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The Effect of Budesonide Mouthwash on Oral Chronic Graft Versus Host Disease

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Oral chronic graft versus host disease (cGVHD) is common and a major cause of morbidity and loss of quality of life in long term survivors. Cyclosporine with prednisone remains the first line therapy for oral manifestations of cGVHD. However, even with routine administration of systemic agents, many patients with oral manifestations of cGVHD do not have resolution of their disease and may benefit from incorporation of local therapy. Budesonide is a highly potent steroid which has minimal systemic side effects and being used for oral cGVHD. We designed a retrospective study to compare treatment results of patients with oral cGVHD who received topical budesonide in addition to systemic therapy that consists of combined prednisone and cyclosporine (Group A, $n = 12$), with the treatment results of patients who were administered the same systemic therapy alone (Group B, $n = 11$) to determine whether budesonide mouthwash had any advantage on response rates. Three mg topical budesonide/10 ml saline was used 3–4 times a day for up to 6 months in group A. Diagnosis, clinical staging, and treatment response scoring for cGVHD were performed according to National Institutes of Health (NIH) consensus criteria. At the baseline examination, there were no statistically significant differences in terms of median oral cGVHD examination scores between two groups. After treatment, there was statistically significant decrease in median oral cGVHD examination scores compared to baseline ($P < 0.001$ and 0.021), and significant differences were found between two groups ($P < 0.032$). Overall response rate was 83% and 36% for group A and B, respectively ($P = 0.036$). However, no statistically significant differences were found between median pain scores of two groups before and after treatment ($P = 0.740$ and $P = 0.091$). No major systemic side effects and oral candidiasis were observed in two groups of patients. We concluded that topical budesonide might be added to systemic therapy to obtain better response rates in patients with oral cGHVD. Am. J. Hematol. 82:349–356, 2007. © 2006 Wiley-Liss, Inc.

Key words: budesonide; oral chronic graft versus host disease; stem cell transplantation

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a lethal and common long-term complication of allogeneic hematopoietic stem cell transplantation (HSCT). The syndrome has many features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodefi-

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ciency. Although the pathophysiology of cGVHD is not understood completely, it is believed to be primarily mediated by T cells recognizing tissue antigens of the recipient [1].

Staging of cGVHD has been limited by the dearth of high-quality studies. The original designation of "limited" and "extensive" cGVHD was established based on a small retrospective study [2] that has limited utility. Efforts to enhance prognostic accuracy have resulted in improvements in grading, but those systems have not adopted wide acceptance [3,4]. Recently, the National Institutes of Health (NIH) have proposed a new consensus statement to improve the accuracy of diagnosis, staging, and treatment response scoring for cGVHD.

Oral GVHD can occur in 25–70% of patients, despite GVHD prophylaxis consisting of immunosuppressives such as, methotrexate, cyclosporine, and corticosteroids [5,6]. The oral findings of cGVHD include white plaques which resemble oral lichen planus, mucosal atrophy, erythema, and ulcers [7]. Involvement of the salivary glands may cause dryness of the oral mucosa and oral pain may be the first presenting symptom [8]. First-line therapy is mostly systemic in nature, consisting of cyclosporin and steroids. The most common salvage treatments for cGVHD are thalidomide, tacrolimus, mycophenolate mofetil, T cell depletion by Campath-1, and phototherapy [9].

Oral manifestations of cGVHD can significantly affect the life quality of patients through discomfort and impairment of the oral intake leading to malnutrition and increased morbidity [10]. It is often refractory to conventional treatment and therefore complementary topical treatment is required. Several agents are currently used for local treatments such as palliative rinses, topical immunosuppressive agents, thalidomide, retinoids, and phototherapy for oral GVHD [11–14].

Budesonide is a highly potent steroid, indicated for the treatment of asthma and gastrointestinal disorders because of a very low bioavailability when absorbed through mucosal surfaces that minimizes systemic side effects [15,16]. Current knowledge regarding the effect of topical budesonide treatment in oral cGVHD is not sufficient. Therefore, we designed a retrospective study according to NIH consensus criteria comparing the treatment results of patients with oral cGVHD who received topical budesonide plus systemic therapy consisting of prednisone and cyclosporine with the treatment results of patients who were administered the same systemic therapy alone to determine whether budesonide mouthwash had any advantage on response rates.

MATERIAL AND METHODS

Patients

Between January 1999 and February 2006, 23 patients with hematologic malignancies who underwent allogeneic peripheral blood stem cell transplantation from HLA-matched sibling donors and had chronic graft versus host disease (cGVHD) including oral manifestations were treated with either oral budesonide rinse in addition to combined prednisone plus cyclosporine or the same systemic therapy alone (Group A; $n = 12$), (Group B; $n = 11$). Different conditioning regimens were used in the patients: BuCy2 [16 mg/kg oral busulphan plus 120 mg/kg cyclophosphamide], IV Bu + Cy2 [12.8 mg/kg intravenous (IV) busulphan plus 120 mg/kg cyclophosphamide], IV Bu-Flu [6.4 mg/kg intravenous busulphan plus 125 mg/m^2 fludarabine], po Bu-Flu [8 mg/kg intravenous busulphan plus 125 mg/m^2 fludarabine], and Flu-Cy [125 mg/m^2 fludarabine plus 120 mg/kg cyclophosphamide]. Cyclosporine and short-term methotrexate were used for GVHD prophylaxis.

Study Design

This study was a cohort analysis examining oral cGVHD outcomes and comparing treatment results of two groups. Two cohorts of patients were evaluated prospectively after allogeneic hematopoietic stem cell transplantation (HSCT) in terms of oral GVHD as a part of routine examination, but the associated outcomes were assessed retrospectively. Before the analysis, the data of our transplant center regarding the diagnosis, staging, and treatment response scoring of cGVHD were adapted according to new criteria recommended by NIH consensus [17,18]. Oral cGVHD was assessed twice weekly by a specialist from the Oral Diagnosis and Radiology Department of the Dental Faculty of Erciyes University as a part of routine clinical care.

Diagnosis of cGVHD

cGVHD was defined as at least one diagnostic or distinctive manifestation of cGVHD confirmed by pertinent biopsy. Infections and other causes related with differential diagnosis of cGVHD have been excluded by routine diagnostic methods such as special stains and cultures.

Oral cGVHD was defined as presence of one of the diagnostic or distinctive features of oral cGVHD such as lichen planus-like changes, hyperkeratotic plaques, mucoceles, mucosal atrophy, pseudomembranes, or ulcers. Infectious pathogens such as yeast or herpes virus have been excluded by the cultures and the serological tests that were performed during

TABLE I. Scoring System for Oral CGVHD Recommended by NIH Consensus [18]

Mucosal change	No evidence of CGVHD	Mild	Moderate	Severe
Erthema	None (0)	Mild erythema or moderate erythema (1)	Moderate (≥25%) or severe erythema (<25%) (2)	Severe erythema (≥25%) (3)
Lichenoid	None (0)	Hyperkeratotic changes (<25%) (1)	Hyperkeratotic changes (25–50%) (2)	Hyperkeratotic changes (>50%) (3)
Ulcers	None (0)	None (0)	Ulcers involving (≤20%) (3)	Severe ulcerations (>20%) (6)
Mucoceles	None (0)	1–5 mucoceles (1)	6–10 scattered mucoceles (2)	Over 10 mucoceles (3)

routine oral examination. All biopsies were taken from extraoral sites of the patients for the diagnosis of cGVHD.

Clinical Scoring of Organ Systems

Each organ or sites were scored according to a four point scale (0–3), with 0 representing no involvement and 3 reflecting severe impairment.

Baseline Clinical Scoring of Oral cGVHD

For oral cGVHD, the definitions of the baseline clinical scores were as follows: Score 0, no symptoms; Score 1, mild symptoms with disease signs but not limiting oral intake significantly; Score 2, moderate symptoms with disease signs with partial limitation of oral intake; Score 3, severe symptoms with disease signs with major limitation of oral intake.

Global Scoring of cGVHD

The terms "mild," "moderate," and "severe" were used for the global scoring of cGVHD at the initial diagnosis. Mild cGVHD was defined as involvement of only one or two organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). Involvement of at least one organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or involvement of three or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites) were considered as moderate cGVHD. Finally, severe cGVHD was described as major disability caused by cGVHD (score of 3 in any organ or site).

Treatment Protocols

Systemic therapy. Combination of prednisone (2 mg/kg/day, po or IV) and cyclosporine (6 mg/kg/day, po or 3 mg/kg/day, IV) were administered for initial therapy to all patients in group A and B having moderate or severe cGVHD. The doses were adjusted according to the treatment responses of cGVHD during routine examinations.

Budesonide mouthwash. Oral budesonide rinse was given to the patients in group A during systemic therapy to provide better local control of oral cGVHD. The 3-mg coated capsule form of the medication was selected for administration. Patients were instructed to crush the budesonide capsule, dissolve it in 10 ml of water, and rinse for 15 min three or four times daily, then expectorate the solution. During the treatment, oral candidiasis was assessed clinically and cultures were taken accordingly.

Oral cGVHD Assessments

Oral cGVHD assessments were performed by using the newly proposed modification of the Schubert Oral Mucositis Rating Scale that scores oral surfaces from 0 to 15, with higher scores indicating more severe involvement. Four cGVHD manifestations were assessed for all areas (lips, labial mucosa, tongue, and soft palate) in the mouth: (1) mucosal erythema (0–3) grading based on the color intensity; (2) lichen-type hyperkeratosis (percent of oral surface area); (3) ulcerations (percent of oral surface area); and (4) presence of mucoceles (total number). Severity of mucosal changes was determined relative to entire mouth as "none," "mild," "moderate," and "severe." Oral cGVHD scoring system was summarized in Table I.

Assessment of Treatment Response

Complete response (CR) was defined as resolution of all manifestations related to oral cGVHD in the mouth. Partial response (PR) was defined as at least 50% improvement in the oral mucositis scale. Stable disease (SD) was defined as no change in cGVHD. Finally, progression of oral cGVHD was defined as the absolute increase of at least 25% in the scale.

Patients' Self Report for Oral Pain

The severity of pain was evaluated by using a visual analog scale (VAS) from 0 (no pain) to 10 (the most severe pain). This method of measuring pain

TABLE II. General Characteristics of the Patients in Group A and B

General characteristics	Group A ($n = 12$)	Group B ($n = 11$)	P-value
Patients (number)			
Male	8	7	1.000
Female	4	4	
Median patient age (range) (year)	29 (23–57)	36 (23–52)	0.525
Diagnosis (number)			
AML	6	3	0.352
ALL	3	1	
MDS	–	1	
CML	2	4	
NHL	–	1	
HD	1	–	
MF	–	1	
Conditioning regimen (number)			
IV Bu + Cy2	8	5	0.063
BuCy2	3	–	
IV Bu-Flu	1	2	
Bu-Flu	–	1	
Flu-Cy	–	3	
Clinical oral cGVHD score at baseline (number)			
Score 1	3	1	0.638
Score 2	5	7	
Score 3	4	3	
Extraoral cGVHD involvement sites (number)			
Skin	10	11	0.478
Eyes	3	2	1.000
GIT	7	3	0.214
Liver	7	6	1.000
Clinical global cGVHD score at baseline (number)			
Severe	10	7	0.371
Moderate	2	4	
Mild	–	–	
Median months after HSCT (range)	8.5 (6–32)	7.0 (4–24)	0.337
Median follow-up periods (range) (day)	108 (84–280)	120 (100–210)	0.266

HSCT, hematopoietic stem cell transplantation; cGVHD, chronic graft versus host disease; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodisplastic syndrome; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin's disease; MF, myelofibrosis; IV Bu + Cy2, IV busulphan plus cyclophosphamide; BuCy2, po busulphan plus cyclophosphamide; IV Bu-Flu, IV busulphan plus fludarabine; Bu-Flu, po busulphan plus fludarabine; Flu-Cy, fludarabine plus cyclophosphamide.

was chosen because it is simple, specific, and reliable for comparing patients' changes within themselves.

Statistics

The statistical evaluations were conducted by a computer program (SPSS version 13.0, SPSS, Chicago, IL). For both groups the median values of the oral CGVHD examination scores and pain scores were calculated. The Wilcoxon signed ranks test was used to compare the data before and after treatment for each group. Comparisons between treatment groups at baseline and posttreatment period were performed by the Mann and Whitney U-test. Comparisons of treatment response rates between two groups were accomplished by the χ^2 test. The Fisher's exact test was used instead of the χ^2 test when any of the cells in a cross-tabulation contained fewer than five subjects. A P-value <0.05 was considered to indicate statistical significance.

RESULTS

General Characteristics of the Patients

General characteristics of total 23 patients in group A (12 patients) and group B (11 patients) were given in Table II. The median age of the patients were 29 (range, 23–57 years) and 36 (range, 23–52 years) for group A and B, respectively. In group A, 6 patients had acute myelogenous leukemia (AML), 3 had acute lymphoblastic leukemia (ALL), 2 had chronic myeloid leukemia (CML), and 1 had Hodgkin's disease (HD). In group B, 3 patients had AML, 1 had ALL, 1 had MDS, 4 had CML, 1 had NHL, and 1 had myelofibrosis (MF). In group A, the conditioning regimens consisted of IV Bu + Cy2 in eight cases, BuCy2 in three cases, and IV Bu-Flu in the remaining one case. In group B, the conditioning regimens consisted of IV Bu + Cy2 in eight cases, IV Bu-Flu in two cases, Bu-Flu in one case, and Flu-Cy in the remaining three cases. Severe oral cGVHD was present in 4 and 3 patients for group A and B, respectively. Most frequent extraoral site with cGVHD involvement was skin for the patients of both groups (10 of 12 in group A and 11 of 11 in group B). Other extraoral sites with cGVHD involvement were eyes, gastrointestinal tract, and liver. No pulmonary involvement was observed in the patients. Global CGVHD scores was severe in 10 patients in group A and in 7 patients in group B. The median time elapsed from the HSCT up to the enrollment in this study was 8.5 months (range, 6–32 months) and 7 months (range, 4–24 months) for the patients in group A and B, respectively.

Median follow-up period of the patients in group A receiving systemic therapy plus budesonide rinse was 108 days (range, 84–280 days). Budesonide mouthwash was initiated at a median of 68.5 days (range, 46–90 days) to obtain higher response rates in this group. Median duration of budesonide treatment was 50 days (range 20–190 days). In group B, median follow-up period of the patients receiving systemic therapy alone was 120 days (range, 100–210). General characteristics of the patients were not significantly different in two groups ($P > 0.05$) (Table II).

TABLE III. Oral cGVHD Examination Scores and Treatment Responses Before and After Treatment for the Patients in Group A

	Before systemic therapy					After systemic therapy with budesonide mouthwash					
Patient	Erythema	Lichenoid	Ulcers	Mucoceles	Total score	Erythema	Lichenoid	Ulcers	Mucoceles	Total score	Response
1	1	2	6	1	10	1	0	6	0	7	SD
2	1	1	6	0	9	1	0	3	0	4	PR
3	2	1	6	0	9	0	0	3	0	3	PR
4	2	1	6	0	9	1	0	3	0	3	PR
5	1	2	6	2	11	0	0	3	1	4	PR
6	1	2	3	1	7	0	0	3	0	3	PR
7	1	2	1	1	5	0	0	0	0	0	CR
8	1	2	6	2	11	0	0	3	1	4	PR
9	1	1	6	1	9	0	0	3	0	3	PR
10	1	3	6	1	11	1	1	6	0	8	SD
11	1	1	3	0	5	0	0	0	0	0	CR
12	0	2	1	1	4	0	0	0	0	0	CR

PR, partial remission; CR, complete remission; SD, stabil disease; Prog, progression.

TABLE IV. Oral cGVHD Examination Scores and Treatment Responses Before and After Treatment for the Patients in Group B

	Before systemic therapy					After systemic therapy					
Patient	Erythema	Lichenoid	Ulcers	Mucoceles	Total score	Erythema	Lichenoid	Ulcers	Mucoceles	Total score	Response
1	1	2	6	1	10	1	2	3	0	5	PR
2	2	1	3	1	7	1	0	0	1	2	PR
3	1	2	6	0	9	1	1	6	0	8	SD
4	1	0	3	0	4	0	0	0	0	0	CR
5	1	0	6	1	8	1	1	6	0	8	SD
6	2	1	6	2	11	0	1	3	1	5	PR
7	1	3	6	2	12	1	2	6	1	10	SD
8	1	1	3	1	6	2	2	3	2	9	Prog
9	1	3	6	1	11	1	2	6	1	10	SD
10	1	2	3	0	6	1	2	0	1	4	SD
11	1	1	3	0	5	1	0	3	0	4	SD

PR, partial remission; CR, complete remission; SD, stable disease; Prog, progression.

Oral cGVHD Assessments: Examination Scores and Response Rates

Erythema and ulcers were major manifestations for both groups (Tables III and IV). Before treatment, median oral cGVHD examination scores were 9 (range, 4–11) and 8 (range, 4–12) for group A and B, respectively. At the baseline examination, there were no statistically significant differences in terms of median examination scores between two groups. After treatment, there was statistically significant decrease in median examination scores compared to baseline ($P < 0.001$ and 0.021), and significant differences were found between two groups ($P < 0.032$) (Table V).

In group A, 3 patients achieved CR and 7 PR at a median of 110 days (range, 92–125 days) and 100 days (range, 84–180 days), respectively. Two patients had SD, and no progression was observed (Table III). In group B, 1 patient achieved CR and 3 patients achieved PR at a median of 117.5 days (range, 100–148 days). Six patients had SD, and 1 progression was observed in this group (Table IV). Overall response rate was 83% and 36% for group A and B, respectively ($P = 0.036$) (Table VI).

Patients' Self Report for Pain

Before treatment, median pain scores were 5.5 (range, 3–9) and 5 (range, 3–9) for the patients in group A and B, respectively. After treatment, there was statistically significant decrease in median pain scores compared to before treatment ($P < 0.001$ and 0.006). However, no statistically significant differences were found between two groups before and after treatment ($P = 0.740$ and $P = 0.091$) (Table VII).

Adverse Effects and Infections

Major systemic side effects and oral candidiasis were not observed in two group of patients treated with budesonide mouthwash plus systemic therapy or systemic therapy alone. One patient causing termination of the budesonide treatment in early period complained about a local oral burning sensa-

TABLE V. Median Oral cGVHD Examination Scores of the Patients in Group A and B at Baseline and Post-treatment Period

Groups	Oral CGVHD examination scores [Median (min–max)]		
	Before treatment	After treatment	P^*-value
Group A	9 (4–11)	3 (0–8)	<0.001
Group B	8 (4–12)	5 (0–10)	0.021
P^{γ}-value	0.880	0.032	

P^*-value, significance of differences within (Wilcoxon signed ranks test) the groups. P^{γ}-value, significance of differences between (Mann and Whitney U-test) the groups.

TABLE VI. The Comparison of Treatment Response Rates of Group A and B

Treatment response	Group A		Group B		P-value
	$n = 12$	%	$n = 11$	%	
Overall response	10	83	4	36	
Stable disease and progression	2	17	7	64	0.036

TABLE VII. Median Pain Scores of the Patients in Group A and B Before and After Treatment

Groups	Patients' self report for pain [Median (min-max)]		
	Before treatment	After treatment	P^*-value
Group A	5.5 (3–9)	2 (0–5)	<0.001
Group B	5 (3–9)	4 (0–6)	0.006
P^{γ}-value	0.740	0.091	

P^*-value, significance of differences within (Wilcoxon signed ranks test) the groups. P^{γ}-value, significance of differences between (Mann and Whitney U-test) the groups.

tion in group A. During the topical treatment, oral herpes-simplex virus infection was seen in one patient who was treated with direct appropriate antiviral therapy.

DISCUSSION

Oral cGVHD is common and a major cause of morbidity and loss of quality of life in long term survivors [10,19]. In a randomized trial of PBSC versus BMSC transplants, oral mucosal changes were the most common manifestation of cGVHD in BMSC recipients and the second most common in PBSC transplants. Overall incidence was around 85% [20]. Furthermore, in many patients severity of oral manifestations of cGHVD does not correlate with systemic manifestations [7].

Systemic immunosuppressive therapy is indicated for severe cGHVD. Because most patients with oral cGVHD have a severe form of the disease, systemic therapy is generally administered. The great disadvantage of systemic immunosupression is significant side-effects such as diabetes mellitus, renal insufficiency, osteoporosis, and increased frequency of opportunistic infections.

Cyclosporine with prednisone remains the first line therapy for severe and moderate cGVHD [21]. However, little is known about the effects of systemically administered cyclosporine and prednisone on the oral component of cGVHD. There are several studies evaluating the effect of cyclosporine and prednisone in patients with cGVHD [22–24]. However, survival was the primary outcome measure in these studies and the effect on oral cGHVD was not presented as a separate outcome measure. Other systemic treatments such as sirolimus, mycophenolate mofetil (MMF), extracorporeal photopheresis, hydroxychloroquine, clofazimine, thalidomide, pentostatin, and methotrexate have been used for cGHVD [25–32]. The response rates with these drugs widely vary from one study to another (24–67%). In the present study, combined cyclosporine-A and prednisone were used for systemic therapy, and the overall response rate in oral cavity disease was 36% in the patients being administered systemic therapy without topical therapy.

Even with routine administration of systemic agents, many patients with oral manifestations of cGVHD do not have resolution of their disease and may benefit from incorporation of local therapy. Topical treatments offer a means to intensify therapy to one area of the body while sparing the host further systemic immunosuppression. Despite this advantage, few controlled trials have examined the efficacy of topical treatments for oral mucosal GVHD. Wolff et al. [33] compared topical dexamethasone rinse (0.1 mg/cc) to ultraviolet light therapy after psoralen administration (PUVA). There were 16 patients in the dexamethasone arm with 9 responding completely and 2 partially. In the same study, complete response was achieved in 4 out of 7 patients and partial in 2 in PUVA arm. Epstein et al. [11] investigated the effect of cyclosporine rinse on a group of 11 patients with oral cGVHD who previously failed in the therapies with topical dexamethasone and topical cyclosporine 100 mg/ml as a rinse. The objective clinical response rate was 45% after 1 month of treatment. Another small trial of cyclosporine in adhesive base applied 4 times a day in 4 cGVHD patients by the same authors reported 75% objective response rate [34]. In a small open-label study, topical azathioprine rinse and gel have been evaluated in the patients who had resistant oral cGVHD. The mean response to topical azathioprine was 60%, with mean duration of the treatment of 16.7 weeks [35]. Recently, Eckardt et al. have

reported good responses by topical tacrolimus in 10 patients with steroid refractory oral GVHD [36]. Grading, staging, and treatment response scoring for cGVHD were different in most of these studies and comparison of the treatment results were more difficult.

Budesonide is a novel corticosteroid and since the side effects are minimal with its recommended dosage for the treatment of mucous membranes, it may be used for oral cGVHD [37–39]. Bertz et al. [40] firstly used the budesonide as a topical treatment for acute intestinal GVHD and concluded that it might be effective for this condition. Previously, Elad et al. [41] used the topical budesonide in chronic resistant oral cGVHD in a study without a control group. The reported overall success measured as reduction in surface area of ulceration and severity of erythema was 58% in this study. However, it was too difficult to determine whether the patients' oral GVHD responded to only topical budesonide treatment while the systemic therapies were continuing. In our study, the NIH consensus criteria were used to evaluate the baseline severity and the improvement of oral cGVHD, before and after treatment. Median cGVHD oral examination scores and pain scores were significantly reduced in two groups, after treatment. Furthermore, the treatment outcomes based on the clinician's examination and scoring in the patients on topical budesonide plus systemic therapy were much better than the control group of the patients who received systemic therapy alone. However, there were no statistically significant differences between the median pain scores of two groups before and after treatment.

In conclusion, combined systemic therapy with cyclosporine and prednisone has been still first choice for oral manifestations of cGVHD. However, topical budesonide may be used on adjunctive therapy for oral cGHVD to control the disease successfully. The addition of topical budesonide to combined systemic therapy had an advantage in terms of examination scores and response rates in patients with oral cGHVD. The role of topical therapies needs to be further investigated by randomized prospective clinical trials conducted with larger series of patients.

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