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Improvement in Oral Chronic Graft-versus-Host Disease with the Administration of Effervescent Tablets of Topical Budesonide—An Open, Randomized, Multicenter Study

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Chronic graft-versus-host disease (cGVHD) frequently involves oral tissues. Although the mucosal changes may be painful and impair oral function, there is currently no topical therapy available for oral cGVHD that has been proven to work in an evidence-based manner. The aims of this study were to (1) assess the response of patients with oral cGVHD to various doses of a new topical budesonide formulation; (2) evaluate the efficacy and safety of the new topical budesonide formulation in these patients. An open, randomized, multicenter phase II pilot study with 4 treatment arms differing in application frequency and duration was performed. Response to treatment was scored by the clinician and patient using several scales. Oral cGVHD improved in all patients, with a median reduction of 70%. Pain reduction was similar in all study arms. The rate of objective improvement (defined as ≥50%) was not significantly different among the 4 study arms. The safety profile was satisfactory. Topical budesonide mouthwash (3 mg/10 mL) improved oral cGVHD in all patients when applied for 5 or 10 minutes, 2 or 3 times daily. The response was similar in all treatment arms. Safety analysis supported a dosing schedule of 3 mg of budesonide 3 times a day for 10 minutes.

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INTRODUCTION

Graft-versus-host disease (GVHD) is the most common complication of allogeneic hematopoietic stem cell transplantation (HSCT) [1]. In the clinical setting, GVHD is divided into acute GVHD (aGVHD) and chronic (cGVHD) forms, which differ in their pathogenesis, symptoms, signs, time of onset, and prognostic significance. The clinical signs and symptoms of cGVHD include liver dysfunction, pulmonary fibrosis, sclerodermatous skin changes, oral and gastrointestinal mucosal changes, and a reduced production of tears and saliva. Chronic GVHD usually develops after the third month (100 days) post-HSCT [1,2].

Oral involvement is seen in 33% to 75% of patients who develop aGVHD and in up to 80% of patients affected by cGVHD [1,3]. Ulcerated and painful mucosal lesions significantly impede normal eating habits and nutritional intake, necessitating appropriate diagnosis and treatment [4].

Management of oral cGVHD includes systemic therapy combined with good oral hygiene and the use of topical medications. Unfortunately, despite the clear clinical significance, only a few controlled trials of systemic treatments for cGVHD assessed oral outcomes [4,5]. Furthermore, oral cGVHD is often refractory to systemic therapies, and additional topical treatment is frequently required. Clearly, in cases where the only disease manifestation is in the oral cavity, topical therapy is advantageous because systemic therapy is associated with numerous side effects. Topical steroid preparations are the mainstay of local treatment for cGVHD, but these drugs are not registered for this indication. In addition,

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immunomodulators, such as cyclosporine, azathioprine, tacrolimus alone, or in combination, have been used as topical therapy in oral cGVHD (reviewed by Meier et al., 2010) [6]. Other treatment modalities, such as phototherapy, have been assessed with varying levels of success [6]. However, current treatment recommendations are based on the clinical experience of respected authorities or very small controlled trials [6,7] and, as such, cannot be considered evidence-based. There are several ongoing clinical trials for the treatment of oral lesions associated with cGVHD [8].

The high potency of the steroid budesonide, combined with its very low bioavailability when absorbed through mucosal surfaces, prompted us to select it as the active component in a new pharmaceutical preparation for topical application for oral cGVHD. Because of its previously mentioned properties, budesonide has few systemic side effects and is used in the management of gut GVHD [9]. The development program of this new preparation is ongoing and included a feasibility study [10], a preclinical safety study in a suitable animal model (R. Mohrbacher, personal communication), and a pharmacokinetic study in healthy individuals and oral cGVHD patients [11]. The current study is the next step in the development process of this formulation of the drug.

The primary aim of this study was to assess the rate of objective response of patients with oral cGVHD to various dosing protocols of the new topical budesonide formulation. The secondary endpoints of this study were (1) to assess efficacy of new budesonide formulations using several scores for oral cGVHD, (2) to evaluate subjective improvement of oral cGVHD following budesonide treatment, and (3) to appraise the safety of the new budesonide formulation.

PATIENTS AND METHODS

Study Design

This study was an open, randomized, multicenter phase II pilot study with 4 treatment arms (randomization 1:1:1:1) as follows:

Arm A: rinse for at least 10 minutes 3 times daily with a 3-mg budesonide effervescent tablet dissolved in 10 mL of water (morning/noon/evening).

Arm B: rinse for 5 minutes 3 times daily with a 3-mg budesonide effervescent tablet dissolved in 10 mL of water (morning/noon/evening).

Arm C: rinse for at least 10 minutes 2 times daily with a 3-mg budesonide effervescent tablet dissolved in 10 mL of water (morning/evening).

Arm D: rinse for 5 minutes 2 times daily with a 3-mg budesonide effervescent tablet dissolved in 10 mL of water (morning/evening).

Four centers participated in the study: (1) Deutsche Klinik für Diagnostik, KMT-Zentrum, Wiesbaden, Germany; (2) Universitätsklinikum Freiburg, Klinik f. Innere Medizin, Abteilung f. Hämatologie und Onkologie, Freiburg, Germany; (3) Universitätsklinikum Essen, Klinik für KMT, Essen, Germany; (4) Hadassah Ein Kerem Medical Center, Jerusalem, Israel.

The ethics boards of all the participating centers approved the study (EudraCT number 2005-002754-22). All patients signed an informed consent form.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) 18 to 75 years of age; (2) symptomatic oral cGVHD of erosive and ulcerative type, diagnosed based on clinical presentation, evidence of systemic cGVHD, and when needed, oral mucosal biopsy; (3) oral cGVHD resistant to therapy (eg, lack of partial response to 4 weeks of systemic prednisone and/or cyclosporine treatment; (4) modified Oral Mucosa Rating Scale (mOMRS) [18] of at least 20 (see below); (5) Karnofsky performance status score [12] of at least 70; (6) conventional primary treatment dosage unchanged or reduced during the 4 weeks before the current trial started.

Exclusion criteria: (1) symptomatic oral cGVHD only presenting as the hyperkeratotic type; (2) active oral bacterial, viral, or fungal infection; (3) additional systemic therapy required; (4) second-line treatment of oral cGVHD with topical steroids (eg, dexamethasone, beclomethasone) during the 12 weeks before the current trial started.

Administration of the following drugs/treatments was permitted during the trial: (1) prophylaxis against infection: chlorhexidine 0.2% mouthwash and topical polyene antifungal agents; chlorhexidine use was limited to twice daily and, if combined with nystatin, they were used at least 30 minutes apart; (2) systemic antiviral prophylaxis, such as acyclovir; (3) systemic antifungal treatment such as fluconazole or voriconazole; (4) prophylaxis against pneumocystis carinii pneumonia with trimetoprim/sulfamethoxazole; (5) anti-GVHD medications if the dose remained unchanged or was adjusted to plasma concentration 4 weeks before the study started and during the study; (6) dose reduction of systemic immunosuppression if there was a remission of cGVHD.

Administration of the following drugs/treatments was not permitted during the trial: (1) budesonide or other corticosteroid-containing drugs, except for conventional primary treatment of cGVHD (ie, systemic prednisone and/or cyclosporine) started before the study; (2) second-line treatments for cGVHD: low-dose total lymphoid irradiation, intraoral PUVA therapy, extracorporeal photochemotherapy, thalidomide, pentostatin; (3) CYP3A-inhibitors: for example, ketoconazole, itraconazole, clarithromycin,

ritonavir (except fluconazole, voriconazole, cyclosporine, tacrolimus/FK506 [dose changes were not permitted during study]); (4) CYP3A-inducers: for example, carbamazepine, rifampicin; (5) nifedipine; (6) macrolide antibiotics except azithromycin; (7) dosages of medications potentially confounding assessment of the inflammatory response (antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants) could remain unchanged or be reduced, but no new medications (or increases in dosages) in this category were accepted during the study.

Study Schedule and Evaluation Protocol

The 8-week study period included 5 evaluations: baseline (day 0)/interim visits (days 14, 28, and 42) and final visit (day 56). Time window for visits was ±4 days. Demographics and medical history were recorded at baseline. Clinical and laboratory assessments included: (1) organ staging (scoring) of cGVHD [12]; (2) assessment of severity of oral cGVHD using the mOMRS (see below), oral cGVHD 5-level scale [10], WHO toxicity scale gastrointestinal/oral [13], and Oral Mucositis Assessment Scale (OMAS) [14]; (3) target organs currently affected by cGVHD (skin, mouth, eyes, vulva/vaginal, gastrointestinal [GI] tract, liver, lung, hematopoietic, musculoskeletal) [12]; (4) Karnofsky Performance Status [12]; (5) cultures of oral lesions for bacterial, fungal, and viral infections; (6) intraoral examination to rule out local irritation/dental trauma; (7) pain assessment—using the WHO toxicity scale pain and WHO pain ladder [15-17]; (8) detailed diary listing all medications and a score regarding eating ability and oral symptoms; (9) blood and urine sampling for laboratory parameters including hematology, serum chemistry, and urine strip test; (10) plasma cortisol levels were measured between 7 and 10 a.m. on each visit beginning on the first day budesonide mouthwash was administered.

Prophylactic drugs/treatments were permitted during the trial. For details, see Inclusion and Exclusion Criteria "Administration of the following drugs/treatments was permitted during the trial."

Modified Oral Mucosa Rating Scale (mOMRS)

Oral assessments were conducted using the mOMRS [18], which divides the oral cavity into 9 anatomical areas (upper and lower lips, upper and lower labial mucosa, right and left buccal mucosa, dorsal and lateroventral aspects of the tongue and soft palate). The mOMRS is a scale from 0 to 81, with higher scores indicating more severe findings. The manifestations of oral cGVHD can be described in terms of the degree of mucosal erythema (0 = normal/no change, 1 = mild redness, 2 = moderate redness, 3 = severe redness [color of fresh oxygenated blood]), lichen-type hyperkeratosis, and pseudomembrane or ulceration (% surface area: 0 = none, 1 = >0, but <25%, 2 = 26%-50% of area, 3 = >50% of area), and presence of mucoceles (presence or absence).

We defined an "objective response" as an improvement of at least 50% at the final/withdrawal visit (compared to baseline) in the mOMRS.

After we initiated our study, the format of the OMRS used by the NIH was altered; therefore, we refer to the scale we used as "modified OMRS."

Study Medication

A new formulation of budesonide, a 3-mg effervescent tablet, was developed for this study (Dr. Falk GmbH, Freiburg, Germany). This preparation targets oral inflammatory sites and is easier to administer than formulations used in previous studies, where the patients had to crush a tablet and dissolve it in water [10,19]. Administration of the drug was immediately following a meal. The patients were instructed to perform oral hygiene (brushing and rinsing), then place the entire 10 mL of the solution in their mouths, rinse for the time specified by their treatment arm (5 or 10 minutes), and then expectorate (not swallow). They were told not to eat or drink for at least 1 hour after administration of the study drug. Patients were not allowed to ingest grapefruit in any form, including juice.

Statistics

Because the study was exploratory in nature, we decided that 5 patients per treatment arm were sufficient to give preliminary insight into the effects of the different treatment regimens, possible major side effects as well as patient compliance. In addition, the pooled sample sizes (n = 10) of the 2 treatments arms with budesonide 6 mg daily and budesonide 9 mg daily, respectively, provided 80% power to yield statistical significance using paired t tests with a 1-sided significance level of 2.5% in cases of intraindividual changes of 10 points on the mOMRS scale at a standard deviation of 10 points.

For quantitative parameters, relative reductions (%) between final/withdrawal visit and baseline were calculated and subjected to descriptive analyses. Categoric variables were presented in frequency tables and treatment arms were compared using the Fisher exact test. For ordinal variables, nonparametric measures of location and dispersion, such as medians and ranges, were derived supplementally using means and standard deviations in cases of quantitative parameters. Unless otherwise stated, Kruskal-Wallis tests were used for treatment arm comparisons of these variables. All P values are 2 sided.

Adverse event verbatim descriptions were coded with MedDRA Version 10.1 (MedDRA[r] the Medical Dictionary for Regulatory Activities terminology is the

international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH]) and presented in a stratified manner using System Organ Classes and Preferred Terms. Serum cortisol concentrations of all patients with at least 1 measurement of serum cortisol were averaged per visit. Serum corisol concentrations were compared between visits using a mixed model with repeated measurements (2-sided test).

All statistical analyses were performed using SAS software package V.9.1.3 (SAS Institute, Cary, NC). A value of $P < .05$ was considered significant.

RESULTS

Patient Characteristics

Nineteen patients were screened and registered between 2006 and 2007; however, because of a screening error, only 18 patients were randomized and treated with budesonide effervescent tablets. Demographic data, baseline characteristics, and medical background are presented in Table 1. Nine patients received oral prophylactic treatment with amphotericin B.

Two patients discontinued prematurely: 1 patient in arm B suffered from esophagitis, and 1 patient in arm D dropped out because of a deterioration of their cGVHD that required systemic steroids.

The 4 arms did not differ significantly ($P > .05$) in any of the scales at baseline (Table 1): mOMRS, frequency distribution of WHO toxicity scale gastrointestinal/oral, and OMAS.

All patient diaries were reviewed to assess compliance, which was confirmed.

Efficacy Evaluation

All patients improved, that is, the severity of their oral cGVHD was reduced: A median relative reduction of 70% for mOMRS and 69% for OMAS was noted (Table 2). Incidence of objective improvement was high: A 50% reduction in mOMRS was noted in 61% of the patients. The incidence of improvement was also high according to the WHO toxicity scale gastrointestinal/oral (61%) (Table 2).

The mean treatment duration until reaching the best oral cGVHD status (lowest score) ranged between 5.28 and 6.50 weeks for the 4 scales used (Table 2).

The results of the primary efficacy endpoint showed that the rate of objective response (more than 50% compared to baseline) using the mOMRS was not significantly different among the 4 study arms (Table 2). The only scale, of the 7 used, that showed significant differences between the study arms regarding the response to treatment was "time to minimal WHO toxicity gastrointestinal/oral score" (Table 2).

Subjective Improvement

There was no difference between the study arms regarding improvements in any of the subjective parameters that were scored: pain (various scales), dryness, and sensitivity (Table 3).

Pooling of Subgroups According to Frequency of Mouthwash Use

Pooling the study arms with the same number of daily doses (groups A+B and groups C+D) allowed us to evaluate the importance of the frequency of mouthwash use. The frequency of mouthwash use had little impact on the response to treatment,

Table 1. Demographics, Medical Background, and Oral cGVHD Status at Baseline

		Arm A	Arm B	Arm C	Arm D	Total
No. of Patients		4	5	4	5	18
Demographics						
Gender	M:F ratio	4:0	4:1	3:1	2:3	13:5
Age	Mean (SD), years	35.8 (8.4)	44.6 (9.6)	53.3 (14.2)	42.0 (8.2)	43.8 (11.1)
	Median (range), years	36.0 (26-45)	45.0 (34-55)	57.0 (33-66)	40.0 (34-55)	42.0 (26-66)
Medical background						
Time between HSCT and trial	Median (range), weeks	272.0 (32-716)	133.0 (64-349)	181.5 (173-216)	162.0 (59-305)	176.5 (32-716)
Anti-GVHD medications	No. of patients (%):					
	Steroids*	4 (100%)	4 (80%)	2 (50%)	5 (100%)	15 (83%)
	Cyclosporine	3 (75%)	4 (80%)	2 (50%)	5 (100%)	14 (78%)
Oral cGVHD status						
mOMRS	Median (range)	34 (23-40)	37 (21-63)	25 (23-26)	24 (20-44)	26 (20-63)
Frequency distribution of WHO toxicity gastrointestinal/oral	No. of patients:					
	Grade 1			1 (25%)	1 (20%)	2 (11%)
	Grade 2	4 (100%)	3 (60%)	3 (75%)	3 (60%)	13 (72%)
	Grade 3		2 (40%)		1 (20%)	3 (17%)
OMAS at baseline visit	Median (range)	2.0 (1.7-2.0)	2.6 (1.0-4.0)	1.8 (0.7-2.0)	1.1 (0.7-2.1)	1.9 (0.7-4.0)

No. indicates number; M, male; F, female; SD, standard deviation; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; mOMRS, modified oral mucosal rating scale; OMAS=Oral Mucositis Assessment Scale.
*Prednisone/prednisolone.

Table 2. Response to Treatment

		Arm A	Arm B	Arm C	Arm D	Total	*P* Value*
Final visit							
mOMRS	No. of patients with objective response (i.e., at least 50% reduction)	2/4 (50%)	2/5 (40%)	3/4 (75%)	4/5 (80%)	11/18 (61%)	.6355 (Fisher exact test)
	No. of patients with any reduction	4/4 (100%)	5/5 (100%)	4/4 (100%)	5/5 (100%)	18/18 (100%)	
	Median relative reduction (%) (range)	−61 (−85.0-−34.8)	−49 (−90.5-−13.5)	−69 (−76.0-−29.2)	−79 (−90.0-−44.4)	−70 (−90.5-−13.5)	.4143
OMAS	No. of patients with any reduction	4/4 (100%)	5/5 (100%)	4/4 (100%)	5/5 (100%)	18/18 (100%)	
	Median relative reduction (%) (range)	−48 (−72-−22)	−64 (−83-−13)	−76 (−83-−72)	−80 (−100-−63)	−69 (−100-−13)	.0874
WHO toxicity gastrointestinal/oral	No. of patients with any reduction (at least 1 step)	1/4 (25%)	3/5 (60%)	3/4 (75%)	4/5 (80%)	11/18 (61%)	.4847 (Fisher exact test)
Duration to best efficacy, mean in weeks (SD)							
Time to lowest mOMRS score		8.08 (0.22)	4.02 (2.52)	7.58 (1.36)	6.86 (3.12)	6.50 (2.61)	.1477
Time to lowest OMAS score		7.25 (1.71)	5.60 (2.67)	7.58 (1.36)	5.56 (2.90)	6.39 (2.32)	.5868
Time to lowest WHO toxicity gastrointestinal/oral score		8.08 (0.22)	4.02 (2.56)	7.90 (0.70)	4.42 (2.02)	5.89 (2.52)	.0265
Time to lowest oral cGVHD 5-level score		6.65 (2.02)	3.30 (2.85)	6.00 (2.71)	5.60 (2.95)	5.28 (2.78)	.3625

OMRS indicates oral mucosal rating scale; cGVHD, chronic graft-versus-host disease.
*Two-sided Kruskal-Wallis test unless otherwise specified.

Table 3. Subjective Parameters and Analgesic Consumption

			Arm A	Arm B	Arm C	Arm D	Total	*P* Value*
WHO toxicity scale pain	No. (%) of patients with any reduction (at least 1 point)		3 (75%)	2 (40%)	2 (50%)	4 (80%)	11 (61%)	.6355 (Fisher exact test)
WHO pain ladder	No. (%) of patients with any reduction (at least 1 point)		1 (25%)	1 (20%)	0 (0%)	2 (40%)	4 (22%)	.8693 (Fisher exact test)
Patient's subjective description	Median in % (range) of relative reduction:	Mouth dryness	−31 (−63-0)	−57 (−60-0)	−25 (−50-0)	−73 (−75-−71)	−54 (−75-0)	.1835
		Mouth pain	−25 (−50-0)	−20 (−63-0)	−20 (−33-0)	−88 (−100-−75)	−27 (−100 -0)	.2057
		Mouth sensitivity	−21 (−29-100)	−25 (−63-0)	−38 (−43-0)	−43 (−67-33)	−25 (−67-100)	.6835
Duration of mouth-throat pain	Median in weeks (range):	WHO toxicity scale pain	8.0 (7.9-8.4)	8.0 (2.0-8.4)	8.0 (7.9-8.7)	6.4 (1.3-8.3)	8.0 (1.3-8.7)	.5050

*Two-sided Kruskal-Wallis test unless otherwise specified.

Table 4. Response to Treatment: Pooling by Frequency of Mouthwash Use

	Arms A+B (Daily dose: 9 mg)	Arms C+D (Daily dose: 6 mg)	*P* Value for Change between A+B versus C+D
Number of patients	N = 9	N = 9	
Frequency of use	X3/day	X2/day	
mOMRS at baseline			
Mean (SD)	34.44 (13.15)	26.00 (7.11)	.2315*
Median (range)	37 (21-63)	24 (20-44)	
mOMRS at final visit			
Mean (SD)	14.56 (8.78)	8.33 (5.24)	.1015*
Median (range)	15 (2-32)	7 (2-17)	
Relative reduction in mOMRS (%) ([final visit−baseline]/baseline)			
Mean (SD)	−55.5 (26.87)	−68.45 (19.6)	.4268*
Median (range)	−48.7 (−90.5-−13.5)	−72.7 (−90.0-−29.2)	
P value for change between baseline and final visit	.0001†	<.0001†	

mOMRS indicates modified oral mucosal rating scale; SD, standard deviation.
*Wilcoxon test, 2 sided.
†Paired *t* test, 1 sided.

determined by the similarities between the pooled groups at the beginning and end of the study (Table 4).

Evidence of the beneficial effect of budesonide mouthwash was noticed when the pooled mOMRS value at baseline was compared with the pooled mOMRS value at the final visit (Table 4). These differences were statistically significant within both groups.

Safety Evaluation

Eight of the 16 patients who suffered from adverse events had events that were at least "possibly related" to the study drug. All of these adverse drug reactions were mild (6 events) to moderate (2 events), including gastrointestinal disorders (cheilitis, esophagitis), fungal infection, and nervous system disorder (taste alteration). Most of the previously mentioned adverse drug reactions resolved with cessation of the study drug or with basic antifungal treatment (6 events), although 1 adverse drug reaction did not resolve (fungal infection) and 1 patient was lost to follow-up (taste alteration). Three patients interrupted treatment because of adverse events (1 patient in Arm B and 2 patients in Arm D), and 2 of them discontinued participation in the study (Arms B and D). One patient suffered from 3 serious adverse events that were not drug related (Arm B) and did not interrupt the study protocol.

At visits 1, 4, and 5 (6.90 ± 3.17, 6.65 ± 2.26, and 6.97 ± 2.74 μg/dL, respectively), the average serum cortisol concentrations were within the normal range (5-25 μg/dL). At visits 2 and 3 (4.51 ± 1.31 and 4.55 ± 1.64 μg/dL), the serum cortisol concentrations were slightly below normal range. The comparison in mean serum cortisol concentrations between visits 1 to 5 did not show a significant difference between the visits ($P = .1108$). The numbers of subjects in the treatment groups (Arms A-D) were too small to conclude any differences between treatment groups regarding the serum cortisol concentrations (a total of 10 patients).

DISCUSSION

Four dosing protocols of a new topical budesonide preparation were evaluated to determine which dosage can achieve a reduction of at least 50% in the mOMRS score (objective improvement) between the initial and final visits of this 8-week trial. All patients showed improvement, and 61% improved objectively. There were no significant differences in response rate among the 4 treatment arms. The other objective and subjective variables examined, which indicate oral cGVHD severity, support the conclusion that this preparation is beneficial, irrespective of the dosing protocol employed.

The dose of topical budesonide reported in the literature for treatment of oral cGVHD is higher than the doses tested in this study. For example, 15-minutes protocols 3 to 4 times daily were reported by Elad et al. [10] and Sari et al. [19]. In a report describing 2 patients, a lower dose (3 mg of budesonide for 3-5 minutes 3 times daily) [20] was used. All studies regarding topical budesonide had favorable results. Although compliance was not an obstacle in our previous study that had a 15-minutes, 3 times a day mouthwashing schedule [10], in this study we reduced the duration to 10 minutes, 2 or 3 times daily in order to make it easier for the patients.

According to the literature, the benefits of topical budesonide treatment increase over time, and the early response within the first 2 to 3 weeks of treatment is enhanced by cumulative effects during the next weeks of treatment [10,19]. Our findings are congruent with these publications, because the greatest improvement was noted after 5 to 7 weeks of treatment. Therefore, patients using topical budesonide should be informed about the lag between treatment commencement and response. The implications for future trials and follow-up periods are clear.

Pharmacokinetic studies of budesonide in healthy individuals showed that only 2% of a buccal dose of

budesonide enters the systemic circulation [11]. However, in patients with oral cGVHD, 10% of the dose entered the circulation, possibly because of altered drug uptake (because of the loss of epithelial integrity in ulcerative lesions) and metabolization [11]. This systemic level is similar to the safe concentrations reached after oral intake of enteric-coated budesonide for inflammatory bowel disease [21,22]. In our study, no severe adverse events were attributed to topical treatment with budesonide. The remaining adverse events possibly associated with the study drug were mainly mild, localized to the mouth and its surrounding tissues, and transient. The absence of adverse effects, together with steady serum cortisol levels, confirms previous studies regarding the safety profile of topical budesonide in oral cGVHD patients [10,19,20].

In summary, this study was designed to determine the best dosing protocol for a novel topical budesonide formulation to be able to continue to the next stage of drug development. We want to manage oral cGVHD in a safe yet aggressive manner, and our safety analysis supports a dosing schedule of 3 mg of budesonide 3 times a day applied for 10 minutes in the form of a mouthwash. Currently, a large-scale, phase III, randomized, controlled, double-blinded study is being conducted in multiple centers to assess the efficacy of this safe dose of the new preparation of topical budesonide in the treatment of oral cGVHD (http://www.clinicaltrials.gov identifier NCT00887263).

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