacrolimus inhibition of calcineurin, by binding to cytoplasmic FK 506-binding proteins, leads to inhibition of nuclear gene transcription of IL-2 and several other pro-inflammatory cytokines such as IL-4 and -5. Consequently, the activation and differentiation of inflammatory cells such as T-lymphocytes, eosinophils and neutrophils are suppressed [40,63,66].

6.1.3 *Pimecrolimus*

Pimecrolimus is an ascomycin macrolactam derivative, which is a calcineurin inhibitor that binds to macrophillin-12 and subsequently inhibits dephosphorylation of nuclear factor of activated T cells by calcineurin, thus, reducing T-cell cytokine production and inhibiting T-cell activation [77].

7. Competitive environment

Although a variety of topical immunomodulators have been studied, the first line of therapy for most inflammatory/immune related oral mucosal conditions are topical glucocorticoids [1,2,84].

The FDA launched a black box warning for topical tacrolimus pointing out a potential malignant association. Although caution has been raised based on dermatologic observations [90] in an animal model [91] as well as one possible case of oral cancer that have been reported in association with topical tacrolimus [57,58,92], a warning of potential malignant association is an important consideration in the competitive environment of non-calrineurin inhibitors. These findings may theoretically also be seen with other agents, although data are very limited at this time.

Additional drugs that are administered topically are reviewed in Part II, including azathioiprine, retinoids, tetracyclines, bacillus Calmette-Guerin polysaccharide nucleic acid, benzydamine, granulocyte CSF, GM-CSF and imiquimod (refer Part II).

Drugs in the research pipeline are potentially competitors. A search on the website of the US National Institute of Health clinical trials registry indicates several agents which are administered topically and affect the immune response (**Table 5**). These drugs were not reported in the medical literature at the time of this review.

8. Potential developmental issues

Topical application is impacted by drug contact time of the vehicle of delivery, substantivity of the medication by binding to oral surfaces and lipid solubility of the medication. Topical formulations that may be used include oral rinses, gels, creams, aerosols and lozenges. Topical therapy is impacted by taste, texture and viscosity of rinse applications, gels and creams by ability to apply locally, and lozenges by the presence of saliva to allow dissolution of the product. Additional factors include convenience of use, shelf life and product cost. All these parameters are of relevance during the developmental process.

Although the potential to increase local doses of topically active medications with limited or no systemic dosing is a reasonable goal, further confirmation in the development of topical preparations remain needed. Therefore, systemic adverse events and pharmacodynamic studies are of interest for newly developed topical preparations.

The majority of topical immunomodulating medications used are those approved for dermatologic use and for vaginal and upper airway delivery. However, some of the treatments that were studied as topical oral preparations were reported earlier as systemic treatment. Currently, calcineurin inhibitors are being used for oral topical application off-label. Future registration of these drugs for oral topical use will open the way for increased use.

9. Conclusions

9.1 Cyclosporine

- *OLP*: Topical CsA was demonstrated to be better than placebo (level of evidence 3b, grade of recommendation B). Topical CsA demonstrated to be non-inferior to triamcinolone (level of evidence 1b, grade of recommendation B), but less effective than clobetasol (level of evidence 2b, grade of recommendation B).
- *Oral GvHD*: Topical CsA was demonstrated to be effective for the treatment of oral GvHD; however, the study design and patient sample are insufficient to provide high level evidence (level of evidence 4, grade of recommendation C).
- *Pemphigus and pemphigoid*: Topical CsA was demonstrated to be effective in the treatment of these bullous diseases; however, the results were inconsistent (level of evidence 4, grade of recommendation D).
- *RAS*: Topical CsA was demonstrated as partially effective in treatment of RAS; however, study design

Table 5. Topical immunomodulating agents under clinical trials.

Intervention	Indication	Status	ClinicalTrials.gov Identifier
Sirolimus	Oral lichen planus	Recruiting	NCT01061853
Manuka honey	Radiotherapy induced mucositis	Recruiting	NCT00615420
Morphine	Oral mucositis	Recruiting	NCT00357942
Chamomilla tincture	Recurrent aphthous stomatitis	Recruiting	NCT01122147
Recombinant human EGF	Oral mucositis	Recruiting	NCT00845819 NCT01099891
Ibuprofen	Soft tissue injuries	Completed	NCT00567528
Thalidomide	Graft-versus-host disease stomatitis	Completed	NCT00075023
Hydroxychloroquine	Oral lichen planus	Completed	NCT00102557
Etanercept	Oral mucositis	Completed	NCT00031551
Curcumin	Chemotherapy-induced mucositis	Completed	NCT00475683
EN3285	Radiotherapy-induced mucositis	Terminated	NCT00574860

and sample size are insufficient to support routine use (level of evidence 4, grade of recommendation D).

- *Plasma cell mucositis*: Anecdotal case report suggests use. No recommendation is possible.

9.2 Tacrolimus

- *OLP*: Topical tacrolimus has shown promising but inconsistent results. Tacrolimus was as effective as, or more effective than, a local corticosteroid in three RCTs (level of evidence 2b, grade of recommendation C). Relapse occurred in a majority of the patients within weeks of cessation of therapy.
- *GvHD*: Topical tacrolimus appears beneficial in patients with oral GvHD in two small case series (level of evidence 4, grade of recommendation C).
- *Desquamative gingivitis*: Tacrolimus was more effective than clobetasol in treatment of desquamative gingivitis as shown in an RCT (level of evidence 2b, grade of recommendation C).
- *Crohn's disease*: Positive effects on oral manifestations reported in one case series. No recommendation is possible.
- *Pemphigoid, pemphigus, psoriasis and pyostomatitis vegetans*: Anecdotal case reports suggest use. No recommendation is possible.

9.3 Pimecrolimus

- OLP: Pimecrolimus was shown to significantly reduce symptoms in four RCTs compared to placebo, but not when compared to a local steroid (level of evidence 2b, grade of recommendation C). Further long-term RCT studies are needed.

10. Expert opinion

Topical immunomodulators have shown activity in oral mucosal immune-mediated diseases. First choice in topical therapy continues to be topical steroids. Evidence supporting use of topical immunomodulators is the strongest in management of oral lichen plauns and to a lesser extent in management of oral GvHD. Cyclosporin has been assessed in mucosal immune-mediated conditions mainly lichen planes and oral GvHD. Tacrolimus is the leading agent in the calcineurin inhibitors; new agents from the mTOR inhibitor family may have effect as topical agents on oral mucosal diseases. Future development of vehicles to increase ease of application and duration of contact time may result in increase compliance; effective management with low doses of medication and reduced potential systemic absorption are encouraged. The ultimate goal is to improve management of oral mucosal diseases with local therapy and enhance effect with no or decreased risk of systemic effects. Improved delivery of topical agents is anticipated to improve local effectiveness, reduce systemic exposure to the medication and have rapid action, while providing options for cost effective, topical therapy.

Declaration of interest

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