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Supportive Care

Long-Term Utilization Patterns of Topical Therapy and Clinical Outcomes of Oral Chronic Graft-versus-Host Disease

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A B S T R A C T

An open-label phase 2 study of topical dexamethasone versus tacrolimus solutions in new-onset oral chronic graft-versus-host disease (cGVHD) revealed the superior efficacy of dexamethasone. The objective of this study was to report long-term patterns of topical therapy utilization and clinical outcomes in this cohort after completing the 30-day trial. A retrospective record review was performed from the date of study completion to January 2017. Topical therapies, systemic immunosuppressive therapies, objective measurements (National Institutes of Health severity score, oral mucosal scores), patient- reported outcomes (dryness, sensitivity, pain), and adverse events were recorded for oral cGVHD-related outpatient visits. Follow-up (FU) periods were defined as FU1 (0-1 month), FU2 (1-3 months), FU3 (3-6 months), FU4 (6-12 months), FU5 (12-18 months), and FU6 (18-24 months). Forty patients (52.5% males, median age, 56 years) completed the clinical trial and were included in the analysis. Topical therapies used were dexamethasone, tacrolimus, clobetasol, or a combination of these agents. At FU1, all 40 patients were receiving topical therapy, which decreased to 54.5% (12 out of 22) at FU6. Clinician-reported oral mucosal scores (0-12) and patient-reported sensitivity scores (0-10) decreased over time from FU1 (median mucosal score, 3; sensitivity, 3) to FU6 (mucosal score, 1; sensitivity, 2). Intralesional steroid therapy was provided to 6 patients for management of refractory oral ulcerations, all within the first year of follow-up. Patients with de novo symptomatic oral cGVHD may require long-term care with topical immunomodulatory therapy for up to 2 years, if not longer. Topical steroid and tacrolimus therapies are safe and effective in managing symptomatic oral cGVHD. Second-line topical therapy for refractory oral cGVHD requires further investigation.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a frequent complication of allogenic hematopoietic stem cell transplantation (alloHCT), affecting up to 70% of recipients and commonly involving the skin, mouth, eyes, gastrointestinal tract, liver, lungs, and joints [1–4]. Among the patients who develop cGVHD, 44%-83% will have manifestations in the oral cavity, characterized by hyperkeratotic reticulations and plaques, erythema, and ulcerations that chiefly affect the buccal mucosa and tongue but can also be present throughout the mouth [5,6]. Patients report a range of symptoms from mild discomfort and irritation to severe pain and sensitivity, which can adversely affect nutrition, oral hygiene, and quality of life [7–11]. Even when other sites of cGVHD are well controlled with systemic immunosuppressive agents or are no longer active, the oral cavity may remain active and necessitate continuous treatment with localized therapy [12,13].

The National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease recommends intensive topical immunomodulatory therapies for the management of oral cGVHD, including corticosteroids and tacrolimus [14]. However, despite these expert recommendations, there are no data available on the long-term outcomes of oral cGVHD management, especially with respect to the duration of therapy and management of disease refractory to first-line topical therapies. We previously reported the results of a phase 2 clinical trial in which patients with previously untreated and symptomatic oral cGVHD were randomized to topical dexamethasone or tacrolimus solutions as a 4-times-daily swish and spit for 1 month [15]. The objective of the present study was to

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report long-term patterns of topical therapy utilization and clinical outcomes in patients with oral cGVHD who completed the phase 2 clinical trial.

METHODS

Oral cGVHD Cohort

Patients with oral cGVHD who completed the randomized, open-label, phase 2 clinical trial of topical dexamethasone versus topical tacrolimus (Clinical Trials.gov identifier NCT00686855) were included in this retrospective analysis. During the clinical trial, patients were instructed to swish with 5 mL of either dexamethasone .1 mg/mL or tacrolimus .1% solution for 5 minutes and then spit, 4 times a day for 30 days [15]. There were no protocol-related limitations concerning topical therapy use after completion of the study. Patients with symptomatic oral cGVHD after study completion were managed with the clinician's preferred topical and/or systemic therapy.

Institutional Review Board approval was obtained by the Dana-Farber/Harvard Cancer Center Office for Human Research Studies. The need for informed consent was waived due to the retrospective nature of the study.

Data Collection

Electronic medical records from oral medicine and oncology visits were reviewed from completion of the clinical trial (defined as the "baseline visit" for the present analysis) to January 31, 2017. Topical therapies, intralesional steroid therapy, systemic immunosuppressive therapies, oral cGVHD assessments, and adverse events were recorded on a standardized collection form.

Clinician-reported oral cGVHD outcomes included the NIH oral cavity severity score (0-3) and oral mucosal scores (erythema, 0-3; lichenoid changes, 0-3; ulcerations, 0-6; composite, 0-12) (13). Patient-reported outcomes included pain (0-10), sensitivity (0-10), and dryness (0-10) scores.

Statistical Analysis

Longitudinal data collected from each patient were categorized into follow-up (FU) intervals, defined as follows: FU1, 0-1 months; FU2, 1-3 months; FU3, 3-6 months; FU4, 6-12 months; FU5, 12-18 months; and FU6, 18-24 months. Patients were included in a given follow-up interval only if there was a recorded clinical visit during that defined time period, and those who did not have a recorded visit were omitted from the analysis of that follow-up interval. Treatments received during each follow-up interval were recorded as combination therapy if both a corticosteroid (dexamethasone or clobetasol) solution and tacrolimus solution were provided to a patient at any given point in the follow-up interval. However, when clobetasol was added to a dexamethasone regimen, only clobetasol was recorded to represent this escalation. The maximum treatment dose and outcome scores per follow-up interval were recorded for each patient.

For each follow-up interval, the number of individual topical therapies and each possible combination of topical treatments were tallied across the cohort. Prednisone dose was calculated by dividing the daily dose of prednisone (in mg) by the weight (in kg) per visit per patient. The median and range of prednisone dose (in mg/kg) for the cohort during each follow-up interval were also calculated. The median and range of clinician and patient-reported outcome scores were calculated for the cohort per interval. Median follow-up time was defined as the median of the difference (in months) between each clinic visit and the baseline visit.

Descriptive data analysis was performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria), and visualization schemes were created with the ggplot2 R package (version 3.0.0, H. Wickham; Springer-Verlag, New York, NY). Final editing was performed using Adobe Illustrator version 23.0.2 (Adobe, San Jose, CA).

A Kaplan-Meier survival analysis was performed to determine the cumulative incidence of first topical therapy discontinuation over time. An event was defined as the first break in topical treatment prescription. Patients who continued on topical therapy for the entire duration of the analysis were censored to their last appointment date.

RESULTS

Patient Characteristics

Forty patients with oral cGVHD (52.5% male) completed the phase 2 clinical trial of topical dexamethasone versus topical tacrolimus and were included in this retrospective analysis (Table 1). The median patient age at baseline was 56 years (range, 24-75 years), and the median duration of follow-up was 7.6 months (range, .7-24 months). The majority of patients were treated with nonmyeloablative conditioning (62.5%) and received a peripheral blood stem cell graft from a matched unrelated donor (65.0%). All patients received GVHD prophylaxis, with short-course methotrexate and a calcineurin inhibitor the most frequently used regimen.

Table 1
Patient Characteristics

Characteristic	Value	
Age, yr, median (range)	56	(24-75)
Follow up duration, months, median (range)	7.6	(.7-24)
Sex, n (%)		
Male	21	(52.5)
Female	19	(47.5)
Diagnosis, n (%)		
AML	16	(40.0)
NHL	7	(17.5)
ALL	5	(12.5)
CLL/SLL/PLL	5	(12.5)
CML	3	(7.5)
MDS	3	(7.5)
HD	1	(2.5)
GVHD prophylaxis, n (%)		
Tacrolimus/methotrexate/sirolimus	16	(40.0)
Tacrolimus/methotrexate	15	(37.5)
Tacrolimus/sirolimus	4	(10.0)
Tacrolimus/methotrexate/bortezomib	3	(7.5)
Methotrexate/sirolimus	1	(2.5)
Cyclosporine/methotrexate	1	(2.5)
Conditioning intensity, n (%)		
Myeloablative	15	(37.5)
Nonmyeloablative	25	(62.5)
Donor type, n (%)		
Matched related	11	(27.5)
Matched unrelated	26	(65.0)
Mismatched unrelated	3	(7.5)

AML indicates acute myelogenous leukemia; NHL, non-Hodgkin lymphoma; ALL, acute lymphoblastic lymphoma; CLL, chronic lymphocytic lymphoma; SLL, small lymphocytic lymphoma; PLL, prolymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; HD, Hodgkin disease.

At the baseline visit, all patients were being treated with some form of systemic immunosuppressive therapy, including tacrolimus (50.0%; n = 20), prednisone (42.5%; n = 17), sirolimus (25%; n = 10), and/or mycophenolate mofetil (7.5%; n = 3) (Table 2). The median prednisone dose at baseline was 0 mg/kg (range, 0-1.11 mg/kg), which subsequently fluctuated from .18 mg/kg (range, 0-.74 mg/kg) during FU2 to .08 mg/kg (range, 0-.35 mg/kg) during FU6 (Supplementary Figure 1). By the end of the 2-year study period, 9 patients (22.5%) had died (Figure 2).

Topical Immunomodulatory Therapy Over Time

During the first month of follow-up (FU1), all patients (n = 40) received topical therapy for oral cGVHD, including dexamethasone solution (n = 25; 62.5%), tacrolimus solution

Table 2
Systemic Immunosuppressive Therapies at Baseline Visit

Immunosuppressive Therapy	Patient Count (N = 40)	Percentage
Tacrolimus	20	50.0
Prednisone	17	42.5
Sirolimus	10	25.0
Mycophenolate mofetil	3	7.5

Table 3
Topical Immunomodulatory Therapies by Follow-Up Interval

Therapy	0-1 Month (N = 40), n (%)	1-3 Months (N = 25), n (%)	3-6 Months (N = 24), n (%)	6-12 Months (N = 36), n (%)	12-18 Months (N = 28), n (%)	18-24 Months (N = 22), n (%)
Dexamethasone	25 (62.5)	5 (20)	9 (37.5)	14 (38.9)	4 (14.3)	6 (27.3)
Clobetasol	1 (2.5)	2 (8)	2 (8.3)	2 (5.6)	1 (3.6)	2 (9.1)
Tacrolimus	5 (12.5)	2 (8)	1 (4.2)	1 (2.8)	1 (3.6)	1 (4.5)
Dexamethasone and tacrolimus	7 (17.5)	7 (28)	4 (16.7)	4 (11.1)	4 (14.3)	3 (13.6)
Clobetasol and tacrolimus	2 (5)	1 (4)	2 (8.3)	3 (8.3)	2 (7.1)	0
Any therapy	40 (100)	17 (68)	18 (75)	24 (66.7)	12 (42.9)	12 (54.5)
None	0	8 (32)	6 (25)	12 (33.3)	16 (57.1)	10 (45.5)

(n = 5; 12.5%), clobetasol solution (n = 1; 2.5%), a combination of dexamethasone and tacrolimus solutions (n = 7; 17.5%), and a combination of clobetasol and tacrolimus (n = 2; 5%) (Table 3). In FU2 (n = 25), 68% of the patients (n = 17) continued to receive topical therapy, including dexamethasone (n = 5; 20%), dexamethasone and tacrolimus (n = 7; 28%), clobetasol (n = 2; 8%), tacrolimus (n = 2; 8%) or clobetasol and tacrolimus (n = 1; 4%). Eight patients (32%) did not receive topical therapy. In FU3 (n = 24), 75% of the patients (n = 18) received topical therapy with dexamethasone (n = 9; 37.5%), dexamethasone and tacrolimus (n = 4; 16.7%), clobetasol (n = 2; 8.3%), tacrolimus (n = 1; 4.2%), or clobetasol and tacrolimus (n = 2; 8.3%). Six patients (25%) did not receive topical therapy. In FU4 (n = 36), 66.7% of the patients (n = 24) were treated with topical therapy, including dexamethasone (n = 14; 38.9%), dexamethasone and tacrolimus (n = 4; 11.1%), clobetasol (n = 2; 5.6%), tacrolimus (n = 1; 2.8%), or clobetasol and tacrolimus (n = 3; 8.3%). Twelve patients (33.3%) did not receive topical immunomodulatory therapy. In FU5 (n = 28), 42.9% of the patients (n = 12) were treated with topical therapy, including dexamethasone (n = 4; 14.3%), dexamethasone and tacrolimus (n = 4; 14.3%), clobetasol (n = 1; 3.6%), tacrolimus (n = 1; 3.6%), or clobetasol and tacrolimus (n = 2; 7.1%). Topical therapy was no longer used in 16 patients (57.1%). In FU6 (n = 22), 54.5% of the patients (n = 12) were treated with topical therapy, including dexamethasone (n = 6; 27.3%), dexamethasone and tacrolimus (n = 3; 13.6%), clobetasol (n = 2; 9.1%), or tacrolimus (n = 1; 4.5%). Topical therapy was not used in 10 patients (45.5%) (Table 3 and Supplementary Figure 2).

When considered in aggregate, the overall median durations of treatment for dexamethasone, tacrolimus, and clobetasol solutions were 6.2, 5.5, and 6.2 months, respectively. Kaplan-Meier survival analysis revealed the median time of first discontinuation of topical dexamethasone as 3.2 months (Figure 1A) and of all topical therapies as 8.2 months (Figure 1B).

Intralesional Steroid Therapy

Two patients were managed with intralesional steroid therapy (IST) for refractory painful ulcers at the baseline visit. Two additional patients received IST during FU1, and 2 other patients were managed with IST during FU4. One patient received a total of 3 injections, at baseline, FU1, and FU4. No IST was provided after FU4 (Figure 2).

Clinical Outcomes

For the entire cohort, there was an overall reduction in the median oral mucosal score from 3 (range, 1-10; n = 40) at FU1 to 1 (range, 0-5; n = 10) at FU6 for all evaluable subjects (Figure 3). The median lichenoid score remained stable at 1 (range, 1-3) at FU1 to 1 (range, 0-2) at FU6, and the proportion of patients with lichenoid changes remained relatively stable from 100% at FU1 to 90% at FU6. There was a reduction in the median erythema score from 1 (range, 0-2) at FU1 to 0 (range, 0-2) at FU6, and the proportion of patients with erythema decreased from 78% at FU1 to 40% at FU6. The median ulceration score remained unchanged from 0 (range, 0-3) at FU1 to 0 (range, 0-3) at FU6, and the proportion of patients with ulcerations decreased from 38% at FU1 to 20% at FU6. The median NIH severity score decreased from 1 (range, 0-3) at FU1 to .5 (range, 0-1) at FU6.

The median sensitivity score decreased from 3 (range, 0-9) at FU1 to 2 (range, 0-3) at FU6 (Figure 4). The median dryness score remained stable at 3 (range, 0-10) at FU1 to 3 (range, 0-7) at FU6. The median pain score was also stable at 0 (range, 0-5) at FU1 to 0 (range, 0-3) at FU6. Sialogogue therapy for xerostomia was prescribed in 4 patients.

Improvements in scores were not due to patients with high scores dropping out of the study, as the subgroup of patients

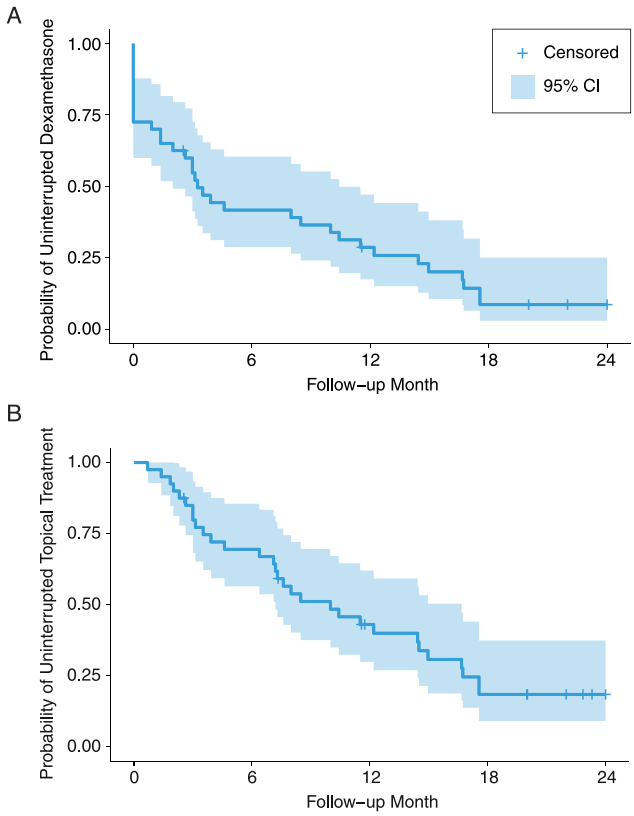

Figure 1. (A) Kaplan-Meier curve, where the "event" is the discontinuation of topical dexamethasone specifically. (B) Kaplan-Meier curve, where the " event" is the discontinuation of all topical treatments.

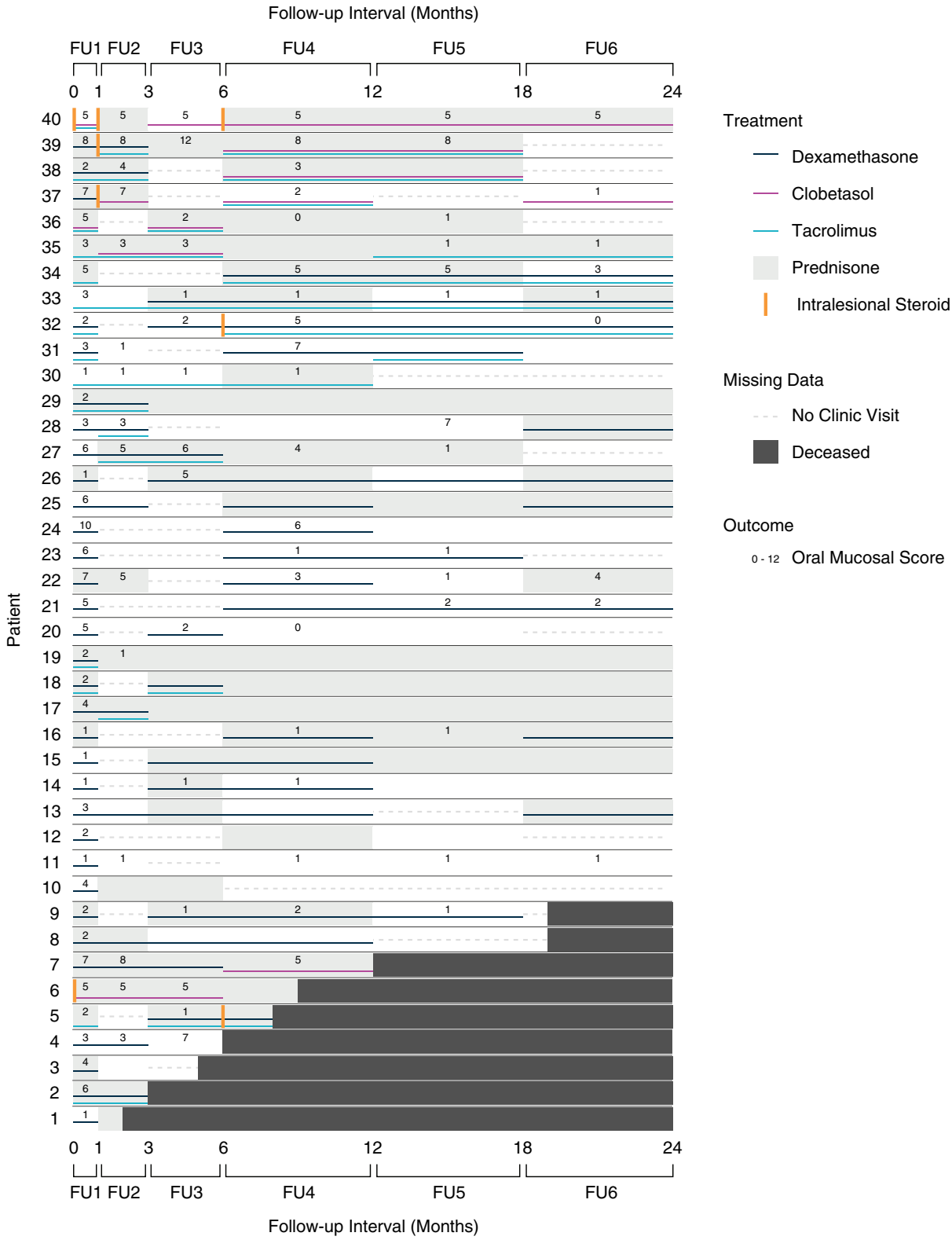

Figure 2. Summary of longitudinal follow-up of patients per time interval.

seen at both FU1 and FU6 (n = 10) presented with higher objective and subjective scores at FU1 compared with the rest of the cohort. For example, the median lichenoid and ulcer scores at FU1 were 1.5 and 1.0, respectively, in this subgroup and 1.0 and 0 in the rest of the cohort. With respect to patient-reported outcomes, median sensitivity (4 versus 3) and pain (2 versus 0) scores were also higher in this subgroup compared with the rest of the cohort.

Adverse Events and Secondary Oral Lesions

Oral candidiasis developed in 7 patients during the study period, all of whom were successfully managed with

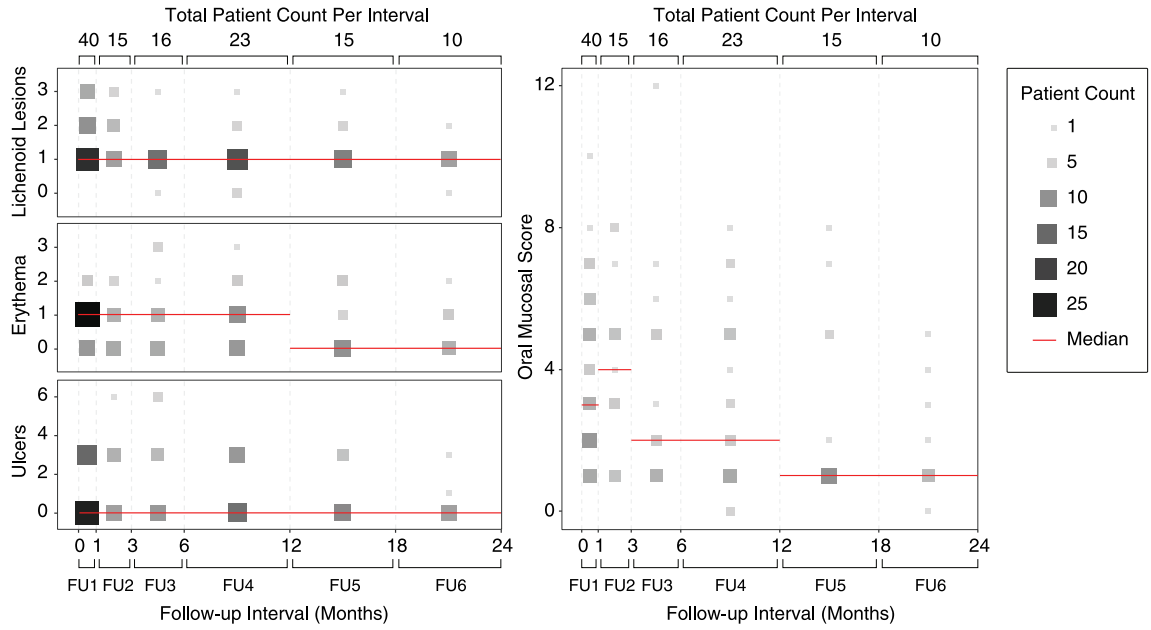

Figure 3. Clinician-reported outcomes: lichenoid lesions, 0-3; erythema, 0-3; ulcers, 0-6; composite oral mucosal score, 0-12. The red line indicates the median score across represented patients for each interval (FU1-FU6). Boxes represent patient count.

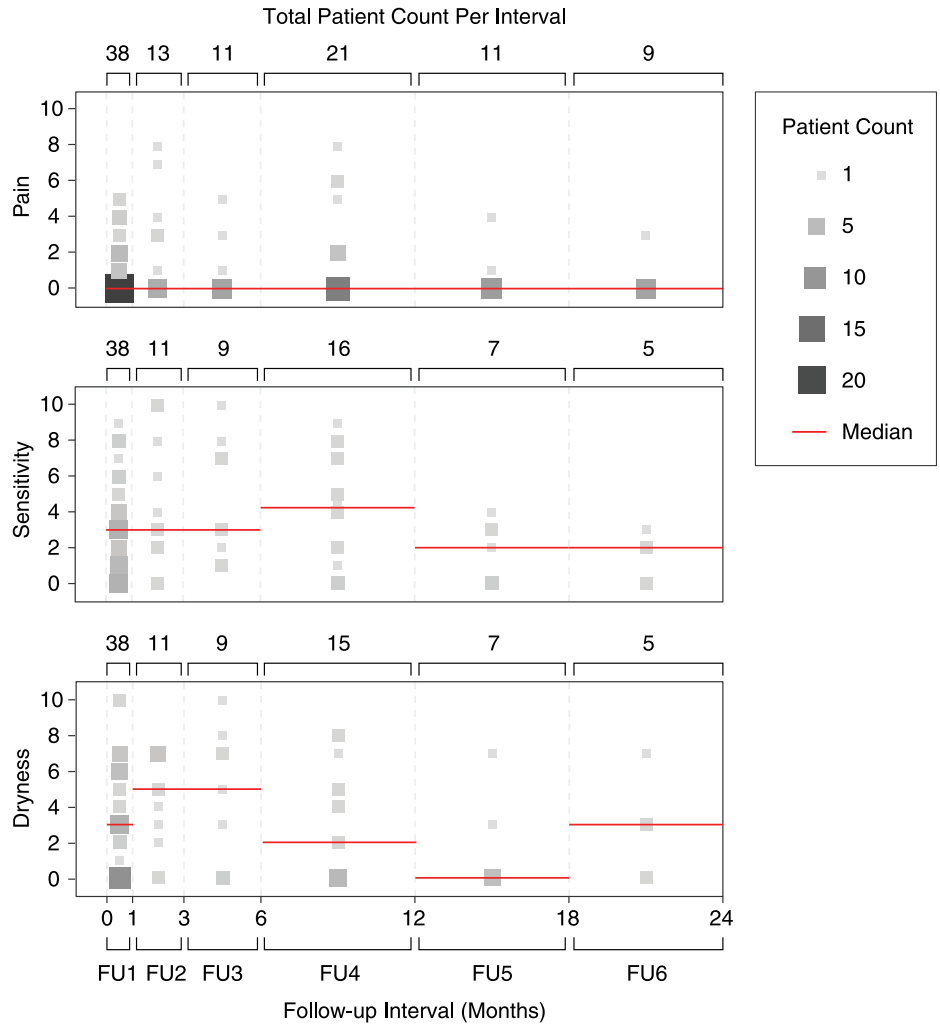

Figure 4. Patient count per interval experiencing each subjective outcome: pain, 0-10; sensitivity, 0-10; dryness, 0-10. The red line indicates the median score across represented patients for each interval.

antifungal therapy (eg, nystatin solution or systemic fluconazole) and were able to continue with their topical immunomodulatory therapy regimen. Breakthrough recrudescent herpes simplex virus infection occurred in 1 patient and was successfully treated with antiviral therapy. A verruciform xanthoma of the anterior mandibular alveolar mucosa was diagnosed in 1 patient and surgically excised.

DISCUSSION

Although there have been several clinical trials of topical immunomodulatory therapies for oral cGVHD demonstrating outcomes at 4 weeks, this is the first study to describe long-term utilization patterns and associated outcomes [8,15–24]. In this well-characterized cohort of patients who had developed de novo onset symptomatic disease and who had already completed 1 month of protocol-directed topical immunomodulatory therapy, a substantial proportion continued to receive topical immunomodulatory therapy throughout the 2-year study period. At FU4 (6-12 months), two-thirds continued to be treated topically, and at FU5 (12-18 months), more than 40% of the original cohort was still managing oral cGVHD with topical therapy. Although it is impossible to determine causality and/or efficacy, median clinician- and patient-reported outcome measures decreased over time, as did the intensity of systemic immunosuppressive therapy.

Similar to the systemic management of cGVHD, which frequently requires intensification and deintensification of immunosuppressive therapy over time according to disease activity, oral cGVHD therapeutic regimens were dynamic [3]. Given that the tacrolimus arm closed early in the phase 2 clinical trial, most of the patients in this follow-up study were receiving first-line dexamethasone solution during FU1 [15]. If there was no improvement, the patient was typically prescribed either tacrolimus in combination with dexamethasone or clobetasol in place of dexamethasone. Both of these treatment protocols have demonstrated efficacy in this quasi-second-line setting [15,21,22]. In recalcitrant cases, intralesional steroid therapy was used to treat ulcers; however, this therapy was provided in only 15% of patients, all within the first 6 months of follow-up.

Given its retrospective nature, this study has several limitations, including recorder bias, inconsistent follow-up, and missing data. Medication lists, including topical therapies, might not have been consistently and accurately reconciled at each visit, and patient compliance with therapy may have varied [25]. Changes in topical therapies may have been precipitated by provider preference, availability, cost, and/or insurance coverage rather than clinical necessity [26]. In addition, an increase or decrease in systemic immunosuppression cannot be attributed solely to manifestations of oral cGVHD. It should be noted that these patients were followed in an oral medicine clinic and at a medical center with significant expertise in cGVHD, and thus may have received more intensive management than a typical oral cGVHD patient and might not be representative of the experience of patients managed without such integrated care.

Although the cohort as a whole seemingly had improved clinician- and patient-reported outcomes over the duration of the study period, it was difficult to determine the extent to which topical immunomodulatory therapies benefitted patients with oral cGVHD refractory to dexamethasone solution. These recalcitrant patients, who were typically treated with either a combination of dexamethasone and tacrolimus solutions or switched to clobetasol as a more potent topical steroid, seemed to do well despite stable and relatively low doses of prednisone (<.5 mg/kg), suggesting some benefit from topical immunomodulatory therapy. The median prednisone dose at baseline was relatively low (0 mg/kg; range, 0-1.11 mg/kg) in the context of cGVHD management; however, given the study design, many patients began treatment of de novo symptomatic oral cGVHD in the absence of other systemic disease. Given these limitations and confounding factors of ongoing systemic immunosuppressive therapy, a causal relationship between topical therapeutics and oral cGVHD outcomes cannot be determined by this study. Future studies are needed to better define both the efficacy and the cost-effectiveness (especially given the potential costs of compound medications, such as clobetasol solution) of second-line topical immunomodulatory therapies to better guide treatment decisions [26].

In summary, this is the first long-term follow-up study of patients with symptomatic oral cGVHD demonstrating that a significant proportion of those who initiate topical immunomodulatory therapy at the onset of the condition continue to need long-term management, for at least up to 24 months, and that these treatments appear to provide long-term clinical benefit with an excellent safety profile. Future studies are needed to determine the most effective second-line approaches to managing oral cGVHD refractory to first-line intervention.

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Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.09.029.

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