

Journal section: *Medically compromised patients in Dentistry*
 Publication Types: *Review*

doi:10.4317/medoral.20968
<http://dx.doi.org/doi:10.4317/medoral.20968>

Management of oral Graft versus Host Disease with topical agents: A systematic review

Rui Albuquerque ¹, Zahid Khan ¹, Ana Poveda ¹, Jonathan Higham ¹, Andrea Richards ¹, Luis Monteiro ², Enric Jané-Salas ³, José Lopez-Lopez ³, Saman Warnakulasuriya ⁴

¹ Oral Medicine Department, Birmingham Dental Hospital/School of Dentistry, University of Birmingham, Birmingham B4 6NN, United Kingdom

² Medicine and Oral Surgery Department, Institute of Research and Advanced Training in Health Sciences and Technologies (IINFACETS), Higher Institute of Health Sciences (ISCS-N), CESPU, 4585-116 Paredes, Portugal

³ Oral Medicine Department. Dental School, University of Barcelona. Pavelló de Govern, 2^a planta, Av. Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain. Oral Health and Masticatory System Group (Bellvitge Biomedical Research Institute) IDIBELL, L'Hospitalet de Llobregat, Barcelona 08907, Spain

⁴ Department of Oral Medicine, King's College London Dental Institute, WHO Collaborating Centre for Oral cancer/Precancer, Bessemer Road, London SE5 9RS, UK

Correspondence:

Oral Medicine Department
 Birmingham Dental Hospital/School of Dentistry
 University of Birmingham
 Birmingham B4 6NN, UK
 R.P.P.D.Albuquerque@bham.ac.uk

Albuquerque R, Khan Z, Poveda A, Higham J, Richards A, Monteiro L, Jané-Salas E, Lopez-Lopez J, Warnakulasuriya S. Management of oral Graft versus Host Disease with topical agents: A systematic review. *Med Oral Patol Oral Cir Bucal*. 2016 Jan 1;21 (1):e72-81.
<http://www.medicinaoral.com/medoralfree01/v21i1/medoralv21i1p72.pdf>

Received: 28/07/2015
 Accepted: 19/08/2015

Article Number: 20968 <http://www.medicinaoral.com/>
 © Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN: 1698-6946
 eMail: medicina@medicinaoral.com

Indexed in:

Science Citation Index Expanded
 Journal Citation Reports
 Index Medicus, MEDLINE, PubMed
 Scopus, Embase and Emcare
 Indíce Médico Español

Abstract

Background: Oral Graft-versus-Host Disease (oGVHD) is a common complication of haematopoietic stem cell transplantation. Choosing the right topical application to be used intra orally can be a challenge. Consequently, the aim of this work is to review the effectiveness and safety of topical agents currently used in the management of the inflammatory mucosal lesions encountered in oGVHD.

Material and Methods: We carried out electronic searches of publications up to May 2015 of the databases Pubmed, National Library of Medicine's Medline, Embase and the Cochrane Central Register of Controlled Clinical trials to identify potentially relevant studies (keywords: "oral", "graft", "versus", "host", "disease" and "treatment"). The main inclusion criterion was the reported use of a topical agent which was not intentionally swallowed when used for the treatment of oGVHD. A 3-point grading system, described by the Swedish Council on Technology Assessment in Health Care and the Centre for Reviews and Dissemination, University of York, was used to rate the methodological quality of the papers.

Results: From the 902 entries identified in the search, 7 studies qualifying for inclusion were analysed. Overall, there is limited evidence with regards to the effectiveness of topical steroids for oGVHD. However, the studies showed some effect of Budesonide alone and when combined with dexamethasone. Topical tacrolimus also appears to have some effect and clobetasol propionate mouthwash had a significantly better clinical response than dexamethasone mouthwash in treating oGVHD.

Conclusions: As the number of clinical trials conducted is limited, there is little evidence to support the use of topical therapies to treat the inflammatory mucosal lesions found in oGVHD. High quality randomised control trials are needed in order to measure the effectiveness of any topical application for the treatment of the inflammatory mucosal lesions found in oGVHD.

Key words: *Oral, graft versus host disease, topical, therapy.*

Introduction

Graft versus host disease (GVHD) is caused by alloreactive donor T cells, which recognise and target host tissues in immunocompromised recipients (1). It is a common post transplant complication which affects up to half of all haematopoietic stem cell transplant (HSCT) patients (2). The 2005 National Institute of Health (NIH) Consensus Conference first proposed new criteria for the diagnosis of GVHD and scoring the severity of chronic GVHD (cGVHD). In 2014, revisions were made to address areas of controversy or confusion, such as the overlap GVHD subcategory and the distinction between active disease and past tissue damage (3).

Patients with cGVHD may suffer from severe morbidity, usually involving the skin, mouth, eyes, GI tract and liver but other systems such as the lungs, joints and genitourinary tract may also be involved (4). The oral cavity is the second most commonly involved organ system, after skin involvement (4). Oral GVHD (oGVHD) can present as generalised mucosal erythema, erosions, ulcerations, white striae or papules resembling oral lichen planus, and the transplanted patient can also develop oral mucocoeles (4-6). Patients may also complain of xerostomia and pain (5). The use of pre-HSCT chemoradiotherapy conditioning, post-HSCT medications or infections can result in changes in the oral mucosa such as oral mucositis and/or result in oGVHD causing difficulties for clinicians in differentiating between symptoms related to cGVHD and other side effects of therapy (5). Oral GVHD can be managed with systemic therapy, or topical treatment alone or in combination in order to achieve pain control and provide local palliation (2). Systemic immunosuppression can usually control the oral lesions of cGVHD but patients may require the use of opiates for the control of their pain symptoms (2). Clinically, oGVHD develops during reduction of systemically administered immunosuppressants after HSCT. The use of topical agents to control inflammation in oGVHD might allow lower doses or faster reduction in the dose of systemically administered immunosuppressants thereby helping to reduce the side effects of systemic therapy (2). We believe a review of the currently reported clinical studies of topical therapies used for the management of the inflammatory mucosal lesions found in oGVHD is advantageous for clinicians in secondary care, to establish the effectiveness of these therapies in the management of this condition. Therefore, the aim of this work

is to review the clinical effectiveness of topical interventions for oGVHD and to prepare a clinical guideline for the management of oGVHD or to identify possible gaps in the evidence in order to carry out future research.

Material and Methods

A systematic review to unify and summarise the published literature on topical agents used for the treatment of the inflammatory mucosal lesions found in oGVHD was undertaken. An electronic search of the databases Pubmed, National Library of Medicine's Medline, Embase, Cochrane Central Register of controlled clinical trials and Scopus up to May 2015 was undertaken, to identify potentially relevant studies. The key words used in the search included "oral", "graft", "versus", "host", "disease" and "treatment".

The inclusion criteria also included randomised controlled clinical trials, cohort studies (retrospective and prospective), and case-controlled studies published in English, Portuguese and Spanish languages for the treatment of oGVHD presenting as inflammatory mucosal conditions such as lichen planus and lichenoid disorders, that included clear descriptions of the topical therapy used and its method of application. The search was limited to human studies. The final criterion was the use of a topical application which was not intentionally swallowed and was used for the treatment of oGVHD. All articles which did not fit into the criteria were excluded, including reviews, author debates, letters to the editor or studies in which it was not clear whether the treatment was for oGVHD or for mucositis secondary to chemotherapy/radiotherapy.

The full papers and abstracts identified through the search engines were independently reviewed by the authors (RA, LM, ZK, AP, JH, SW, AR, EJS & JLL) for inclusion in this systematic review. If there was insufficient information provided in the abstract or if there was a disagreement between the reviewers, the authors reviewed the full text before reaching an agreement through discussion.

Data extraction was then completed in duplicate by the same independent reviewers. The following data were collected: study characteristics (year, design, number enrolled/analysed, patient median/mean age, intervention, length of follow-up and outcome). The search strategy and the flow diagram of article selection are shown in figure 1.

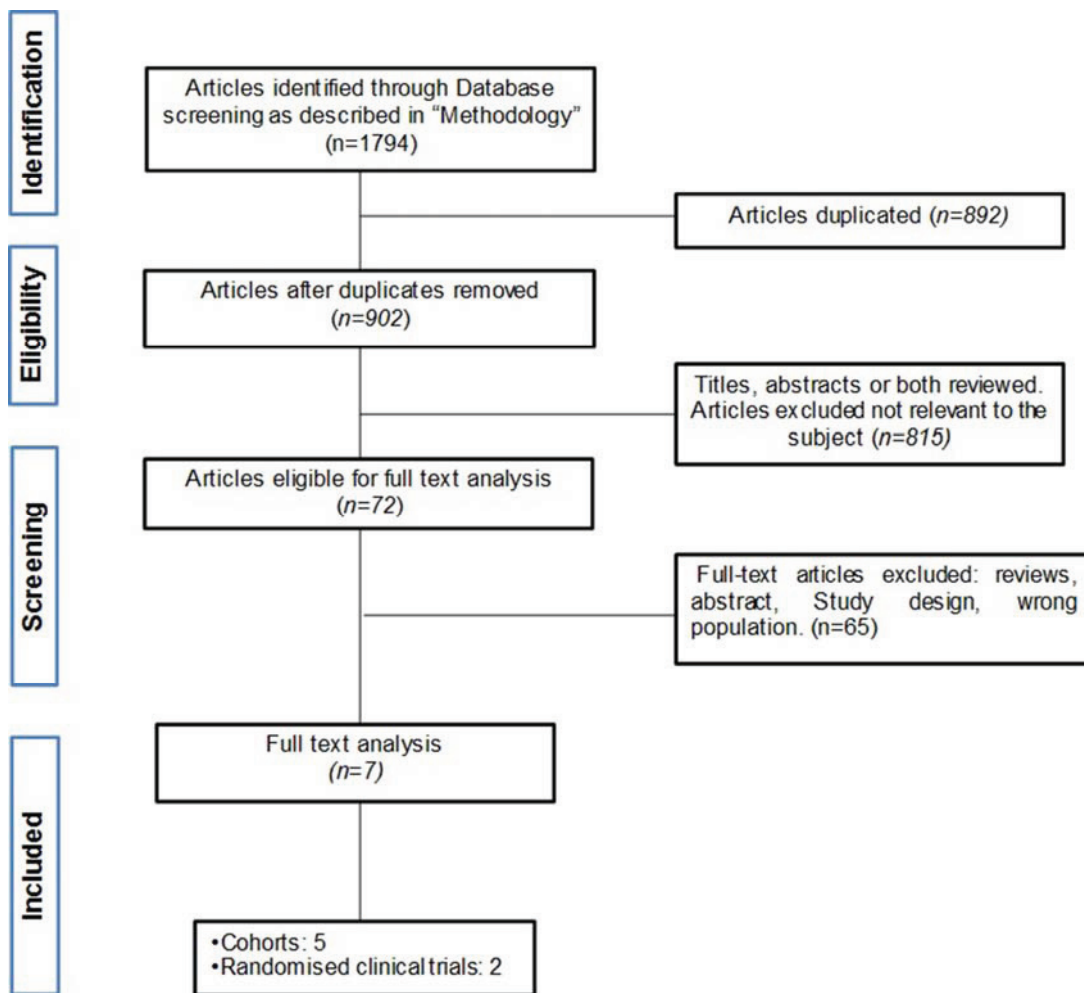


Fig. 1. Flow diagram of article selection.

From those studies, the methodological quality was reviewed as an indication of the strength of evidence provided by the study. Flaws in the design or in the conduction of the study were analysed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as well as a 3-point grading system, described by the Swedish Council on Technology Assessment in Health Care (SBU) and the Centre for Reviews and Dissemination, University of York (accessed 30th June, 2015 https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf). With regards to the grading of the studies, this was assessed by all of the authors and any inter examiner conflicts were resolved by discussion of each study to reach a consensus (Table 1). Other methods to appraise literature have been described with well known advantages and disadvantages (7). This current method has been successfully used in other systematic reviews providing a good opportunity to assess clinical trials and observational studies as reported in other studies (8,9).

The SBU tool permitted the assessment of the level of

the available evidence for reports according to the following grading: Strong: at least two studies of level ‘A’; Moderate: one study of level ‘A’ and at least two studies of level ‘B’; Limited: at least two studies of level ‘B’; Scarce: fewer than two studies of level ‘B’. Authors (ZK, EJS, JLL) prepared data extraction tables and all authors contributed to summary reports of the selected journal articles, critical appraisal and review of the literature.

Results

From the 7 studies listed in table 2, it is apparent that budesonide, dexamethasone and tacrolimus were the most common topical medications used in published studies. Of the reviewed studies, there were 2 randomised clinical trials (10,11) and 5 cohort studies (12-16). The median age, length of study, topical application, grading and outcome for each study are reported in table 2. The side effects reported in each study are listed in table 3.

The excluded articles were, one case series of the topi-

Table 1. Swedish Council on Technology Assessment in Health Care.

Grade A - high value of evidence
All criteria should be met: -Randomised clinical study or a prospective study with a well-defined control group -Defined diagnosis and endpoints -Diagnostic reliability tests and reproducibility tests described -Blinded outcome assessment
Grade B - moderate value of evidence
All criteria should be met: -Cohort study or retrospective case series with defined control or reference group -Defined diagnosis and endpoints -Diagnostic reliability tests and reproducibility tests described
Grade C - low value of evidence
One or more of the conditions below: -Large attrition -Unclear diagnosis and endpoints -Poorly defined patient material

Table 2. Study reports on the use of topical applications in management of oGVHD.

Author/ Country/ Year	Sample	Age (years) (median/mean)	Length of study/ Follow up	Type of study/ Grade (if applicable)	Topical agent	Outcome
Elad <i>et al</i> Israel/Germany 2012	18	Median 42	8 weeks	Randomised clinical trial/ Grade B	3mg budesonide /10 ml mouthrinse.	Topical budesonide mouthrinse improved oral cGVHD in all patients. The response was similar in all treatment arms
Sari <i>et al</i> Turkey 2007	23	Median Group A: 29 Group B: 36	Median Group A: 8.5 months Group B: 7 months	Retrospective Cohort Grade B	3mg budesonide 10 ml mouthrinse	Topical budesonide might be added to systemic therapy to obtain better response rates in patients with oGVHD.
Park <i>et al</i> South Korea 2013	50	Mean Group A: 5.2 Group B: 6.2	1 month	Prospective Cohort/ Grade C	Budesonide 0.03%, 10ml mouthrinse vs dexamethasone 0.01% mouthrinse 5-10ml	Decreased cGVHD severity and pain scores but no statistical differences were seen between both groups
Noce <i>et al</i> Brazil 2014	32	Median 49.5	Median 471 days	Randomised double-blind clinical trial/ Grade B	Clobetasol propionate 0.05%, 5ml mouthrinse vs dexamethasone 0.1mg/ml, 5ml mouthrinse	Clobetasol was significantly more effective than dexamethasone (symptoms and clinical appearance of oral lesions)
Mawardi <i>et al</i> USA 2010	14	Median 54	Median 60 days (first follow up 12-49 days and second follow up 49-86 days)	Retrospective Cohort Grade B	Dexamethasone (0.25mg/2.5ml)/ Tacrolimus (0.25mg/2.5ml). (mouthrinse)	Combined topical DEX/TAC therapy appears to be effective in reducing symptoms attributable to oGVHD
Albert <i>et al</i> Germany 2007	6	Average 10 (6-16 years of age)	16 to 354 days	Prospective Cohort (children)/ Grade C	Tacrolimus 0.1% ointment BD orally	Topical TAC holds promise as a safe and efficacious treatment for oGVHD in children
Epstein <i>et al</i> Canada 1994	11	39 (average age)	Mean: 11.2 weeks	Retrospective Cohort Grade C	Cyclosporin oral rinse (100mg/ml, 5ml)	Signs and symptoms improved \geq 50% in 64% of patients

BD = Twice daily, DEX = Dexamethasone, TAC = Tacrolimus.

Table 3. Reported side effects.

Author/ Country/Year	Topical formulation	Side effects
Elad <i>et al</i> Israel/Germany 2012	3mg budesonide / 10 ml mouthrinse	Gastrointestinal disorders (cheilitis, oesophagitis), oral candidosis, taste alteration
Sari <i>et al</i> Turkey 2007	3mg budesonide /10 ml mouthrinse	One complaint of local oral burning sensation
Park <i>et al</i> South Korea 2013	Budesonide 0.03%, 10ml mouthrinse vs dexamethasone 0.01% mouthrinse 5-10ml	Budesonide : 4 patients had oral candidosis, 1 complained of bitterness/astringency sensation Dexamethasone : 1 patient had oral candidosis, 2 patients complained of bitterness/astringency sensation, 2 patients described local oral dryness
Noce <i>et al</i> Brazil 2014	Clobetasol propionate 0.05%, 5ml mouthrinse vs dexamethasone 0.1mg/ml, 5ml mouthrinse	Clobetasol : one patient reported burning sensation Dexamethasone : one patient reported burning sensation
Mawardi <i>et al</i> USA 2010	Dexamethasone (0.25mg/2.5ml)/ tacrolimus (0.25mg/2.5ml). Total 5ml mouthrinse	4 patients had increased tacrolimus serum peak levels but none exceeded the upper therapeutic range limit
Albert <i>et al</i> Germany 2007	Tacrolimus 0.1% ointment BD orally	1. Local oral burning sensation 2. ‘Odd sensation’ after intake of food 3. Systemic exposure (increased plasma levels) in 4 out of 6 patients – 1 case related to accidental over dosage
Epstein <i>et al</i> Canada 1994	Ciclosporin oral rinse (100mg/ml, 5ml)	Blood levels of ciclosporin increased significantly in 2 patients. No toxicity was observed

cal use of azathioprine (17) and seven case reports of the use of topical tacrolimus (18-24) (Table 4). These were excluded as they did not fulfil the SBU criteria. With regards to the scales used for disease assessment

in the selected studies, the majority were based on the National Institutes of Health consensus for GVHD to assess the clinical stage of oral manifestations as well as response to treatment (10-12,14,16). Activity of the dis-

Table 4. Table of case reports and case series studies: topical applications in patients with oGVHD.

Author/ Country/Year	Sample size	Age (years) (median/mean)	Length of study/ Follow up period	Topical formulation
Eckardt <i>et al</i> Germany, 2004	3	23, 41, 63	8 weeks / 14 weeks	Tacrolimus 0.1% ointment BD orally
Sanchez <i>et al</i> USA, 2004	1	51	2 months	Tacrolimus 0.1% ointment TDS orally
Conrotto <i>et al</i> Italy, 2006	1	55	2 weeks / 3 months	Tacrolimus 0.1% ointment BD orally
Fricain <i>et al</i> France, 2007	3	41 58 61	2 months >1 month 3 months / 7 months 1 year 1 year	Tacrolimus 0.1% ointment BD orally
Rojas <i>et al</i> Chile, 2009	1	17	Response to treatment 7 days	Tacrolimus 0.1% ointment TDS orally
Brown <i>et al</i> USA, 2013	1	41	4 weeks / 14 months	Tacrolimus 0.1% ointment BD applied onto custom trays
Conrotto <i>et al</i> Italy, 2014	1	63	2 months	Tacrolimus 0.1% ointment BD orally
Epstein <i>et al</i> Israel/Canada/ USA, 2001	8 6 With oral GVHD	38.5 (mean age)	Mean follow up 16 weeks	Topical azathioprine rinse 5 mg/mL . Rinse 5 mL TDS-QDS for over 1 minute and to expectorate. Azathioprine gel (5 mg/mL) in 3% methylcellulose base

BD = Twice daily; TDS = Three times daily; QDS = Four times daily.

ease was classified based on the oral mucosa rating scale (OMRS) (10,11) and clinical response graded under complete response, partial response, stable disease or progression (15,16). In some cases, the disease was categorised into 3 stages; mild, moderate or severe (13) and response to treatment labelled as “objective response as an improvement of at least 50% at the final/ withdrawal visit (compared to baseline) in the OMRS” (10).

Subjective evaluation of symptom severity as well as the use of visual analogue scale (VAS) for patient’s self-reporting for oral pain was also used (11,12,16). Albert *et al.* (14) assessed response at baseline and at each visit by asking for subjective evaluation of symptom severity (pain, burning, and discomfort) and by inspection of the oral cavity, assessing the response as complete response, very good partial response, partial response, and non-response. Epstein and Reece (12) evaluated the oral cavity based on the presence of erythema, lichenoid patterns and ulceration, including calculation of the size of any ulcers and the total area of ulceration.

Multiple sources of bias were found in the clinical trials (10,11) such as the lack of adequate description of randomisation. There was a lack of information on who was responsible for generating the randomisation, allocation concealment, assigning participants to interventions, and whether the clinician responsible for the clinical assessment was blinded (10,11). Both studies reported outcomes listed in the methods section and both applied power of the study (10,11). However, both reported limitations of a small sample size, and possible confounding factors such as concomitant immunosuppressive therapies and the duration of topical therapy. In the cohort studies there was a lack of blinding of providers, participants and assessors. Furthermore, intention to treat analysis and power were not used (12-16).

Although Albert *et al.* (14) reported good tolerability and safety as well as potent activity of topical tacrolimus ointment in 6 paediatric patients, their study had many limitations due to the small size and its non-comparative nature. Their response criteria lacked reliability as there was no explanation of who interpreted the results or whether there was more than one rater leading to possible observational bias. In addition, there was no standardised response criteria used at the time of the study, no statistical analysis of results, and possible confounding factors were not identified nor addressed.

Mawardi *et al.* (13) recognised a possible selection bias in their inclusion criteria, such as the selection of severe/refractory cases only of oral cGVHD. This study aimed to describe the clinical outcomes of combined dexamethasone and tacrolimus topical rinses in the management of patients with symptomatic oral cGVHD. Potential confounders and effect modifiers were not clearly defined, and there was a lack of standardisation in the application of the oral solution with its frequency rang-

ing between twice and four times daily amongst patients included in the study.

Sari *et al.* (16) designed a retrospective study according to NIH consensus criteria comparing the use of topical budesonide plus systemic therapy (prednisolone and ciclosporin) compared to those receiving systemic therapy alone. Their results suggested that there may be a potential benefit in the use of topical budesonide as an adjuvant to systemic therapy. This study lacked random allocation and potential confounding factors were not taken into account, hence there were no adjustments to the statistical analysis. The authors commented on this limitation and suggested further studies where randomisation and larger groups should be considered.

Epstein & Reece (12) trial was based on the use of oral ciclosporin rinses in patients with cGVHD who were not responding to systemic therapy and dexamethasone oral rinses, concluding that this may be a possible coadjuvant in refractory cases. However, without the use of standardised response criteria at the time of the study, it is difficult not to interpret the results with caution. The lack of blinding, power sample size, description of the statistical analysis of the results, and no effort to address potential sources of bias limit the impact and application of this study.

Park *et al.* (15) compared the efficacy of topical budesonide relative to dexamethasone treatment, with there being no statistical differences found between the two groups. This was a well-structured study where statistical analysis of the results were reported and interpreted appropriately. Unfortunately, this study had no power calculation and possible confounders were not adjusted for. Finally there was the limitation of a short follow up period in this study.

We present a resume of the effectiveness of the topical interventions used in the selected studies:

Randomised clinical trials:

There were two clinical trials included in this review, neither study included a control group, one study evaluated the effectiveness of budesonide mouthwash (10) and the other compared the effectiveness of clobetasol propionate mouthwash vs dexamethasone mouthwash (11). A third trial will also be mentioned despite being presented as a letter to the editor evaluating the use of topical thalidomide gel (25).

Elad *et al.* 2012 (10) in a double blind clinical trial, divided 18 participants into four groups that used budesonide 3mg as a mouthwash twice daily for 5 or 10 minutes compared to two other groups who used the mouthwash three times daily for either 5 or 10 minutes. The participants enrolled all completed the 8 week study period. The oral lesions improved in all patients, but the rate of objective improvement (defined as $\geq 50\%$) and pain reduction was not significantly different between the 4 study arms ($P < 0.05$).

Noce *et al.* 2014 (11) in an open randomised trial, enrolled 32 participants who were divided between study groups that received either clobetasol propionate (0.05%) mouthrinse or dexamethasone (0.1mg/5ml) mouthrinse. The median length of the study was 471 days. The use of clobetasol propionate (0.05%) resulted in a significant reduction in the oral mucosa rating scale total score ($P = 0.04$) and in the ulcer score ($P = 0.03$) when compared with topical dexamethasone. In both groups, there was significant symptomatic improvement but the response was significantly greater in the clobetasol group ($P = 0.02$).

John *et al.* 2013 (25) reported a phase II, randomised, placebo-controlled, double-blind clinical trial as a letter to the editor. When including this study for analysis using the 3 point grading system, the amount of information was restricted and therefore did not allow for fair grading. They recruited 10 participants and compared the use of topical thalidomide 20mg gel against a placebo controlled group in patients with oGVHD. The length of the study was 4 weeks, with an 8 week follow up period. Only 6 subjects completed the study, 3 in each group. The authors recognised the small sample size precluded statistical confirmation of topical thalidomide's efficacy in the management of oral ulcerative cGVHD, They also considered that the placebo effect of the Orabase plain product and/or the waxing and waning nature of cGVHD might impact on their findings. Overall, there was a 66% mean percentage decrease in the total surface area of oral ulceration at week 4 compared with the baseline presentation. It was also observed that the TNF α levels in saliva and ulcer exudates decreased with therapy but with no significant difference in the salivary levels of TNF α compared with baseline in both thalidomide ($P=1.0$) and placebo ($P=0.109$) groups. However, there was a decrease in salivary IL6 concentration in the thalidomide group ($P=0.465$) when compared with the baseline, with no decrease in the placebo group.

- Cohort studies:

Park *et al.* 2013 (15) enrolled 50 participants, dividing them into two groups and compared the use of budesonide 0.03% oral rinse with 0.01% dexamethasone rinse. All participants completed the one month study period. No statistical difference in the response was noted between the two groups ($p = 0.093$). However, recently, in 2014, Zadik *et al.* (26), carried out a re-analysis of the reported data, excluding patients with a (NIH) consensus criteria score of 1 and 2, considered not to be fully eligible for topical steroids, and a further statistical analysis revealed a significantly better response to budesonide than to dexamethasone ($p = 0.015$).

Albert *et al.* 2007 (14) recruited six children (aged 6-16 years) and presented a cohort study reporting the responses of children treated with topical tacrolimus 0.1% ointment. The first response to treatment was docu-

mented after a median of 21 (range 6-31) days. The follow up period ranged from 16 to 354 days. A complete response was achieved in two of the six patients with a partial response in the remaining four patients.

Mawardi *et al.* 2010 (13) enrolled 14 subjects looking at the efficacy of combined topical dexamethasone (DEX) and tacrolimus (TAC) solutions in the management of oral cGVHD.

The median length and follow up of the study was 60 days. The study showed a median improvement in the NIH total score at the second follow up visit (range from 2 to 6, $P=0.06$), though unchanged at the first follow up (range from 2 to 5, $P=0.41$). Both erythema and lichenoid feature scores demonstrated a statistically significant improvement at the second follow up. Mawardi *et al.* (13) recognised the selected cases could be biased by the type of disease that they could include in the study.

Epstein and Reece 1994 (12) recruited 11 participants and evaluated the use of ciclosporin A (100mg/ml) administered as an oral rinse (5ml) in patients with active oral lesions, despite the concurrent use of systemic immunosuppressants plus topical dexamethasone. The mean length of the study was 11.2 weeks. The study showed an improvement in ulceration of $\geq 50\%$ in 7 of 11 patients (64%) treated with the addition of topical ciclosporin A.

Sari *et al.* 2007 (16) divided 23 participants into two groups of which one group received topical budesonide (3mg in 10 ml) oral rinse in addition to systemic therapy (prednisone and ciclosporin) (Group A, $n = 12$), compared to another group of subjects who were administered the systemic therapy alone (Group B, $n = 11$). The median length of the study was 8.5 months and 7 months for groups A and B respectively. The median follow up period was 108 days for group A and 120 days for group B. There was an overall clinical response rate of 83% and 36% for groups A and B, respectively ($P = 0.036$). However, no statistically significant differences were found between median pain scores of the two groups before and after treatment ($P = 0.740$ and $P = 0.091$).

Discussion

Based on this systematic review, the number of randomised clinical trials reporting the use of topical steroids or immunosuppressants in the management of the inflammatory mucosal lesions encountered in oGVHD appears to be very low. Using the Swedish Council on Technology Assessment in Health Care and the Centre for Reviews and Dissemination, University of York 3-point grading system, there is limited evidence to support these therapies based on the analysed papers. The reported studies presented different lengths of follow up and also differently scaled schemes of assessment of outcome. The sample sizes were generally small, however both clinical trials provided a statistical power of

80%, a commonly accepted value (10,11). In all of the selected studies it is not recorded whether the outcome assessors were blinded when assessing the response to treatment. This bias could have been prevented by ensuring outcome assessors are blind to treatment allocation, for example by using independent clinicians who are not otherwise involved in the trial to assess patients, or using a blinded adjudication committee to determine the outcome (27). However, the nature of the study can preclude this, as reported by Kahan *et al.* (28) who reported that a “blinded outcome assessment may not always be feasible due to the nature of the trial, for example, when all researchers in a centre are aware of treatment allocation, or relevant clinical information cannot be sent to a blinded assessor”.

Currently, the literature search in systematic reviews and the quality assessment of included studies are well-established processes in evidence-based medicine and dentistry (29). However, the precise methods for the process can differ among various systematic reviews (7). Meier *et al.* (6) (2011), provided a review of topical applications used for GVHD. We believe this new systematic review could provide new data, acknowledging observational studies as well as clinical trials. We included five cohort studies in addition to two clinical trials based on the SBU guideline. We acknowledge that one of the limitations of this review is that the search methodology/parameters used in this review cannot guarantee that all articles pertinent to the topic were included; other databases may include information in this field. Apart from English, we included Portuguese and Spanish language studies, however we acknowledge that searches including other languages may have returned relevant articles and further reviews including other languages might be considered.

A notable finding was the lack of randomised controlled trials in the effectiveness of topical therapy in the management of oGVHD. The randomised controlled trial is acknowledged to be the most powerful tool to evaluate the effectiveness of treatment and the quality of the study significantly affects the validity of the conclusions drawn (9). John *et al.* (25) showed thalidomide (20mg gel) was effective in individuals with oral cGVHD, although the authors did recognise the potential influence of the small size of the sample in the reporting of their results. As this was presented as a ‘letter to the editor’, there was a lack of detailed description of randomisation, allocation, concealment and blinding, and as such the conclusions drawn from these data need to be interpreted with caution. However, we felt that the nature of this study was relevant to this review and as such its inclusion was warranted. The lack of randomised control trials on this topic could be due to practical difficulties secondary to the nature of patients with oGVHD, which can raise both ethical and logistical issues.

The majority of the studies had a cohort design including two retrospective cohorts and two prospective cohorts. From an evidence-based point of view, the scientific value of a retrospective study is limited although some authors have argued that well-designed prospective or retrospective studies should not be ignored when assessing the available scientific literature (8).

The majority of patients in the selected studies were also taking systemic medications along with the topical application studied. The intention was to analyse the effect of the topical applications on the disease. As a result it is difficult to ascribe any improvements described to the systemic medication or the topical therapies. As such these results should be interpreted with caution. Dilger *et al.* (30) report that in patients with oral cGVHD, 10% of the topical dose of budesonide can enter the circulation, possibly due to the loss of epithelial integrity that can occur in ulcerative lesions in oGVHD and metabolism. When compared with the systemic concentrations attained after the oral intake of enteric-coated budesonide for inflammatory bowel diseases, the levels reported are within recognised safety thresholds.

A multicentre questionnaire undertaken by Elad *et al.* (31) regarding the treatment of oral cGVHD showed that steroids were the first-line topical management of choice (91.7 %). The topical steroids budesonide (3mg/10ml) and dexamethasone (0.1mg/5ml) were the most commonly studied. Tacrolimus (TAC) was studied as a single topical application or in combination with dexamethasone. TAC binds to the immunophilin FK506 binding protein, inhibiting calcineurin phosphatase. It inhibits calcium-dependent events, such as interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis (32).

With regards to the side effects and safety, a cohort study undertaken by Mawardi *et al.* (13) found that when topical DEX and TAC were used in combination, 4 patients (37%) had increased TAC serum peak levels that corresponded with the application of topical treatment. Following the use of topical TAC, many reports have raised concerns on the clinically significant elevation of tacrolimus serum levels (13,22). Some case reports have shown elevated levels of TAC although the actual absorption via the oral mucosa remains ambiguous (14,22). A retrospective study by Thomson *et al.* (33) described the safety of TAC when used to treat individuals with erosive lichen planus. They noted minor local side effects but an absence of evidence of systemic absorption.

As has been frequently reported there is an increased risk of oral malignancy in oral GVHD (5), although to our knowledge, this increased risk of malignancy has not been associated with the use of topical tacrolimus in cases of oral GVHD. Another calcineurin inhibitor; ciclosporin, has been studied for the treatment of

continuous oral ulceration used as both a topical and systemic agent. Epstein & Reece (12) showed improvements in oGVHD using topical ciclosporin. Many studies on mucosal inflammatory conditions such as lichen planus did not report improved outcomes with the use of this calcineurin inhibitor when compared with topical steroids (34). The appropriate follow up time to assess the response to treatment is debatable, particularly with regards to the monitoring of potential oral malignancy (35). The increased risk of secondary malignancies is a major late complication of HSCT. A study showed that 2-6% of post-HSCT patients had developed a secondary solid tumour within 10 years (35). Approximately one-third of these secondary solid tumours were squamous cell carcinomas (SCCs) of the skin or the oral cavity. The oral cavity accounted for up to half of the SCC cases alone. Development of malignancy was not reported during the short length of the included studies and longer follow up periods could be considered with this in mind. Curtis *et al.* (36) reported that in 16 cases of oral SCC associated with oGVHD, the most frequent site of SCC was the tongue, followed by the lips, and gingivae. From the 16 cases, 11 had received immunosuppressive drugs for two or more years and the risk of SCC in the oral cavity appears to be higher in patients who have undergone HSCT.

The use of budesonide has also been studied by Elad *et al.* in an open label trial (37), involving twelve patients diagnosed with chronic and resistant oral GVHD. They were managed with topical budesonide (3 mg /5 ml saline) 2 to 3 times a day for up to 3 months. Their findings showed that 7 of the 12 patients had scores of “good” or “complete” recovery following evaluation by the examiner and assessment of the subject. In some patients in this study, the systemic management with both prednisolone and ciclosporin was gradually reduced as early as 2 weeks following the commencement of budesonide mouthwashes. The authors stated that 3 examiners were used to carry out the clinical examinations and recognised that inter-observer calibration was not implemented. Van Schandevyl *et al.* (38) have presented a protocol where budesonide mouthwash was used as an adjuvant (Budenofalk® 3 mg gastro-resistant capsules) and results of a large-scale, phase III, randomised, controlled, double-blinded multicenter study assessing this new preparation of topical budesonide for the treatment of oral cGVHD is awaited.

Noce *et al.* (11) compared the use of topical clobetasol with dexamethasone, demonstrating significant symptomatic improvements over baseline in both groups, but with the response being significantly greater in the clobetasol group. The authors recognised the limitations of this study such as the small number of patients enrolled and other confounding variables, and suggested that further studies with larger samples and subject

stratification, taking into account the influence of these variables on the topical therapy for oral cGVHD lesions, might be considered. Erosive oral lichen planus (OLP) has close similarities in its disease presentation to oGVHD. It is therefore pertinent to consider what topical treatments are used for the management of erosive OLP. In a Cochrane review of topical applications for the treatment of oral lichen planus, the authors concluded there is no evidence that any one topical steroid is more effective than another (39). Different treatment regimens using clobetasol have been proposed in the literature (40). Previous studies have used 0.05% topical clobetasol applications, 2 or 3 times a day, for a period between 2 weeks and 2 months (11,39,40). Topical dexamethasone has been used in a 1 mg/mL solution or in a 0.043% paste, 3 to 4 times a day, for 1 month (11). Reported symptomatic improvement of erosive oral lichen planus lesions varied from 63.6% to 100% with topical clobetasol, and from 38.50% to 72.51% with topical dexamethasone (11,39,40).

Budesonide was potentially linked to some side effects including gastrointestinal tract disorders (cheilitis, oesophagitis), oral candidosis and taste disturbance (10). Similar findings of side effects were reported in other studies using budesonide, as well as oral burning sensations (15,16,37). In studies where dexamethasone mouth rinse was used, side effects were reported including oral burning sensations, oral candidosis, local dryness and bitterness/astringency sensations (11,15). A local oral burning sensation was reported by one patient using topical clobetasol propionate (11) (Table 2).

In conclusion, the evidence for the use of topical therapies in the management of the inflammatory mucosal lesions encountered in oGVHD is limited and the results of this review should be interpreted with some caution. Oral GVHD is a very debilitating condition particularly with respect to the effect on quality of life (QOL). We suggest that high quality randomised controlled trials of the effectiveness of topical therapies in oGVHD, with good statistical power and standardised outcome measures are needed to establish the effectiveness of both established and novel therapies in order to allow the development of clinical guidelines for the topical management of the inflammatory mucosal lesions found in oGVHD.

References

1. Billingham RE, Hings IM. The H-Y antigen and its role in natural transplantation. *Hum Genet.* 1981;58:9-17.
2. Mays J, Fassil H, Edwards D, Pavletic S, Bassim C. Oral chronic graft-versus-host disease: current pathogenesis, therapy, and research. *Oral Dis.* 2013;19:327-46.
3. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant.* 2015;21:389-401.

4. Schubert MM, Correa ME. Oral graft-versus-host disease. *Dent Clin North Am.* 2008;52:79-109.
5. Imanguli MM, Alevizos I, Brown R, Pavletic SZ, Atkinson JC. Oral graft-versus-host disease. *Oral Dis.* 2008;14:396-412.
6. Meier JK, Wolff D, Pavletic S, Greinix H, Gosau M, Bertz H, et al. International Consensus Conference on Clinical Practice in cGVHD. Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGVHD. *Clin Oral Investig.* 2011;15:127-39.
7. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. *Clin J Am Soc Nephrol.* 2008;3:253-60.
8. Rossini G, Parrini S, Castorflorio T, Deregibus A, Debernardi CL. Periodontal health during clear aligners treatment: a systematic review. *Eur J Orthod.* 2015;37:539-43.
9. Bondemark L, Holm A, Hansen K, Axelsson S, Mohlin B, Brattstrom V. Long-term stability of orthodontic treatment and patient satisfaction. A systematic review. *Angle Orthod.* 2007;77:181-91.
10. Elad S, Zeevi I, Finke J, Koldehoff M, Schwerdtfeger R, Wolff D, et al. Improvement in oral chronic graft-versus-host disease with the administration of effervescent tablets of topical budesonide-an open, randomized, multicenter study. *Biol Blood Marrow Transplant.* 2012;18:134-40.
11. Noce CW, Gomes A, Shcaira V, Corrêa ME, Moreira MC, Silva Júnior A, et al. Randomized double-blind clinical trial comparing clobetasol and dexamethasone for the topical treatment of symptomatic oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2014;20:1163-8.
12. Epstein JB, Reece DE. Topical cyclosporin A for treatment of oral chronic graft-versus-host disease. *Bone Marrow Transplant.* 1994;13:81-6.
13. Mawardi H, Stevenson K, Gokani B, Soiffer R, Treister N. Combined topical dexamethasone/tacrolimus therapy for management of oral chronic GVHD. *Bone Marrow Transplant.* 2010;45:1062-7.
14. Albert MH, Becker B, Schuster FR, Klein B, Binder V, Adam K, et al. Oral graft vs. host disease in children--treatment with topical tacrolimus ointment. *Pediatr Transplant.* 2007;11:306-11.
15. Park AR, La HO, Cho BS, Kim SJ, Lee BK, Rhie JY, et al. Comparison of budesonide and dexamethasone for local treatment of oral chronic graft-versus-host disease. *Am J Health Syst Pharm.* 2013;70:1383-91.
16. Sari I, Altuntas F, Kocyigit I, Sisman Y, Eser B, Unal A, et al. The effect of budesonide mouthwash on oral chronic graft versus host disease. *Am J Hematol.* 2007;82:349-56.
17. Epstein JB, Gorsky M, Epstein MS, Nantel S. Topical azathioprine in the treatment of immune-mediated chronic oral inflammatory conditions: a series of cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91:56-61.
18. Conrotto D, Broccoletti R, Carcieri P, Giaccone L, Arduino PG. Topical tacrolimus and periodontal therapy in the management of a case of oral chronic GVHD characterized by specific gingival localization. *Case Rep Dent.* 2014;2014:127219.
19. Brown RS, Edwards D, Walsh-Chocolaad T, Childs RW. Topical tacrolimus with custom trays in the treatment of severe oral chronic graft-versus-host disease refractory to a potent topical steroid therapy: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;115:e26-30.
20. Rojas AG, González GN, Venables GC, Araos HD. [Gran versus host disease with oral involvement: report of one case]. *Rev Med Chil.* 2008;136:1570-3.
21. Fricain JC, Sibaud V, Swetyenga N, Tabrizi R, Campana F, Taieb A. Long-term efficacy of topical tacrolimus on oral lesions of chronic graft-versus-host disease. *Br J Dermatol.* 2007;156:588-90.
22. Conrotto D, Carozzo M, Ubertalli AV, Gandolfo S, Giaccone L, Boccadoro M, et al. Dramatic increase of tacrolimus plasma concentration during topical treatment for oral graft-versus-host disease. *Transplantation.* 2006;82:1113-5.
23. Eckardt A, Starke O, Stadler M, Reuter C, Hertenstein B. Severe oral chronic graft-versus-host disease following allogeneic bone marrow transplantation: highly effective treatment with topical tacrolimus. *Oral Oncol.* 2004;40:811-4.
24. Sánchez AR, Sheridan PJ, Rogers RS. Successful treatment of oral lichen planus-like chronic graft-versus-host disease with topical tacrolimus: a case report. *J Periodontol.* 2004;75:613-9.
25. St John L, Gordon SM, Childs R, Marquesen M, Pavletic SZ, Wu TX, et al. Topical thalidomide gel in oral chronic GVHD and role of in situ cytokine expression in monitoring biological activity. *Bone Marrow Transplant.* 2013;48:610-1.
26. Zadik Y, Nakdimon I, Meyerowitz C, Shapira MY, Elad S. Topical budesonide for severe oral chronic graft-versus-host disease. *Am J Health Syst Pharm.* 2014;71:181-2.
27. Dechartres A, Boutron I, Roy C, Ravaud P. Inadequate planning and reporting of adjudication committees in clinical trials: recommendation proposal. *J Clin Epidemiol.* 2009;62:695-702.
28. Kahan BC, Cro S, Doré CJ, Bratton DJ, Rehal S, Maskell NA, et al. Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomised trials. *Trials.* 2014;15:456.
29. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
30. Dilger K, Halter J, Bertz H, Lopez-Lazaro L, Gratwohl A, Finke J. Pharmacokinetics and pharmacodynamic action of budesonide after buccal administration in healthy subjects and patients with oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2009;15:336-43.
31. Elad S, Jensen SB, Raber-Durlacher JE, Mouradian N, Correa EM, Schubert MM, et al. Clinical approach in the management of oral chronic graft-versus-host disease (cGVHD) in a series of specialized medical centers. *Support Care Cancer.* 2015;23:1615-22.
32. Thomson AW, Bonham CA, Zeevi A. Mode of action of tacrolimus (FK506): molecular and cellular mechanisms. *Ther Drug Monit.* 1995;17:584-91.
33. Thomson MA, Hamburger J, Stewart DG, Lewis HM. Treatment of erosive oral lichen planus with topical tacrolimus. *J Dermatolog Treat.* 2004;15:308-14.
34. Thongprasom K, Chaimusig M, Korkij W, Sererat T, Luangjarmekorn L, Rojwattanasirivej S. A randomized-controlled trial to compare topical cyclosporin with triamcinolone acetonide for the treatment of oral lichen planus. *J Oral Pathol Med.* 2007;36:142-6.
35. Mawardi H, Elad S, Correa ME, Stevenson K, Woo SB, Almazroo S, et al. Oral epithelial dysplasia and squamous cell carcinoma following allogeneic hematopoietic stem cell transplantation: clinical presentation and treatment outcomes. *Bone Marrow Transplant.* 2011;46:884-91.
36. Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socie G, Travis LB, et al. Solid cancers after bone marrow transplantation. *N Engl J Med.* 1997;336:897-904.
37. Elad S, Or R, Garfunkel AA, Shapira MY. Budesonide: a novel treatment for oral chronic graft versus host disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003;95:308-11.
38. Van Schandevyl G, Bauters T. Formulation of budesonide mouthwash for the treatment of oral chronic graft-versus-host disease. *J Oncol Pharm Pract.* 2014;pii: 1078155214560654. [Epub ahead of print].
39. Thongprasom K, Carozzo M, Furness S, Lodi G. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev.* 2011;7:CD001168.
40. Carbone M, Arduino PG, Carozzo M, Caiazzo G, Broccoletti R, Conrotto D, et al. Topical clobetasol in the treatment of atrophic-erosive oral lichen planus: a randomized controlled trial to compare two preparations with different concentrations. *J Oral Pathol Med.* 2009;38:227-33.