Durable discontinuation of systemic therapy in patients affected by chronic graft-*versus*-host disease

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Abstract

Successful treatment of chronic graft-*versus*-host disease (GvHD) often requires long-term systemic therapy (ST). Durable discontinuation of ST reflects the resolution of active chronic GvHD. We evaluated the factors associated with durable ST discontinuation, defined as cessation of all ST for ≥12 months, using data from two prospectively followed cohorts from the Chronic GvHD Consortium (n=684). Transplant sources were peripheral blood (89%), bone marrow (6.6%), and cord blood (4.4%) from HLA matched related (37.6%), HLA matched unrelated (45%), and other donor types (18%). Half of the patients received non-myeloablative conditioning. The median time from transplantation to chronic GvHD diagnosis was 7.7 months (range, 1.0–141.3) and the median time from chronic GvHD onset to enrollment into the cohorts was 0.9 months (range, 0.0-12.0). The cumulative incidence estimate of durable ST discontinuation was 32% (95% confidence interval: 28%-37%) at 10 years after enrollment into the cohort. Among patients who discontinued ST, the median time from chronic GvHD diagnosis to durable ST discontinuation was 3.6 years (range, 1.2-10.5). In multivariate analysis, patients who received myeloablative conditioning, had chronic GvHD manifested as moderate/severe lower gastrointestinal involvement, and had a higher (worse) Lee symptom overall score were less likely to attain durable ST discontinuation. In contrast, mild lower gastrointestinal involvement and cord blood (*vs*. peripheral blood) as the graft source were associated with a greater likelihood of ST discontinuation. Although a minority of patients can discontinue ST permanently, most patients require prolonged ST. Viewing chronic GvHD in this way has implications for management approaches.

Introduction

Chronic graft-*versus*-host disease (GvHD) is a major complication of allogeneic hematopoietic cell transplantation (HCT).[1] It is a leading cause of non-relapse mortality in long-term survivors of allogeneic HCT,[2] and is associated with impaired quality of life and lower performance status in patients.[3,4]

Approximately 30-50% of patients surviving for more than 100 days after allogeneic HCT will develop chronic GvHD and require treatment with systemic immunosuppression.[1] Systemic immunosuppression can impair immunological function, increase the risk of opportunistic infections, and expose patients to the risks of medication-specific side effects such as those associated with chronic glucocorticoid therapy.

Successful therapy of chronic GvHD often requires long-term systemic therapy (ST). Previous studies of ST discontinuation reported rates as low as 27.7% and as high as 68%.[5-7] The variation in rates of ST discontinuation may have resulted from the populations which were studied. Higher rates of discontinuation were observed in cohorts of patients with less heavily treated chronic GvHD from single institutions while lower rates were observed in cohorts of heavily pretreated patients from a quaternary referral center. Despite this variability, less severe chronic GvHD was associated with an increased likelihood of ST discontinuation across these studies. A significant limitation to the interpretation of these trials is that different definitions of ST discontinuation were used. Two studies defined ST discontinuation without specifying a minimal amount of time that the patient needed to be off ST[6,7]

while other studies defined successful discontinuation as 9 and 6 months off any ST.[5,8]

Approximately 50% of patients stopping ST for the first time will experience a flare in chronic GvHD symptoms at a median of 3.4 months (interquartile range, 2.3-8.0 months) and may require resumption of ST.[8] Discontinuation of ST for a limited time may not represent true resolution of chronic GvHD. Therefore, we evaluated the durable discontinuation of ST, defined as discontinuation of ST for 12 or more months. This definition was proposed to ensure that patients were truly unlikely to flare and need to restart ST.

Methods

Patients

Subjects (n=684) came from two prospectively followed cohorts enrolled onto Chronic GvHD Consortium studies (NCT00637689, NCT01902576).

NCT00637689 "Improving outcomes assessment in chronic GvHD" was a cross-sectional study of chronic GvHD regardless of time since transplantation. The primary objective was testing of National Institutes of Health (NIH) recommended tools to assess chronic GvHD. Eligibility criteria included: (i) a clinical or histological diagnosis of chronic GvHD, and (ii) a need for ST. Severity of chronic GvHD was not an exclusion criterion. Clinical follow-up occurred at 3 months for incident cases, and every 6 months for the duration of the study. Long-term outcomes were determined through review of clinical charts. Six hundred and one subjects were accrued from 2007 to 2012.

NCT01902576 "Chronic GvHD response measures validation" was a prospective cohort study of patients with chronic GcHD starting new ST. The primary objective was testing of the NIH response criteria. Eligibility criteria included: (i) a diagnosis of chronic GvHD according to NIH consensus conference diagnostic and scoring criteria, and (ii) initiation of new ST for chronic GvHD. Severity of chronic GvHD was not an exclusion criterion. The patients had a clinical follow-up at 3, 6, and 18 months and if a new chronic GvHD treatment was started. Long-term outcomes were determined through review of the clinical charts. Three hundred eighty-three subjects were enrolled from 2013 to 2019.

Subjects selected for this analysis had either incident or prevalent chronic GvHD. Patients with prevalent chronic GvHD were limited to those within 12 months from diagnosis to allow evaluation of the defined endpoint of durable discontinuation of ST (off ST for at least 12 months). The treatments used are listed in *Online Supplementary Table S1*. Incident cases consisted of those enrolled less than 3 months after diagnosis of chronic GvHD (n=490; 70.6%), and prevalent cases comprised those enrolled 3-12 months after diagnosis of chronic GvHD (n=194; 28.4%). Subsetting according to incident and prevalent status was not significantly associated with the time to durable discontinuation of ST. Therefore, these two groups were combined for subsequent analyses.

Demographic and transplant characteristics are presented in Table 1 and *Online Supplementary Table S2*.

This study was approved by the Institutional Review Boards of all participating centers, and all participants provided signed informed consent.

Statistical analysis

Descriptive statistics were used to summarize baseline demographic and chronic GvHD characteristics. Chronic GvHD was graded according to NIH severity scales. Baseline grade at enrollment, rather than most severe chronic GvHD status over the observed period, was used. The main endpoint was time to durable ST discontinuation, defined as the cessation of all ST for at least 12 months. Subjects who stopped ST but restarted for any reason within 12 months were considered to have been continuously on ST. These subjects did not meet the endpoint and were censored at last follow-up. The cumulative incidence of durable ST discontinuation was calculated with the competing risks of death and relapse of the disease for which HCT was performed.

Cox proportional hazards models were used to examine associations between durable ST discontinuation and transplant, clinical, and patient-reported variables, first in univariate models (*Online Supplementary Table S3*), and then in multivariate models. A stepwise procedure was used in the multivariate analysis, with entry into and exit from the model based on a *P*-value of 0.1, first with the transplant variables, then adding the clinical variables to the transplant model, then adding the patient-reported variables to the model including clinical plus transplant variables. Analyses were performed using SAS/STAT software, version 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Chronic graft-*versus*-host disease clinical and patient-reported outcomes

Chronic GvHD characteristics at enrollment are presented in Tables 2 and 3, and *Online Supplementary Table S4*. The median time from HCT until the diagnosis of chronic GvHD was 7.7 months (range, 1.0-141.3). The median time from the diagnosis of chronic GvHD to enrollment into the Consortium cohorts was 0.9 months (range, 0.0-12.0). Most patients were affected by moderate (51.2%) or severe (32.2%) chronic GvHD. Grade II-IV acute GvHD preceded the development of chronic GvHD in 51.6% of cases. The

most common sites of chronic GvHD manifestations were the skin (63.6%), mouth (63.2%), and eyes (51.5%). Most patients had involvement of two or more sites. The median baseline Lee symptom overall summary scale score was 19.8 (range, 0.0-74.4). The median follow-up since transplantation for surviving patients was 95.3 months (range, 11.3-181.5).

Table 1. Demographic characteristics (684 patients).

Characteristics	N (%) or median (range)
Age at transplant in years), median (range)	51.9 (18.0-78.0)
Age at transplant, N (%)	
18-30	74 (10.8%)
31-60	460 (67.3%)
>60	150 (21.9%)
Diagnosis, N (%)	
Acute leukemia	323 (47.2%)
Chronic leukemia	72 (10.5%)
Lymphoma	105 (15.4%)
MDS + MPD	120 (17.5%)
Other	64 (9.4%)
Donor type, N (%)	
HLA-identical sibling	257 (37.6%)
HLA-matched other relative	14 (2.0%)
HLA-mismatched relative	15 (2.2%)
HLA-matched unrelated donor	306 (44.7%)
Mismatched unrelated donor	92 (13.5%)
Graft source, N (%)	
Peripheral blood	609 (89.0%)
Bone marrow	45 (6.6%)
Cord blood	30 (4.4%)
Myeloablative, N (%)	341 (50.0%)
Missing	N=2
GvHD prophylaxis, N (%)	
CNI + MTX +/- others	346 (51.0%)
CNI + MMF +/- others	271 (40.0%)
Other	61 (9.0%)
Missing	N=6
Female donor, male recipient, N (%)	185 (27.2%)
Missing	N=3
Donor-recipient CMV match, N (%)	
Negative/negative	227 (33.7%)
Positive/negative	78 (11.6%)
Negative/positive	197 (29.3%)
Positive/positive	171 (25.4%)
Missing	N=11
Months from HCT to chronic GvHD, median (range)	7.7 (1.0-141.3)
Months from chronic GvHD to enrollment, median (range)	0.9 (0-12.0)
Months from HCT to DOLC (survivors), median (range)	95.3 (11.3-181.5)

MDS: myelodysplastic syndrome; MPD: myeloproliferative disorder; HLA: human leukocyte antigen; GvHD: graft-*versus*-host disease; CNI: calcineurin inhibitor; MTX: methotrexate; MMF: mycophenolate mofetil; CMV: cytomegalovirus; HCT: hematopoietic cell transplantation; DOLC: date of last contact.

Durable discontinuation of systemic therapy

The cumulative incidence of durable ST discontinuation among all patients was 24% (95% confidence interval [95% CI]: 21-28%) at 5 years and 32% (95% CI: 28-37%) at 10 years (Figure 1). Of the 519 subjects who initially stopped ST, 16 (3.1%) did not have sufficient follow-up to document ST discontinuation for ≥12 months. These subjects were considered not to have achieved durable ST discontinuation and follow-up was censored at the last contact. The NIH severity at enrollment among these 16 subjects was mild in 12.5%, moderate in 50% and severe in 37.5%. With regard to clinical outcomes at 5 years, 21% had died without relapse, 17% had relapsed from their underlying disease, 38% were alive but on ST, and 24% were alive and off ST. By 10 years, 27% had died without relapse, 18% had relapsed from their underlying disease, 23% were alive but on ST, and 32% were alive and off ST. The most frequent

Table 2. Chronic graft-*versus*-host disease characteristics at enrollment (684 patients).

Variables	N (%) or median (range)
Chronic GvHD NIH global severity	
None	10 (1.5%)
Mild	104 (15.2%)
Moderate	350 (51.2%)
Severe	220 (32.2%)
Prior grade II-IV acute GvHD	350 (51.6%)
Missing	N=6
Prior grade III-IV acute GvHD	64 (9.4%)
Missing	N=6
Onset type	
De novo	253 (37.0%)
Quiescent	273 (39.9%)
Progressive	158 (23.1%)
KPS (self-report), median (range)	80.0 (40.0-100.0)
Platelet count at chronic GvHD diagnosis	
<100x10^9/L	136 (20.3%)
≥100x10^9/L	534 (79.7%)
Missing	N=14
Bilirubin (mg/dL) at chronic GvHD diagnosis, median (range)	0.5 (0.1-17.9)
N. of sites involved	
0	10 (1.5%)
1	88 (12.9%)
2 or more	586 (85.7%)

GvHD: graft-*versus*-host disease; NIH: National Institutes of Health; KPS: Karnofsky performance status scale,

causes of non-relapse death were chronic GvHD, unknown, and infection (*Online Supplementary Table S5*). The median time from development of chronic GvHD until discontinuation of ST for at least 12 months was 3.6 years (range, 1.2-10.5). The median time from cohort enrollment until discontinuation of ST for at least 12 months was 3.4 years (range, 0.7-11.9).

Transplant, clinical, and patient-reported variables evalu-

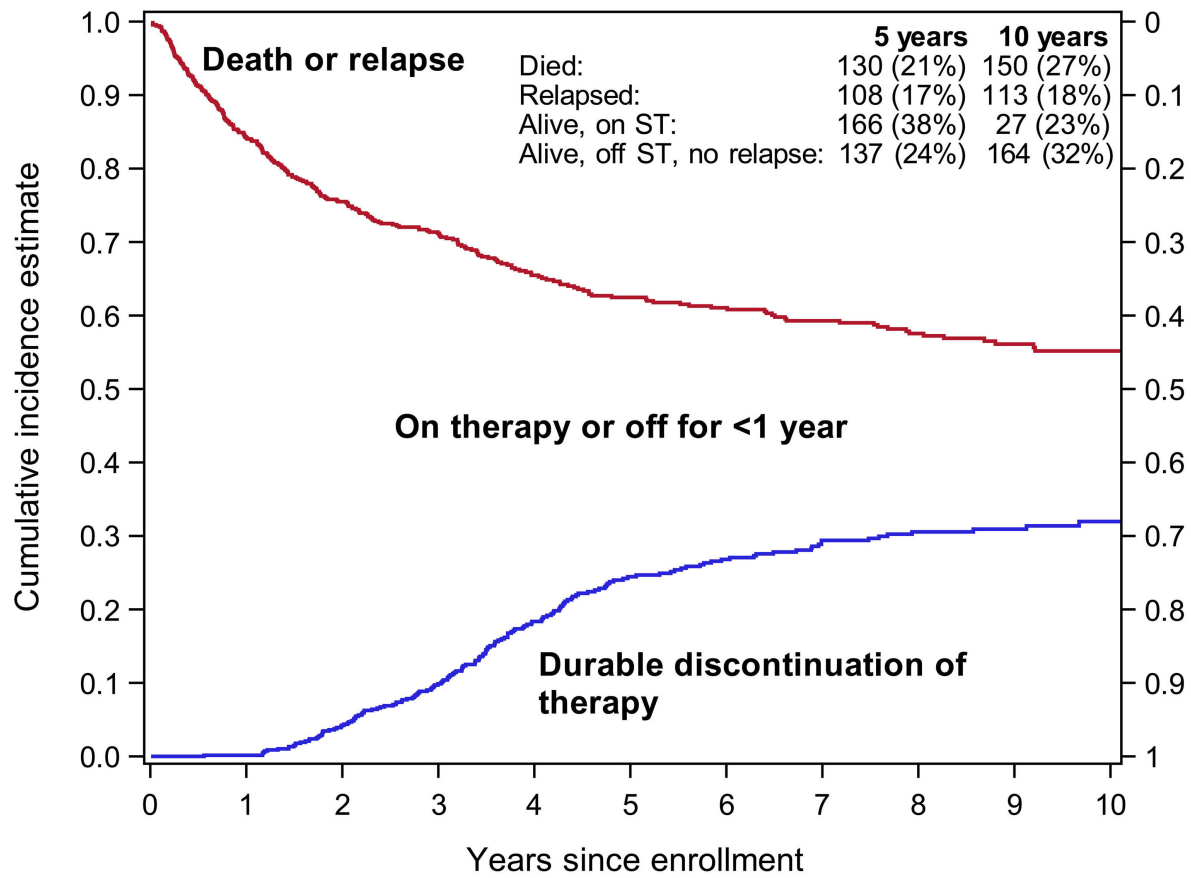

Figure 1. Durable discontinuation of systemic therapy occurred in 32% (95% CI: 28-37%) of patients who developed chronic graft-*versus*-host disease. Among relapse-free patients surviving at 10 years, 57% (95% CI: 50-63%) had discontinued systemic therapy (ST) for at least 12 months. The curve for ST discontinuation is flat during the first year, reflecting the requirement to demonstrate that the discontinuation of ST was durable for at least 12 months. Durable discontinuation of systemic therapy is shown in blue and measured along the left-sided Y axis, competing risks of relapse and death are shown in red and measured along the right-sided Y axis.

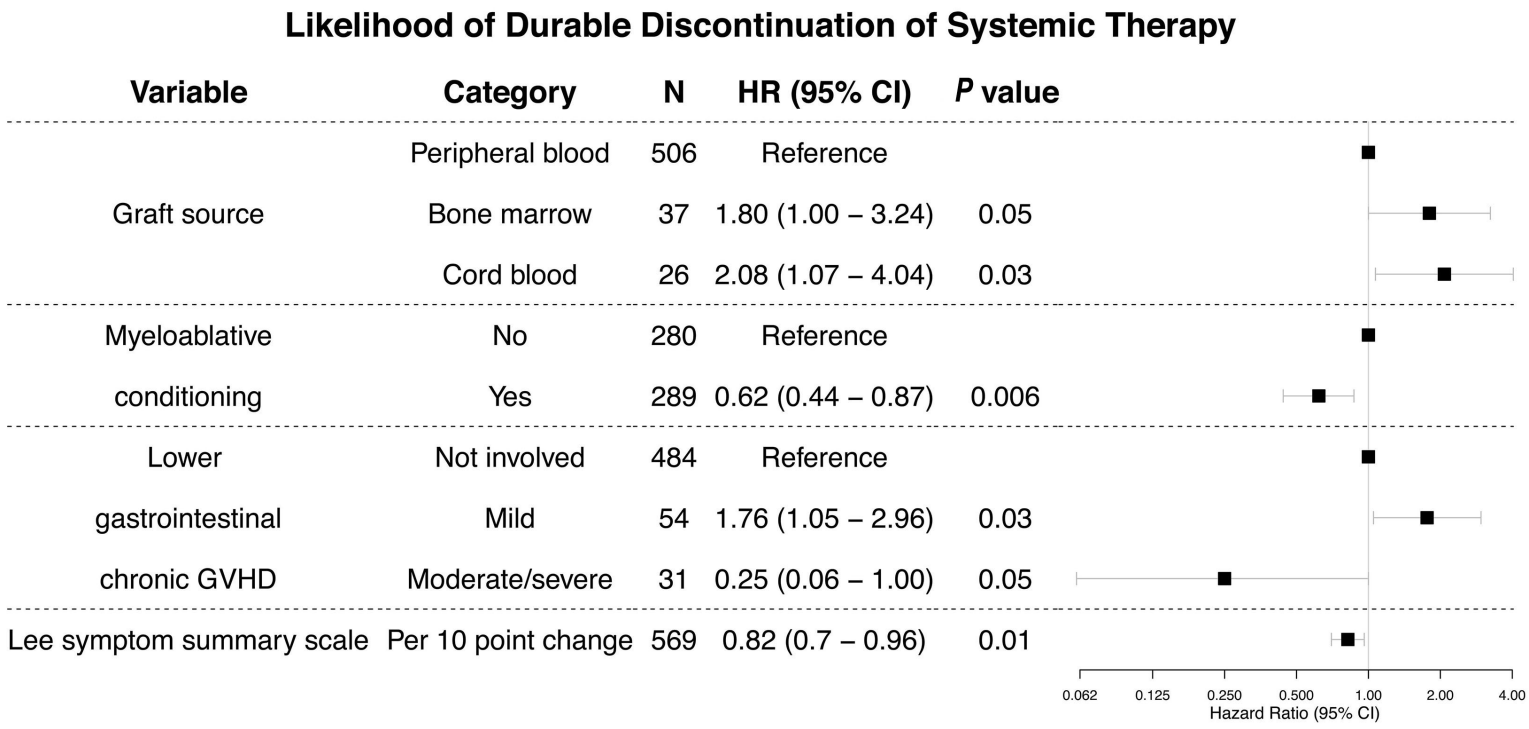

Figure 2. Likelihood of durable discontinuation of systemic therapy. Durable discontinuation was defined as 12 months or more. Patients receiving cord blood grafts or with mild chronic graft-*versus*-host disease (GvHD) of the lower gastrointestinal tract were more likely to durably discontinue systemic therapy. Myeloablative conditioning and moderate/severe chronic GvHD of the lower gastrointestinal tract were less likely to durably discontinue systemic therapy. The chance of durably discontinuing systemic therapy decreased by 18% for every 10-point worsening (increase) in the Lee symptom scale overall score. Hazard ratios for these factors are illustrated on the right.

ated for association with durable ST discontinuation are presented in *Online Supplementary Table S3*. In the multiple regression model (Figure 3), patients who received an umbilical cord blood transplant were 2.08 times (95% CI: 1.07-4.04, *P*=0.03) and those who received a bone marrow transplant were 1.80 times (95% CI: 1.00-3.24, *P*=0.05) more likely to discontinue ST compared to patients who received a peripheral blood stem cell transplant. Patients with mild lower gastrointestinal (GI) involvement were 1.76 (95% CI: 1.05-2.96, *P*=0.03) times more likely to discontinue ST. Patients who underwent myeloablative conditioning (hazard ratio [HR]=0.62, 95% CI: 0.44-0.87, *P*=0.006), those with moderate to severe lower GI involvement (HR=0.25, 95% CI: 0.06-1.0, *P*=0.05), and those with a higher Lee symptom summary score at enrollment (HR=0.82 per 10-point increase, 95% CI: 0.70-0.96, *P*=0.01) were less likely to discontinue ST. The chance of discontinuing ST decreased by 18% for every 10-point increase in the Lee symptom scale overall score. Results were qualitatively similar when the analysis was limited to incident cases. In an analysis including NIH overall chronic GvHD severity and excluding individual organ involvement because of overlapping content, those with severe chronic GvHD were less likely to durably discontinue ST (HR=0.53, 95%CI: 0.31-0.90, *P*=0.02) than those with mild or moderate severe GvHD. The presence and severity of individual organs involved by chronic GvHD, including the lungs, was not associated with the probability of ST discontinuation.

Recipient age, recipient and donor HLA mismatching, and transplants with male recipients of grafts from female donors, all factors which have been associated with the development of chronic GvHD, were not associated with the probability of achieving durable ST discontinuation.

Table 3. Chronic graft-*versus*-host disease organ involvement at enrollment (684 patients).

Organ/NIH Grade	N (%)	Organ/NIH Grade	N (%)
Eye		Joint	
0	332 (48.5%)	0	478 (69.9%)
1	231 (33.8%)	1	138 (20.2%)
2,3	121 (17.7%)	2,3	68 (9.9%)
Genital		Liver	
0	488 (87.3%)	0	533 (78.8%)
1	43 (7.7%)	1	48 (7.1%)
2,3	28 (5.0%)	2,3	95 (14.1%)
Missing	N=125	Missing	N=8
GI		Lung	
0	452 (66.1%)	0	510 (74.6%)
1	168 (24.6%)	1	126 (18.4%)
2,3	64 (9.4%)	2,3	48 (7.0%)
GI - esophagus		Mouth	
0	582 (85.1%)	0	252 (36.8%)
1	77 (11.3%)	1	327 (47.8%)
2,3	25 (3.7%)	2,3	105 (15.4%)
GI - upper		Skin	
0	540 (78.9%)	0	249 (36.4%)
1	95 (13.9%)	1	134 (19.6%)
2,3	49 (7.2%)	2,3	301 (44.0%)
GI - lower			
0	586 (85.9%)		
1	61 (8.9%)		
2,3	35 (5.1%)		
Missing	N=2		

NIH: National Institutes of Health; GI: gastrointestinal.

Discussion

Upon developing moderate or severe chronic GvHD, patients and their caregivers face a great deal of uncertainty about the duration and success of ST. With a median follow up of almost 8 years, we found that the majority (67%) of patients with chronic GvHD are unable to discontinue ST for more than 12 months.

In previous studies, differences in the populations studied and different definitions of what constituted ST discontinuation may have resulted in variability in the discontinuation rates that were reported.[5-7] We used a multi-institutional cohort of incident and prevalent cases of chronic GvHD that were within 1 year of diagnosis in order to reduce center bias, and further reduced variability by requiring follow-up for at least 12 months to ascertain that ST discontinuation was durable. This duration was proposed to be long enough to classify patients as having discontinued ST without a significant risk that resumption of ST would be necessary. To our knowledge, this is the largest study with the longest follow-up performed to date exploring the issue of ST discontinuation.

Similar to prior studies, we found that less severe chronic GvHD and use of umbilical cord blood grafts were associated with a shorter time to ST discontinuation.[5-7] Previous studies did not use validated patient-reported instruments to measure the severity of chronic GvHD. We demonstrated that more severe chronic GvHD symptoms, as indicated by higher (worse) Lee symptom scores, were associated with a decreased probability of durable ST discontinuation, consistent with the effect of increased disease burden and emphasizing the importance of measuring patient-reported outcomes. It is intuitive that more symptomatic patients would be less likely to stop ST.

Notably, our observed rate of ST discontinuation (24% at 5 years) was closest to that from a quaternary referral center (27.7% at 5 years) with a high number of heavily treated chronic GvHD cases in their clinical population and which similarly defined ST discontinuation as requiring 6 (rather than 12) months without any therapy.[5] In contrast, the population we studied was composed of 71.9% incident cases of chronic GvHD, many of whom had not prog-

ressed to second-line therapy. These results suggest that other than having a biomarker indicative of chronic GvHD, a mandatory 6- to 12-month observation period is needed to support the conclusion that ST has been discontinued permanently.

Most patients are unable to discontinue ST for at least 12 months. Patients who received peripheral blood grafts, received myeloablative conditioning, had a higher (worse) Lee symptom score, and moderate/severe lower GI involvement were less likely to achieve durable ST discontinuation.

We observed contradictory effects from lower GI chronic GvHD severity on the likelihood of discontinuing ST: mild lower GI chronic GvHD increased and moderate/severe lower GI chronic GvHD decreased the likelihood compared to no lower GI chronic GvHD. We were unable to separate the effects of moderate *versus* severe lower GI chronic GvHD because of the small number of cases wth severe lower GI-GvHD, limiting our interpretation of the data. An association between low levels of short chain fatty acids at around day +100 and subsequent development of chronic GvHD was recently reported, implying a role for the microbiome in chronic GvHD.[9] Although association is not causation, it is possible that mild lower GI chronic GvHD may reflect an underlying perturbation in the microbiota that is more amenable to intervention by non-chronic GvHD ST such as changes in antibiotics, diet, or hospitalization. Further investigation on this subject will be necessary.

We also found that many factors (age, HLA mismatch, recipient/donor sex mismatch) associated with the development of chronic GvHD were not associated with the likelihood of ST discontinuation, suggesting that the pathophysiology of chronic GvHD treatment and control may differ from its development.

This study is limited by its reliance on clinical examination/practice to determine chronic GvHD status and on the 12-month waiting period to determine when chronic GvHD had been fully treated and was unlikely to recur. Practitioners may be less likely to discontinue and more likely to restart ST in patients with manifestations of severe chronic GvHD. This was controlled by the long 12-month waiting period which allowed an adequate time off therapy to ensure that chronic GvHD flares were unlikely. Indeed, only a small proportion of subjects (3%) restarted systemic therapy within the 12-month period in this study. Of these, the minority had severe chronic GvHD, suggesting that practitioner anxieties about stopping ST in subjects with severe chronic GvHD are less likely to bias the outcomes. Within a single institution and across a multi-institutional consortium there may be slight variations in chronic GvHD-related definitions. Unfortunately, a clear-cut biomarker of chronic GvHD status, which could provide additional precision, is not yet available, despite the application of powerful discovery and analytical techniques. The 12-month waiting period was not based on the underlying pathophysiology of tolerance induction after allogeneic HCT but rather was a practical cutoff based on the observed time to restart ST. It may still be possible to completely taper ST after many years.

The applicability of this study is limited by the population studied. A diagnosis of chronic GvHD was required for inclusion. Consequently, patients at low risk of developing chronic GvHD, such as young children or those who received post-transplant cyclophosphamide, antithymocyte globulin, or *in vivo/ex vivo* T-cell depletion as acute GvHD prophylaxis are not well represented. Our findings may not be applicable to these specific populations when they do not develop chronic GvHD. Finally, our findings are based on the clinical course of patients who agreed to participate in observational research. Despite these limitations, we believe our results are still valid and generalizable to patients under treatment with chronic GvHD.

Our findings suggest that for most patients, ST is likely to be a long-term proposition and that there is a much lower probability of being able to discontinue treatment than had been anticipated from earlier studies.[6,7] Chronic GvHD may behave more like an ongoing autoimmune disease without resolution than a temporary state in which eventual tolerance is expected. Viewing chronic GvHD in this way has implications for management approaches and the development of therapeutic agents for chronic GvHD. The goal of defining a regimen that minimizes (rather than discontinues) ST or fosters operational immunological tolerance may need to be given higher priority to avoid the see-saw of stopping and restarting ST. Similarly, addressing the factors that contribute to persistent immune deficiency may improve outcomes by decreasing the risk of infections, a major cause of death.

Disclosures

No conflicts of interest to disclose.

Contributions

GLC, LO, SJL, and MA designed the research, analyzed the data, and wrote the manuscript. All authors provided subjects, and read, critiqued, and revised the paper.

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Data-sharing statment

For access to data, please contact Stephanie Lee, sjlee@fredhutch.org

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