Expert Opinion

A systematic review of topical immunomodulators for management of oral mucosal conditions. Part II: miscellaneous agents

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Importance of the field: Topical immunomodulating preparations have utility in inflammatory/immune-mediated oral mucosal disease resistant to topical steroids, in immunologically mediated systemic disease with primary oral involvement or more severe lesions primarily involving the oral mucosa.

Areas covered in this review: This paper is the second part of a systematic review of a variety of topical immunomodulators for management of immune/inflammatory oral mucosal conditions. The literature search revealed studies of azathioprine, benzydamine, GM-CSF and G-CSF, tetracyclines, retinoids, imiquimod, amlexanox, sirolimus and bacillus Calmette-Guerin polysaccharide nucleic acid.

What the reader will gain: The reader will find weighted conclusions for the topical use of each of the immunomodulators reviewed in the management of these oral diseases.

Take home message: Topical immunomodulators may be useful as second line treatment in several oral diseases, particularly oral lichen planus and recurrent aphthous stomatitis. Benzydamine was found to be preventive in radiotherapy-induced mucositis; however, it is unclear if this outcome is related to its immunomodulating effects or other mechanisms of action. Topical application of tetracyclines and retinoic acid also shows potential anti-inflammatory actions.

Keywords: azathioprine, bacillus Calmette-Guerin polysaccharide nucleic acid, benzydamine, evidence-based, G-CSF, GM-CSF, imiquimod, mechanism, mucosal, oral, retinoids, tetracyclines, therapy, topical

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1. Background

This is the second half of a paper exploring topical immunomodulatory drugs for management of oral mucosal conditions published in this review series [1]. Oral mucosal conditions are accessible for surface topical treatment, and topical steroids are widely used. When the pathogenesis of the condition has an immunologic component, treatment with topical immunomodulators is relevant. The purpose of this review is to assess immunomodulating medications that have been studied for topical application to the oral mucosa. This review is focused on topical immunomodulators that are non-calcineurin inhibitors.

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1.1 Methods

In order to identify all existing topical non-calcineurin inhibitor immunomodulators, a literature search was conducted on Pubmed for data starting from the year 1948 (as early as Pubmed database allows) through April 2010. The search terms used were topical, oral, mouth, tongue, mouthwash and a list of known immunomodulators: azathioprine, mycophenolate mofetil, thalidomide, tetracycline, minocycline, benzydamine, dapsone, levamizole, albendazole, efalizumab, infliximab, GM-CSF, G-CSF, retinoic acid, sirolimus, griseofulvin and oxpentifyllin. Steroids and calcineurin inhibitors were excluded from this review. The search was limited to studies involving human subjects and published in English. Publication types included were meta-analyses, reviews, randomized controlled trials (RCTs), nonrandomized studies, cohort studies, case studies and opinion papers. The meta-analyses and reviews were used to identify studies that should be added to the review, including other immunomodulators.

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 (University of Oxford Center for Evidence Based Medicine [CEBM]) [2].

2. Medical need

Due to local oral access, the potential of topical immunomodulation of oral mucosal conditions including local epithelial lesions, oral manifestations of immunologic diseases and oral complications of systemic treatment that modifies the oral epithelium or oral immunology is recognized.

Topical therapies may allow increased concentration of medication for management of local oral disease with no or limited systemic effects. In some cases oral manifestations of systemic conditions may persist despite systemic therapy that has effectively controlled signs and symptoms at other sites. In these settings boosting local concentration with topical application may lead to improved control of the oral presentation without an increase in systemic treatment.

The potential indications for the topical immunomodulators reviewed here reflect the market that may benefit from such treatment. For example, oral lichen planus (OLP) affects 0.1 – 2.2% of the population [3], recurrent aphthous stomatitis affects 0.89% [4] and oral mucositis affects up to 100% of patients treated with head and neck radiotherapy [5]. Other immune mediated conditions are less common.

Since the indications that will be listed here are chronic in nature and may be resistant to treatment, new treatment options are desirable. Furthermore, local and systemic side effects may be associated with topical application of steroids or calcineurin inhibitors [6]. Therefore, attempts to develop new topical immunomodulators or to extend the indications for current immunomodulators continue.

3. Existing treatment

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

3.1 Azathioprine

Azathioprine (AZA) has been in use for half a century as an immunomodulator in organ and tissue transplantation and for the management of autoimmune disease. AZA has been used as a steroid sparing agent as well as a 'maintenance' drug used after initial control of severe systemic autoimmune diseases in combination with other immunosuppressive agents including cyclophosphamide [7].

Topical AZA was suggested for management of graft versus host disease (GvHD) [8,9], pemphigus vulgaris [8] and mucous membrane pemphigoid (MMP) [8], based upon case reports or case series. Recurrent aphthous stomatitis (RAS) is the only indication tested in an RCT (**Table 2**) [10].

3.1.1 Oral GvHD

A total of six patients with GvHD used topical AZA in management [8,9] (one patient was reported in both papers). The rinse was prepared by dissolving AZA in a 1% methylcellulose vehicle with cherry flavoring (5 mg/ml) and patients were instructed to rinse 5 ml of solution for over 1 min and to expectorate, 3 – 4 times/day. AZA gel was compounded in 3% methylcellulose base and applied directly to the site of the oral lesions [8,9]. Systemic therapy was continued unchanged throughout the treatment period, thus the topical applications represented an increase in local dosing. Patients were followed for a mean of 8 weeks. Mean estimated global improvement (a calculated magnitude of reduction of the sum of scores of the visual analogue scale (VAS) and the severity of erythema and ulceration) was 60% with ulcers, erythema and pain reduced by 58, 55.3 and 62.8%, respectively [8]. It is noteworthy that these patients were resistant to other management approaches in both reports [8,9] and that the positive response to AZA treatment was evident in several episodes of oral cGvHD in the same patient [9].

3.1.2 Pemphigus and MMP

Topical AZA preparations as described for GvHD were used in one patient with pemphigus and in one with MMP [8]. Both patients had failed to improve with topical steroids, or combined topical and systemic steroids. Patients were followed for 12 weeks. A study-specific scale named 'estimated global improvement' (see paragraph about AZA describing treatment in GvHD) showed improvement of 95 – 96%. The authors suggested that topical AZA can be used for management of oral immune-mediated inflammatory conditions, and that it can allow improved control of oral findings with lower systemic dosing for patients who are provided with systemic immunosuppressives.

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

	Azathioprine	Benzydamine	GM/G-CSF	Tetracyclines	Retinoids	Imiquimod	BCG-PSN	Amlexanox	Sirolimus
Total publications retrieved	12	14	12	13	12	1	1	9	1
Publications about systemic treatment	-7	0	0	2	2	0	0	0	0
Case reports	-2	0	-1	5	0	0	0	0	0
CEBM score for therapy/prevention									
1a Systematic reviews (with homogeneity) of RCT	0	0	0	0	0	0	0	0	0
1b RCT	0	11	5	3	6	0	1	4	0
2a Systematic reviews (with homogeneity) of cohort studies	0	0	0	0	0	0	0	0	0
2b Individual cohort study (including low quality RCT; e.g., < 80% follow-up)	1	0	0	1	2	0	0	3	0
2c Outcomes research; ecological studies	0	0	0	0	0	0	0	0	0
3a Systematic review (with homogeneity) of case-control studies	0	0	0	0	0	0	0	0	0
3b Individual case-control study	0	0	1	0	0	0	0	0	0
4 Case series (and poor quality cohort and case-control studies)	1	2	5	2	2	1	0	1	1
5 Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	1	1	0	0	0	0	0	1	0

BCG-PSN: Bacillus Calmette-Guerin - polysaccharide nucleic acid; CEBM: University of Oxford Center for Evidence Based Medicine; RCT: Randomized controlled trial.

Table 2. Azathioprine: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation AZA	Dose AZA	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Eggleston (1972) [10]	RAS	RCT, cross-over *	Pellets	0.5 mg, x 4 times/day	Placebo, 0.5 mg, x 4 times/day	26	26	• Frequency of ulcers • No. of days with no RAS • Mean change between no. of ulcers at the first and last days of treatment	N	• Less than 80% of patients were followed-up • 4 out of the 8 patients that withdrew did so because of sudden deterioration of the RAS

AZA: Azathioprine; RAS: Recurrent aphthous stomatitis; RCT: Randomized controlled trial.

3.1.3 RAS

One randomized cross-over study tested the effect of AZA in 18 patients (2 mg/day, pellets dissolved in the mouth, for 2 weeks) versus placebo [10]. No significant differences between the drug and the placebo in the mean number of ulcers, in the change in the number of ulcers between the first and the last day and in the number of ulcers during the investigation period were seen. Four of the eight patients that withdrew from the study did so due to sudden deterioration of the RAS simultaneously with the development of leukocytosis. Therefore, AZA at the dose tested was seen to be of no value for the treatment of RAS.

3.2 Benzydamine

Benzydamine hydrochloride (Bzd) is a nonsteroidal drug that has shown topical anti-inflammatory, analgesic, anesthetic and antimicrobial activities [11-14].

Topical Bzd has been reported to provide prophylaxis or treatment for three oral mucosal diseases: mucositis (**Table 3**) [15-24], RAS [25,26] and burning mouth syndrome (BMS) [27]. Many of these mucositis studies were RCTs (**Table 3**).

3.2.1 Oral mucositis

Effectiveness of Bzd for the management of oral mucositis was assessed mainly in patients undergoing radiotherapy for head and neck cancer [15,18,19,22-24]. In some of the studies adjuvant chemotherapy was also administered [16,17,21]. In one study some of the patients underwent chemotherapy for solid tumors and for leukemia; 17 out of 44 patients in this study underwent chemotherapy with concomitant total body irradiation [20].

The oral Bzd rinse was administered (15 ml, 0.15%), with rinse time ranging from 0.5 to 5 min, 2 – 8 times/day. In studies assessing radiation-induced mucositis, Bzd administration began upon initiation of radiotherapy and continued to the end of radiotherapy. In some of the studies, it was noted that if symptoms of burning occurred with use of the study rinses, the patient could dilute the rinse with water (1:1).

In the six RCTs focusing on radiation-induced mucositis, the control group was placebo [15,22-24], or chlorhexidine [18,19]. When Bzd was compared to placebo (total of 185 patients for Bzd versus 166 for placebo) a statistically significant reduction in mucositis severity [15,22], pain [23] and use of systemic analgesics was reported [22]. However, when compared to chlorhexidine in smaller studies (total of 20 patients for Bzd versus 19 for chlorhexidine) the results were not conclusive in one study [18], and Bzd did not provide increased symptomatic relief compared to chlorhexidine in another trial [19].

In the two RCTs Bzd and placebo rinse were evaluated in radio-chemotherapy induced mucositis [16,21]. These studies included a total of 49 patients for Bzd and 52 with placebo. The dosing protocols were similar to the studies assessing Bzd in radiation-induced mucositis. Both studies

Table 3. Benzydamine: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation Bzd	Dose Bzd	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Epstein (2001) [22]	Mucositis-RT	RCT	M	1.5 mg/ml, 15 ml, 2 min, × 4 – 8 times/day	Placebo, 2 min, × 4 – 8 times/day	84	88	Mucositis Pain	Y	
Kim (1986) [15]	Mucositis-RT	RCT	M	1.5 mg/ml, × 8 times/day	Placebo, × 8 times/day	37	30	Mucositis Pain Pain on swallowing Hyperemia	Y	
Epstein (1986) [23]	Mucositis-RT	RCT	M	1.5 mg/ml, 15 ml, 30 s, × 4 times/day	Placebo, 15 ml, 30 s, × 4 times/day	18	11	Pain Systemic analgesics needed Topical lidocain needed	Y	
Epstein (1989) [24]	Mucositis-RT	RCT	M	1.5 mg/ml, 15 ml, 30 s, × 4 times/day	Placebo, 15 ml, 30 s, × 4 times/day	25	18	Mucositis Pain	Y	
Kim-Fong Cheng (2006) [18]	Mucositis-RT	RCT	M	0.15%, 30 s	0.2% CHX, 30 s	7	7	Mucositis WHO scale Pain Dysphagia	Partial	Trend of a lessening of mucositis severity, pain and dysphagia
Samaranayake (1988) [19]	Mucositis-RT	RCT	M	0.15%, 15 ml, 30 s, ×2 times/day	0.2% CHX, 15 ml, 30 s, × 2 times/day	13	12	Mucositis, Pain Microbiological tests	Good as control	CHX acceptance is better than Bzd.; little difference in pain control, mucositis and oral flora
Prada (1985) [16]	Mucositis-RT-CT	RCT	M	0.15%, 15 ml, 5 min, × 6 times/day	Placebo, 15 ml, 5 min, × 6 times/day	10	10	Burning Pain Dysphagia Hyperemia Edema Epitheliolysis and necrosis	Y	No data about RT protocol
Kazemian (2009) [21]	Mucositis-RT-ChT	RCT	M	0.15%, 15 ml, 2 min, × 4 times/day	Placebo, 15 ml, 2 min, × 4 times/day	39	42	Mucositis RTOG scale	Y	
Prada (1987) [17]	Mucositis-RT-ChT	RCT	M	0.15%, 15 ml, 5 min, × 6 times/day	Placebo, 15 ml, 1 min, × 6 times/day	19	17	Pain Dysphagia Hyperemia Edema Epitheliolysis and necrosis	Y	Study population heterogenous (includes RT or CT or RT + CT)
Schubert (1987) [20]	Mucositis-ChT	RCT	M	0.15%, 15 ml, 1 min, × 5 – 12 times/day	Placebo, 15 ml, 1 min, 5 × 12 times/day	25	19	Mucositis Pain, report by patient Pain, report by observer	Partial	Only observer score for pain showed significant superiority for Bzd
Sardella (1999) [27]	BMS	RCT	M	0.15%, 1 min, × 3 times/day	Placebo, 1 min, × 3 times/day; no therapy	10	20	Burning sensation	N	Two control groups: 'placebo' and 'no therapy'

BMS: Burning mouth syndrome; ChT: Chemotherapy; CHX: Chlorhexidine; CT: Controlled trial; M: Mouthwash; RCT: Randomized controlled trial; RT: Radiotherapy; WHO: World Health Organization.

demonstrated significant reduction in mucositis severity, frequency and intensity of pain. Adjunctive chemotherapy was found to be a significant predisposing factor for mucositis in these patients [21], which supports assessing radiotherapy-induced mucositis separately from radio-chemotherapy induced mucositis. Another RCT including head and neck cancer patients examined the preventive effect of Bzd [17]. Generally, the study confirmed the preventive effect of Bzd on oral mucositis; however, due to the mixed study population receiving different cancer treatment (radiotherapy, intra-arterial chemotherapy or combinations of both) it is difficult to analyze separately the preventive effect of Bzd in radiotherapy-induced oral mucositis.

One RCT assessed topical Bzd for management of chemotherapy-induced mucositis [20]: 20 patients in the treatment arm versus 19 in the control arm. Although some of these patients were treated with concomitant total body irradiation, this radiation was not directed at the oral tissues. Subjects swished and held 15 ml of the study solution for 1 min every 2 h for a minimum of five doses per day [20]. The only significant improvement noted was in the Observer Global Rating while the Patient Global Rating was not significantly improved. This study suggests potential use of Bzd for prevention and management of chemotherapy-induced mucositis, although additional studies are needed.

3.2.2 *BMS*

An RCT involving patients with idiopathic BMS compared Bzd treatment (10 patients) to placebo (20 patients) [27]. Patients were instructed to rinse with Bzd (0.15%) for 1 min 3 times a day for 4 weeks. Nine patients in the Bzd group and 8 in the placebo group reported the topical treatment to be ineffective.

3.2.3 *RAS*

Bzd was studied in the treatment of minor RAS in two case series [25,26]. Both studies were comparative; however, they were not well-randomized [26], or well-controlled [25]. In a comparison of Bzd, chlorhexidine and placebo rinses, group analysis showed no statistically significant differences between the treatments in the size, number of ulcers, site frequency or pain severity [26]. However, 8 of 18 patients stated a preference for Bzd due to pain relief following rinsing [26]. In the second study, 29 patients used Bzd rinse (0.15% Bzd every 1.5 – 3 h) or Bzd as a spray (four – eight puffs every 1.5 – 3 h for adults and four puffs/1.5 – 3 h for child 6 – 12 years old) [25]. When patient's preferences for various topical therapies for RAS were analyzed, Bzd oral rinse attracted the largest proportion of 'very effective' reports attributed to pain relief, but was not the most often used product overall, presumably because of cost.

3.3 GM-CSF and G-CSF

GM-CSF is a glycoprotein that is produced by a variety of human cells that induces the growth of granulocytes, macrophages and eosinophils. G-CSF is a protein that acts primarily on the neutrophil lineage to stimulate the proliferation, differentiation and activation of committed progenitor cells and functionally active neutrophils [28].

Ten studies evaluated GM-CSF (**Table 4**) [29-38], and two tested G-CSF [39,40] for topical therapy of oral mucosal damage (**Table 4**). Oral mucositis was assessed in nine of these studies. Topical GM/G-CSF was studied for treatment of RAS and Behcet disease.

3.3.1 *Oral mucositis*

Topical GM-CSF for chemotherapy-induced mucositis was studied in three RCTs [31,32,36]. Each of these RCTs used a different placebo (methylcellulose [32], 0.1% albumin solution [36] or povidone-iodine antiseptic agent [31]). One RCT demonstrated that topical application of GM-CSF by mouthwash significantly abbreviated the duration and relieved symptoms of chemotherapy-induced mucositis and was superior to topical povidone-iodine [31]. However, two studies showed no beneficial effect for topical GM-CSF for prevention or treatment of chemotherapy-induced mucositis [32,36]. It should be noted that various concentrations were used and it was not possible to identify a GM-CSF concentration in which the therapeutic effect may be obtained. In addition to these RCTs, a cohort study of 24 patients added that GM-CSF mouthwash can significantly reduce severity, morbidity and duration of chemotherapy-induced oral mucositis [34].

A small RCT of G-CSF demonstrated reduction in incidence and course of methotrexate-induced mucositis and associated complications [40].

Topical GM-CSF was studied for the treatment of radiotherapy-induced mucositis in a comparative study using historical case-matched controls [35]. A total of 12 patients in the study group rinsed with 20 ml of a solution (300 mcg GM-CSF in 250 ml of water for 5 min). Patients repeated the same process for 1 h once a day. Of the 12 patients (75%) 9 using GM-CSF had oral ulcerations heal during radiotherapy, whereas mucositis progressed during radiotherapy in all patients in the control group. In addition, GM-CSF was reported to reduce pain, allow increased oral intake and reduce weight loss. A case report including two AIDS patients treated with radiotherapy for Kaposi sarcoma and paranasal sinus lymphoma supports this impression [37]. In contrast, an RCT enrolling patients treated with combined chemotherapy and radiotherapy demonstrated no superiority of GM-CSF when compared to treatment with mouthwash containing hydrocortisone and pantocain [30].

In a series of patients with radiotherapy-induced mucositis treated with GM-CSF a good response was reported in 14 out of 17 patients [38]. An additional case series evaluated prophylaxis and treatment of chemotherapy or radio-chemotherapy induced mucositis. The authors found GM-CSF effective, particularly as prophylaxis, based on a comparison of the prophylactic group to the treatment group while no true control was used in this study [29].

Table 4. GM/G-CSF: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation GM/G-CSF (M/G)	Dose GM/G-CSF	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Hejna (2001) [31]	Mucositis-ChT	RCT	M	400 mcg/250 ml, 25 ml, 3 min and repeat × 10/30 min, × 3 times/day	Povidone-iodine 4ml/125 ml, 3 min, × 6 times/day	15	16	Mucositis (NCI-CTC scale) Pain (WHO scale) Patient score (functional mucositis)	Y	GM-CSF (malgramostim)
van der Lelie (2001) [32]	Mucositis-ChT	RCT	G	300 mcg, 5 ml, × 2 times/day	Placebo, 5 ml, × 2 times/day	18	18	Mucositis (WHO scale) Pain Combined score for items related to mucositis	N	GM-CSF (malgramostim); after rinse solution was swallowed
Cartee (1995) [36]	Mucositis-ChT	RCT	M	0.01, 0.1, 1 and 10 mcg/ml, 15 ml, 2 min, × 4 times/day	Placebo, 15 ml, 2 min, × 4 times/day	9,9,9,9	9	Mucositis (CALGB scale)	N	GM-CSF (malgramostim); 4 concentrations of GM-CSF; no dose-response
Rovirosa (1998) [35]	Mucositis-RT	CT	M	300 mcg/250 cc, 20 ml, 5 min, repeatedly within 1 h, × 1 times/day	No therapy	12	12	Mucositis (WHO scale) Pain	Y	GM-CSF (malgramostim); historical control
Sprinzl (2001) [30]	Mucositis-RT-ChT	RCT	M	400 mcg/250 ml, repeatedly within 1 h, × 1 times/day	Pentocaine, hydrocortisone, cional kreussler and bepanthen solution, 250 ml	17	18	Mucositis (WHO scale) Pain	N	GM-CSF (malgramostim); after rinse solution was swallowed
Karthaus (1998) [40]	Mucositis-ChT	RCT	M	120 mcg/0.4 ml, 1 min, × 4 times/day	Placebo, 0.4 ml, 1 min, × 4 times/day	16	16	WHO mucositis study specific scale Pain Hospitalization duration	Y	G-CSF, marginal significant reduction in mucositis score, significant reduction in hospitalization days

BMS: Burning mouth syndrome; ChT: Chemotherapy; CT: Controlled trial; G: Gel; M: Mouthwash; NCI-CTC: National cancer institute, toxic criteria; RCT: Randomized controlled trial; RT: Radiotherapy; WHO: World Health Organization.

It should be noted that in some of the studies, patients were instructed to swallow the solution after oral rinse, and in these cases a systemic effect may supplement the topical effect [29,30,32,38].

3.3.2 RAS

One case series reported using GM-CSF for the treatment of RAS in HIV patients [33]. Three patients were treated with 400 mcg GM-CSF (in 200 ml of 5% glucose), divided into three doses, rinsed for 20 min thrice a day. From the first application, all patients showed significant improvement of their lesions and amelioration of pain, and lesions resolved in a few days. The patients did not show relapse of RAS during a follow-up that ranged between 4 and 18 months, suggesting carryover effect or low recurrence rate in these patients.

3.3.3 Behcet disease

A case series of patients treated with topical G-CSF for oral ulcers in patients with Behcet disease was reported [39]. G-CSF decreased mean healing time and pain, however, benefits did not continue following initial treatment.

3.4 Tetracyclines

Since first described by Duggar over 60 years ago [41], tetracyclines are extensively used for treatment of a variety of gram-positive bacterial infections and infections due to intracellular chlamydiae, mycoplasmas, rickettsiae and protozoan parasites [42]. Moreover, treatment with tetracyclines have demonstrated beneficial effect on controlling noninfectious cutaneous diseases such as bullous pemphigoid [43], cicatricial pemphigoid [44] and linear IgA disease [45].

The topical efficacy of tetracycline and its derivatives was assessed in RCTs only in RAS (**Table 5**) [46-49]. A few case reports have reported the beneficial effect of topical tetracycline on white sponge nevus (WSN) [50-54]. There are anecdotal reports of the clinical improvement of symptoms associated with erosive OLP [55] and cicatricial pemphigoid [56].

3.4.1 RAS

Three RCTs examined the effect of tetracycline and derivatives upon RAS, two were placebo controlled and one compared the efficacy of tetracycline and minocycline. A combined topical-systemic double-blind trial on the efficacy of tetracycline in controlling symptoms associated with RAS was conducted [46]. A total of 25 RAS patients were randomized for treatment with tetracycline solution (5 ml of 5% swish and swallow) or placebo. A significant reduction in duration, size and pain was seen in the tetracycline group compared with placebo. The effect of topical minocycline, a semisynthetic tetracycline, for the management of RAS was demonstrated in two randomized, double-blind, cross-over studies. The first study demonstrated the superiority of minocycline suspension (0.2%, 5 ml for ≥ 1 min, 4 times a day) over placebo in reduction of the severity and duration of pain due to RAS [47]. The study included 33 patients who completed the study protocol, 18 patients in the minocycline group and 15 in the placebo group (and a subset of 7 patients in whom cross-over was completed). In the second study 17 patients with a high frequency of RAS were randomly allocated to a topical therapy with minocycline (0.2%) or tetracycline aqueous solution (0.25%) applied 4 times a day. Minocycline rinses resulted in significantly improved pain control, by reducing the severity and duration of pain compared to tetracycline rinse [48]. Another RCT studying tetracycline for the treatment of RAS was reported, however, this study included only 7 patients with no statistical analysis, and, therefore, provided little insight in treatment of RAS [49].

3.4.2 WSN

A few case reports have reported the beneficial effect of topical tetracycline (0.25% suspension) on WSN [50-54]. WSN symptoms were dramatically improved in four patients, and in two patients a single application daily was sufficient to control the symptoms [50]. The number of daily applications in the other two was not reported. In a case-report WSN resolved following a single application of tetracycline solution [51]. Improvement in WSN was shown following twice daily use of tetracycline mouthwash for 3 months and remission for 4 months [52]. The same author then reported four cases of WSN treated with complete response in two patients and with partial response in two, with tetracycline rinses twice daily for 15 – 90 days [53]. After 1 year recurrence was reported in one patient. Clinical improvement of symptoms associated with WSN was reported in a 12-year-old girl after 3 weeks of tetracycline 0.25% mouthwash twice daily [54].

3.4.3 OLP

A significant improvement in the symptoms of erosive OLP was reported in one patient with topical tetracycline solution (0.25%; rinse 3 times per day and hold 2 – 4 min) [55]. Symptomatic improvement was reported as soon as 1 week after the initiation of tetracycline treatment. After 6 weeks of topical tetracycline, erosive lesions had resolved and re-epithelization was observed, although white lichenoid changes remained.

3.4.4 Pemphigus and pemphigoid

Topical tetracycline was found to be effective in a single case of oral MMP [56]. The rinse was compounded with 250 mg in 5 – 10 ml of water (2.5 – 5%), and used 4 times a day for 5 min. Within weeks a considerable improvement was reported.

3.5 Retinoids

Vitamin A is required in the normal pathway of epithelial cell differentiation [57]. Retinoids are a family of drugs that are closely related to vitamin A. Retinoids have been used in medicine for over 50 years, primarily due to their ability to regulate epithelial cell growth. In addition,

Table 5. Tetracyclines: list of controlled studies.

Reference	Indication	Study design (RCT/CT)	Preparation tetracyclines (M/G/OB)	Dose tetracyclines	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Graykowski (1978) [46]	RAS	RCT	M	Tetracycline 5%	Placebo	113 ulcers	224 ulcers	Location Number Size Duration Pain	Y	Swish and swallow
Gorsky (2008) [47]	RAS	RCT	M	Minocycline 0.2%	Placebo	18	15	Pain	Y	
Gorsky (2007) [48]	RAS	RCT	M	Tetracycline 0.25% vs minocycline 0.2%		17	17	Pain	Minocycline more effective than tetracycline	

CT: Controlled trial; M: Mouthwash; RAS: Recurrent aphthous stomatitis; RCT: Randomized controlled trial.

retinoids are believed to act as immunomodulators and as anti-inflammatory medications [58].

Topical retinoids have been evaluated in the management of OLP [59-64]. There are three RCTs [65-67] and one open trial [68] regarding the use in oral leukoplakia, and one case series of use for chronic hyperplastic candidiasis (**Table 6**) [69].

3.5.1 Oral lichen planus

Five RCTs have assessed retinoids in OLP [59-63]. In addition, effectiveness was reported in a case series of seven patients [64].

The efficacy of tretinoin in an adhesive base (0.1%) was compared with placebo (23 and 15 patients, respectively) [59]. In the tretinoin-treated group, 71% of the atrophic-erosive lesions improved while 29% improved with the vehicle ($p < 0.05$). Reticular-plaque lesions improved in 74% of those using tretinoin and in 15% with the vehicle ($p < 001$).

The efficacy of isotretinoin was studied in a cross-over study where isotretinoin gel (0.1%) was applied twice daily for 8 weeks on 20 patients with OLP [60]. Six of the patients were given placebo for 8 weeks followed by cross-over to the active treatment for 8 weeks. Patients treated with the isotretinoin gel displayed significantly greater improvement than patients receiving the placebo. Patients who were treated initially with placebo showed statistically significant improvement after cross-over.

Isotretinoin (0.1%) was evaluated in an RCT in 20 patients with OLP [61]. Patients were instructed to use the isotretinoin gel or placebo topically 3 times a day for 4 months. At the end of 4 months, patients who had been given the placebo gel were provided the active medication for 4 months. Of the ten patients given isotretinoin gel, all showed improvement with four achieving almost complete healing. The patients given placebo showed virtually no change, but when switched to isotretinoin, all showed improvement, with complete resolution in six cases.

The efficacy of retinoic acid in an oral base (0.05%) was compared with fluocinolone acetonide in an oral base (0.1%) for treatment of OLP [62]. A total of 33 patients were randomly assigned to treatment 4 times a day. After 4 weeks of treatment, 18 patients receiving fluocinolone acetonide improved significantly, whereas 15 receiving retinoic acid showed only minor improvement ($p = 0.01$). They concluded that fluocinolone acetonide reduced the severity of OLP more rapidly than retinoic acid.

The effectiveness of different concentrations of topical isotretinoin (0.05 and 0.18%) was assessed in 70 patients with OLP [63]. The results were evaluated clinically and histologically. Significant improvement was noted among 26 patients using 0.18% concentration compared with only 9 patients using the lower concentration ($p < 0.01$).

Beneficial effects of topical vitamin A (0.1%; applied twice daily) in a small cohort of seven patients were reported [64]. Five of seven patients showed dramatic improvement of symptoms in < 7 days.

Table 6. Retinoids: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation retinoids (G/OB)	Dose retinoids	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Sloberg (1979) [59]	OLP	CT	OB	Tretinoin 0.1%	Placebo	23	15	Size of erosions Pain	Y	
Giustina (1986) [60]	OLP	RCT	G	Isotretinoin 0.1%	Placebo	14	6	Pain	Y	Refers to the first part of the study
Piattelli (2007) [61]	OLP	CT	G	Isotretinoin 0.1%	Placebo	10	10	Clinical appearance	Y	Refers to the first part of the study
Buajeeb (1997) [62]	OLP	RCT	OB	Retinoic acid 0.05%	Fluocinolone acetonide 0.1%	15	18	Clinical appearance Pain	Partial	
Scardina (2006) [63]	OLP	RCT	G	Isotretinoin 0.18 vs 0.05%		35	35	Clinical appearance Pain	0.18% was better than 0.05%	Refers to the first part of the study
Piattelli (1999) [65]	Leukoplakia	RCT	G	Isotretinoin 0.1%	Placebo	5	5	Size Histology bcl-2 immunostaining	Y	Refers to the first part of the study
Tete (1999) [66]	Leukoplakia	RCT	G	Isotretinoin 0.1%	Placebo	8	7	Size Histology bcl-2 immunostaining	Y	Refers to the first part of the study
Scardina (2006) [67]	Leukoplakia	RCT	G	Isotretinoin 0.18 vs 0.05%		20	20	Size Clinical appearance Histology	0.18% was better than 0.05%	Refers to the first part of the study

CT: Controlled trial; G: Gel; OB: Oral base; OLP: Oral lichen planus; RCT: Randomized controlled trial.

3.5.2 *Leukoplakia*

Two small RCTs evaluating the efficacy of topical retinoids in oral leukoplakia were identified [65,66].

In a double-blind study 10 patients with oral leukoplakia were treated with topical isotretinoin gel (0.1%) or placebo 3 times a day for 4 months [65]. Patients who had received the placebo were then provided active medication for an additional 4 months and 1 patient was lost to follow-up. All patients treated with the isotretinoin showed a significant improvement of the oral lesions and in one case the lesion resolved. In the patients receiving only the placebo, the size of the lesions remained the same. A similar study in 15 patients with oral leukoplakia was performed [66]; 1 patient was lost to follow-up. The lesions totally resolved in 3 patients and significantly improved in 11.

One RCT compared two concentrations of topical retinoids for oral leukoplakia [67]. In this study 40 oral leukoplakia patients were randomly treated with isotretinoin at 0.05 or 0.18% concentrations. Patients treated with the higher concentration demonstrated significantly better clinical and histological outcomes compared with patients treated with the lower concentration.

The use of topical tretinoin gel (0.05%) 4 times a day was evaluated for the treatment of oral leukoplakia in 26 patients [68]. After a mean follow-up period of 23 months, ~ 27% of the patients had a complete clinical remission. Recurrence of leukoplakia was observed in ~ 40% of patients in whom complete clinical remission occurred if topical applications were discontinued. When the pre- and post-treatment biopsies from 10 of the patients were evaluated, no change in the mean histologic grade (between mild and moderate dysplasia) was noted; however, reduction in the histologic grade was noted in 3 of these patients (30%). The authors concluded that the use of topical vitamin A acid showed a limited effect in controlling dysplasia in oral leukoplakia.

3.5.3 *Chronic hyperplastic candidiasis*

Six patients with nystatin resistant chronic hyperplastic candidiasis were treated with isotretinoin (0.18%) twice a day for a month [69]. The study stated a control group was employed; however, there is no description of this group. Clinical and histological examinations were used to diagnose chronic hyperplastic candidiasis. According to the authors after 1 month of isotretinoin treatment, five of the six patients were negative for candida.

3.6 Imiquimod

Imiquimod is 1-[2-methylpropyl]-1H-imidazo[4,5-c]quinolin-4-amine. Topical imiquimod is a US FDA-approved treatment for external genital warts, actinic keratoses and superficial basal cell carcinomas. Imiquimod has been demonstrated to be useful in the treatment of a number of conditions beyond the FDA-approved indications, mostly neoplastic and infectious but also fibrotic and some degenerative conditions [70].

Imiquimod was reported for few oral indications compared to its use in dermatology.

3.6.1 *Focal epithelial hyperplasia*

Imiquimod cream (5%) was studied in three children with focal epithelial hyperplasia [71]. Diagnosis was based on clinical presentation. Treatment was ended successfully with no serious side effects. In two of the cases, herpes reactivated in an oral surface outside the field of topical treatment. No recurrence was observed during the 1-year follow-up period.

3.7 Bacillus Calmette-Guerin-polysaccharide nucleic acid

Bacillus Calmette-Guerin (BCG) had been widely applied to prevent tuberculosis, enhance immune responses and inhibit neoplasia. However, there were some adverse effects, including red swelling at the injection site and fever. Therefore, a derivative of BCG was generated by removing the protein components of BCG and extracting from BCG the polysaccharide nucleic acid ingredient, the bacillus Calmette-Guerin-polysaccharide nucleic acid (BCG-PSN) [72].

BCG-PSN was studied for the treatment of OLP (**Table 7**).

3.7.1 *OLP*

Refractory OLP patients were randomly assigned to intralesional injection of 0.5 ml BCG-PSN every other day (31 patients) or intralesional injection of 10 mg triamcinolone acetonide (TA, 40 mg/ml) (25 patients) every week for 2 weeks [72]. After 2-week treatment, 87.1% of BCG-PSN treated patients and 88% of TA-treated patients healed. There were no statistical differences between the two groups in erosive areas and pain scores. Thus the study has demonstrated that the intralesional BCG-PSN injection achieved as good clinical effects in the treatment of erosive OLP lesions as TA. It was seen that 3 of 31 BCG-PSN-treated patients and 2 of the 25 TA-treated patients experienced swelling and burning sensations at the injection site. There were no statistical differences in the occurrence of adverse reactions and 3 months recurrence rate between the two groups.

3.8 Amlexanox

Amlexanox has been studied for the treatment of RAS (**Table 8**).

3.8.1 *RAS*

There are four RCTs assessing amlexanox for RAS [73-76]. Three of these RCTs compared amlexanox to placebo [73,75,76] and one compared amlexanox to topical clobetasol [74]. The concentration of amlexanox in these studies was 2 or 5%. It was applied as adhesive pellicles containing 2 mg amlexanox or oral paste, 4 times daily [74-76] or as tablets [73]. Patients were followed for 5 – 6 days. All comparisons to placebo showed amlexanox to be superior in reducing ulcer size and alleviating pain, with statistically significant results in 2 out of 3 RCTs [73,75]. Comparison to topical clobetasol demonstrated no significant differences were found between the two groups [74].

Two additional RCTs are available in the literature, however, they are of lower quality and do not mention the number of patients in each group [77,78].

Table 7. BCG-PSN: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation BCG-PSN	Dose BCG-PSN	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Xiong (2009) [72]	OLP	RCT	IL	0.5 ml, x 6/course	Triamcinolone acetonide 40 mg/ml, 10 mg, x 2/course	31	25	Erosions Pain	Y	

CT: Controlled trial; IL: Intralesional injection; OLP: Oral lichen planus; RCT: Randomized controlled trial.

A cohort of 679 patients treated with topical 5% amlexanox paste and 79 patients treated with topical 1% amlexanox paste participated in several studies documenting safety and pharmacokinetics results [79]. No significant irritation or sensitization was noted. Average maximal concentration of amlexanox in blood after application of 100 mg of 5% amlexanox past was 120 ng/ml at 2.4 h after application. The half-life for elimination was 3.5 h and there was no evidence of accumulation after multiple applications.

Another comparative study assessed the preferred timing for topical treatment: treatment at the onset of prodromal symptoms or treatment at ulceration [80]. It was found that treatment with amlexanox at the onset of prodromal RAS symptoms can prevent progression to ulcer development and significantly reduce symptoms if ulcers do develop. A reduction in the mean maximum ulcer size and the mean maximum pain scores subjectively was reported when amlexanox was provided at the prodrome compared with the scores recorded at the no-treatment run-in period.

3.9 Sirolimus

Sirolimus has been studied for the treatment of oral lichen planus.

3.9.1 Oral lichen planus

The topical efficacy of sirolimus was studied in a small open-label trial [81]. Seven patients with erosive oral lichen planus applied 1 mg/ml of sirolimus solution (1 mg/ml) on to oral erosive lesions twice a day for 3 months. One patient dropped out of the study because of the burning sensation upon the application of the sirolimus. At 3 months, 4 patients had complete remission and the other 2 patients had partial remission.

3.10 Miscellaneous agents: mofetil mycofenolate, thalidomide, dapsone, levamizole, albendazole, oxpentifyllin, infliximab, efalizumab and griseofulvin

While we anticipate that mofetil mycofenolate (MMF), thalidomide, dapsone, levamizole, albendazole, oxpentifyllin, infliximab, efalizumab and griseofulvin may have local oral effects with topical application, we did not identify studies assessing the use of these topical immunomodulators for management of oral mucosal disease.

4. Current research goals

This paper provides a review of evidence yielded from trials with high-quality study-design using the methodology of the Oxford University Center for Evidence Based Medicine. Future trials are needed to define algorithms for best options in topical immunosuppressive and anti-inflammatory treatment. Development of improved topical vehicles to enhance local topical therapies is needed.

Table 8. Amlexanox: list of controlled studies.

Ref.	Indication	Study design (RCT/CT)	Preparation amlexanox	Dose amlexanox	Dose control	Study arm (no. of pts)	Control arm (no. of pts)	Parameter evaluated	Effective (Y/N/partial/ good as control)	Comments
Meng (2009) [73]	RAS	RCT	Oral adhesive pellicle	5%, × 4 times/day	Placebo, × 4 times/day	108	105	Ulcer size Ulcer pain	Y	
Rodríguez (2007) [74]	RAS	RCT	Oral paste	5%	Clobetasol propionate, 0.05%	48	48	Ulcer size Ulcer pain	Good as control	Number of applications of either medicine by the study participants was not evaluated
Liu (2006) [75]	RAS	RCT	Oral adhesive tablets	5%, × 4 times/day	Placebo, × 4 times/day	104	108	Pain scale Size change Degree of erythema and exudation Efficacy index	Y	
Murray (2006) [76]	RAS	RCT	Oral patch	2 mg/Oradisc (= 2% amlexanox), × 4 times/day	Placebo	26	26	Ulcer development Ulcer size Erythema scores Thermographic area Pain elicited	N	
Greer (1993) [77]	RAS	RCT	Oral paste	5%, × 2 times/day	Placebo			Pain Erythema Size	Y	A total of 32 patients. Assumingly, 16 patients in each group; no mention of how many patients were lost to follow up
Khandwala (1997 p220) [79]	RAS	RCT	Oral paste	5%, × 4 times/day	Placebo or no-treatment			Ulcer size Ulcer pain	Y	A total of 1335 patients; exact number of control patients not mentioned
Murray (2005) [80]	RAS	RCT	Oral paste	5%, × 4 times/day	5%, × 4 times/day	At prodorma: 17	At ulceration: 29	Ulcer presence Extent of ulcer, Pain level	Y	Study included a comparison of parameters to the no-treatment run-in period.

CT: Controlled trial; IL: Intralesional injection; RAS: Recurrent oral stomatitis; RCT: Randomized controlled trial.

5. Scientific rationale

Each of the agents reviewed modify the immune response.

5.1 Mechanisms of action

5.1.1 AZA

AZA is inactive as administered and is converted to the purine antagonists 6-mercaptopurine (6-MP) and 6-thioinosinic acid. Although 6-MP is the major active metabolite, additional metabolites may also be active. AZA inhibits cellular immunity by reducing the numbers of T-cells, B-cells and natural killer cells, suppresses autoantibody formation and inhibits prostaglandin synthesis [7].

5.1.2 Bzd

The mechanism by which benzydamine reduces radiation induced mucosal toxicity may lie in its ability to suppress selected pro-inflammatory cytokine production [22]. Bzd has been shown to be an effective inhibitor of TNF-a production, which may explain its anti-inflammatory effects [82-84].

5.1.3 GM/G-CSF

GM-CSF causes differentiation and proliferation of granulocyte/macrophage progenitor hematopoietic cells and regulates the survival and function of several mature cell lineages (e.g., neutrophils, macrophages and dendritic cells). In addition, GM-CSF functions as an inflammatory mediator, acting on a number of different cells types and modulating antigen-presenting cell function [28]. G-CSF induces the release of neutrophils from the bone marrow and enhances the phagocytic capacity, generation of superoxide anions and bacterial killing by these cells [28].

5.1.4 Tetracyclines

Tetracycline reversibly inhibits bacterial protein synthesis by binding to the ribosomal complex, preventing the association of aminoacyl-tRNA with the bacterial ribosome [42]. However, their immunomodulatory and anti-inflammatory effects are believed to derive from other characteristics of these drugs. Both laboratory and clinical studies have investigated the anti-inflammatory properties of tetracyclines. The immunomodulatory effect of tetracycline may be due to its ability to suppress T-lymphocytes and neutrophils, leading to reduction of tissue destruction attributed to activity of these cells [47,85]. Tetracyclines may also reduce the production of cytokines involved in inflammation and epithelial damage such as IL-2, IFN-γ and TNF-α [86,87]. In addition to their anti-inflammatory effect, they inhibit MMPs that play an important role in the remodeling of the connective tissue. MMPs that break down fibrillar collagens are known as collagenases (MMP-1, MMP-8, MMP-13) and those that can affect basement membrane collagen are known as gelatinases (MMP-2, MMP-9). Tetracycline and its analogues can inhibit both collagenases and gelatinases [88].

5.1.5 Retinoids

The mechanisms of retinoid action are not completely understood, however, it is well known that retinoids induce apoptosis, leading to normal maturation of dividing cells, and suppress carcinogenesis [57]. Their biologic effects are mediated and regulated by nuclear hormone receptors and cytosolic binding proteins. The receptors are classified as: the retinoic acid receptors (RARs) and retinoid X receptors (RXRs) and they induce the expression or down-regulation of target genes in a ligand-dependent manner [89].

The *in vivo* and *in vitro* anti-inflammatory activity of retinoids is believed to be related to their ability to significantly inhibit oxygen free radicals release from PMNs and to inhibit chemotaxis of PMNs [58]. Retinoids are also associated with inhibition of the lipoxygenase pathways and inhibition of leukotriene production [58].

5.1.6 Imiquimod

Imiquimod triggers cytokine production, which enhances the ability of antigen presenting cells (APCs) to present viral or tumor antigens to reactive T lymphocytes, and amplifies type 1 helper T cell (T(H) 1)-mediated immune responses [70]. The cellular receptors for imiquimod and its analogues are toll-like receptors (TLR) 7 and 8. These two receptors are part of a larger family of TLRs that are critical components of innate immunity, which has evolved to detect dangerous bacterial, viral, fungal, and parasitic infections [70].

5.1.7 BCG-PSN

Most data available are related to BCG, showing regulation of cell mediated immunologic responses. This cell regulation is obtained by the direct regulation of the maturity and differentiation of CD4 and CD8 T lymphocytes and induces the secretion of IFN-c from Th1 lymphocytes [72]. When peripheral blood mononuclear cells of OLP patients were stimulated with BCG-PSN, secretion of IFN-c increased and it was thought that BCG-PSN regulates T lymphocytes [72].

Some of the agents have additional mechanisms of action. However, this is beyond the scope of this review. One such exceptional case was included in this review (burning mouth syndrome treated with benzydamine) because no specific pathogenesis is recognized for burning mouth syndrome and the immunomodulating effect of benzydamine may be an added value to its analgesic/anesthetic effect.

5.1.8 Amlexanox

Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-(1)benzopyrano-(2,3-b)-pyridine-3-carboxylic acid, a topical anti-inflammatory and anti-allergic drug [90].

5.1.9 Sirolimus

Sirolimus or rapamycin is an immunosuppressant drug used to prevent the rejection of transplanted organs. By inhibition of the mammalian target rapamycin (mTOR) pathway sirolimus inhibits the response to interleukin-2 and there by block the activation of T- and B-cells [91].

6. Competitive environment

Although a large variety of topical immunomodulators have been studied, the first line of therapy in most of the inflammatory/immune conditions discussed in this review is topical glucocorticoids. Topical steroids have an extensive pool of evidence supporting their efficacy, safety and side-effect profile.

With studies reporting several calcineurin and non-calcineurin inhibitors to be effective and with no severe adverse events, cost of the medication and convenience of administration becomes meaningful. However, there are no comparative trials of the various agents to confirm enhanced effectiveness of specific agents other than placebo or topical steroids. Ease of use and improved outcomes may be seen with the development of new vehicles of delivery of topical medications that may increase contact time and tissue penetration (see 'potential developmental issues' in this article).

The FDA launched a black box warning for topical tacrolimus pointing at its malignant potential. Although this caution is based on dermatologic observations and two circumstantial case-reports [92,93], such a warning is an important consideration in the competitive environment of non-calcineurin inhibitors. These findings may theoretically also be seen with other agents, although data are lacking.

The variety of topical agents tested for immune-mediated oral mucosal diseases leaves the clinician with uncertainty as to what is the preferred second and third line of treatment.

As inflammatory/immuno-mediated disease is a relatively broad subject including various oral mucosal conditions, it is difficult to cluster all diagnoses into one management flowchart. The clinician should consider the specific diagnosis, the adverse event of each agent, the kind of preparation and the compliance of the patient when in need for selecting a second line treatment. In addition, resistance for topical treatments raises the dilemma regarding the appropriate point in which systemic treatment should be employed.

7. Potential developmental issues

Topical application is impacted by drug contact time of the vehicle of delivery, substantivity by binding to oral surfaces and lipid solubility of the medication. Topical formulations that may be used include oral rinses, gels, creams, aerosols, tablets, lozenges and adhesive patches. Topical therapy is impacted by taste, texture and viscosity of rinse applications, and by ability to apply locally. Tablets/lozenges are also impacted by the presence of saliva to allow dissolution of the product. All these parameters are relevant during the developmental process and in clinical application.

Although the potential to increase local doses of topically active medications with limited or no systemic dosing appears desirable, this issue needs to be confirmed in the development of the topical preparations. Therefore, systemic adverse events and pharmacodynamic studies are of interest for newly developed topical preparations.

The majority of topical immunomodulating medications currently used are those approved for dermatologic use and for vaginal and upper airway delivery. However, some of the treatments that were studied as topical preparations were reported earlier as systemic treatment. Except for two (Bzd and retinoids), the vast majority of agents reported in the literature are used for oral topical application off-label. Future trials and registration of these drugs for oral topical use will pave the way for their increased use.

8. Conclusion

8.1 AZA

- *GvHD*: Topical AZA was demonstrated to be effective for the treatment of oral GvHD when combined with systemic immunosuppressive treatment; however, study-design and patient-sample are insufficient to provide high level evidence (Level of Evidence 4, Grade of Recommendation C).
- *Pemphigus & MMP*: Topical AZA has demonstrated inconsistent findings in the treatment of these bullous diseases; (Level of Evidence 4, Grade of Recommendation D).
- *RAS*: Topical AZA is no better than placebo (Level of Evidence 2b, Grade of Recommendation B).

8.2 Bzd

- *Oral mucositis*: Topical Bzd was demonstrated to be more effective than placebo in radiation-induced mucositis (Level of Evidence 2b, Grade of Recommendation A). This conclusion may also be valid in radiochemotherapy induced mucositis. For chemotherapy-induced mucositis the information is limited (Level of Evidence 2b, Grade of Recommendation D).
- *BMS*: Topical Bzd is not recommended for treatment of BMS. However, since this conclusion is based on one RCT with only 10 patients with BMS, the grade of recommendation is relatively low (Level of Evidence 1b, Grade of Recommendation B).
- *RAS*: Topical Bzd was not demonstrated to be effective for the treatment of the lesions of RAS, however, there appears to be a positive effect upon associated pain. This conclusion is based on only one comparative study, therefore, the level of recommendation is relatively low (Level of Evidence 1b, Grade of Recommendation B).

8.3 GM/G-CSF

- *Mucositis*: Although several RCTs are available, study results are not consistent regarding utility of GM-CSF in chemotherapy-induced mucositis (Level of Evidence 2b, Grade of Recommendation D). For topical G-CSF there is less evidence-based data; however, some benefit in the treatment of chemotherapy-induced mucositis has been shown (Level of Evidence 2b, Grade of

Recommendation B). GM-CSF has not been thoroughly evaluated for the treatment of radiotherapy-induced mucositis, and, therefore, the evidence is limited (Level of Evidence 2b, Grade of Recommendation B). In patients with mucositis induced by a combination of radiation and chemotherapy results were positive for GM-CSF (Level of Evidence 1b, Grade of Recommendation B).

- *RAS*: Little information is available about the effectiveness of GM-CSF in RAS (Level of Evidence 4, Grade of Recommendation C).
- *Behcet disease*: Little information is available for use of GM-CSF in RAS (Level of Evidence 4, Grade of Recommendation C).

8.4 Tetracyclines

- *RAS*: Combined topical-systemic tetracycline treatment was found to be more effective than placebo in one RCT (Level of Evidence 1b, Grade of Recommendation B). Topical minocycline was found to be more effective than placebo in one RCT (Level of Evidence 1b, Grade of Recommendation B) and demonstrated better clinical results compared with topical tetracycline (Level of Evidence 1b, Grade of Recommendation B). Therefore, topical minocycline may be more effective for RAS.
- *WSN*: Limited case reports showed dramatic improvement of WSN with short-term use of tetracycline rinses (Level of Evidence 4, Grade of Recommendation C). Although no RCTs are available, the consistent results together with the absence of side effects support the clinical use of tetracycline in symptomatic WSN patients.
- *Lichen planus*: Only one anecdotal case report was identified (Level of Evidence 5, Grade of Recommendation D). No recommendation could be given.
- *Pemphigus and MMP*: Only one anecdotal case report was identified (Level of Evidence 5, Grade of Recommendation D). No recommendation could be given.

8.5 Retinoids

- *Oral Lichen planus*: Topical retinoids were found to be more effective than placebo (Level of Evidence 1b, Grade of Recommendation A). Topical isotretinoin was found to be more effective in the concentration of 0.18 than 0.05% (Level of Evidence 1b, Grade of Recommendation B).
- *Leukoplakia*: Topical retinoids may have a beneficial effect upon oral leukoplakia based upon clinical outcomes (Level of Evidence 2b, Grade of Recommendation B).
- *Chronic hyperplastic candidiasis*: One anecdotal report described a beneficial effect of retinoid application in nystatin resistant lesions (Level of Evidence 4, Grade of Recommendation D).

8.6 Imiquimod

- *Focal epithelial hyperplasia*: There is insufficient evidence to support its use for this indication.

8.7 BCG-PSN

- *Oral lichen planus*: BCG-PSN may have a beneficial effect in OLP patients similar to that of topical triamcinolone acetonide (Level of Evidence 2b, Grade of Recommendation C).

8.8 Amlexanox

- *RAS*: Amlexanox may have a beneficial effect in RAS compared to placebo, similar to that of topical clobetasol propionate (Level of Evidence 2b, Grade of Recommendation A).

8.9 Sirolimus

- *Oral lichen planus*: There is insufficient evidence to support the use for this indication.

9. Expert opinion

Clinical trials have shown that topical immunomodulating agents are effective when applied to oral mucosa. Studies with a number of agents have shown that effective therapy can be achieved without significant systemic absorption, thereby avoiding systemic effects of the agent used. While the standard of care for topical therapy and typically the first choice in local management of oral inflammatory conditions are topical steroids, a number of other choices for topical care are available. Topical steroids may promote secondary oral candidiasis and may be absorbed systemically. Topical immunomodulators have shown activity in oral mucosal immune-mediated diseases. In addition to CsA and calcinuerin inhibitors (reviewed in Part I), a number of miscellaneous agents have been shown to be effective in topical therapy. AZA has been assessed as a single agent and in combination with systemic agents with GvHD. Benzydamine has been shown to be effective in prevention of mucosal ulceration in radiation therapy with and without cancer chemotherapy, but limited study has been conducted in chemotherapy. Benzydamine has been shown in RAS to provide symptomatic relief. Pain relief has been reported in a number of conditions. Hematopoietic growth factors have shown conflicting results in initial studies, although there have been conflicting outcomes and cost of product use has been very limited. Tetracyclines have been shown as effective in prevention and management of mucosal ulceration and inflammatory conditions, without risk of immunosuppression, and are used at a low dose likely affecting inflammatory mediators, rather than antimicrobial effects. Topical retinoids have shown benefit in producing anti-inflammatory effects and may have a role in treatment of oral leuoplakia. Risk of secondary infection and elevation of blood glucose that may occur with steroids are not anticipated with retinoids and other immunomodulators.

The potential utility of topical approaches for oral mucosal lesions has been shown, and further controlled studies are indicated. Improved vehicles increasing contact time for oropharyngeal therapy may further enhance effect and convenience of treatment with reduced risk for drug-drug interactions and reduced systemic effects. Future development of vehicles to increase ease of application and duration of contact time may result in increased compliance; more effective management with low doses of medication and reduced potential systemic absorption is encouraged. Multicenter studies are required in management of oral mucosal disease in order to provide adequate sample size in many of the oral conditions described in the studies to date.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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