Quality of life associated with sirolimus for prevention of graft-*versus*-host disease: results from a randomized trial

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ABSTRACT

Several studies have examined sirolimus-based immune suppression for the prevention of graft-*versus*-host disease after allogeneic hematopoietic cell transplantation, but little is known regarding its effects on quality of life. The current study reports on changes in quality of life to Day 360 in a randomized phase II trial of sirolimus and tacrolimus *versus* methotrexate and tacrolimus. Quality of life was assessed prior to transplant and on Days 30, 90, 180, 270, and 360 with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant Trial Outcome Index. Random effects models examined the effects of study arm on change in Trial Outcome Index scores from Day 30 to 360, controlling for base-line Trial Outcome Index. The sirolimus/tacrolimus arm (n=37) showed less improvement in Trial Outcome Index scores over time compared to the methotrexate/tacrolimus arm (n=34) (P=0.02). Patients receiving sirolimus and tacrolimus were more likely to endorse nausea and a lack of energy over time ($PS \leq 0.01$). These data suggest that sirolimus-based immune suppression is associated with less improvement in quality of life in the first year post-transplant compared to methotrexate/tacrolimus. Quality of life differences may be due to increased fatigue and nausea in patients treated with sirolimus. These findings should be considered in the clinical management of patients treated with sirolimus. (*Clinicaltrials.gov identifier:00803010*).

Introduction

Graft-*versus*-host disease (GVHD) is a common and debilitating complication of allogeneic hematopoietic cell transplantation (HCT). Severe and treatment-unresponsive acute GVHD, as well as moderate-severe chronic GVHD, are associated with increased mortality.[1-3] In addition, acute and chronic GVHD are associated with significant morbidity and reduced quality of life (QOL) across multiple individual domains and overall QOL.[4-9,10,11] While acute and chronic GVHD may themselves contribute to reduced QOL, greater infectious complications, hospitalizations, and treatment with immunosuppressive medications may also result in lower QOL.[7] Interestingly, the effects of acute and chronic GVHD on QOL appear to be independent from one another, suggesting that patients diagnosed with both acute and chronic GVHD have worse QOL than patients diagnosed with either alone.[7]

As the current standard prophylaxis regimen including a calcineurin inhibitor and methotrexate (MTX) inadequately prevents acute and chronic GVHD, investigators have explored alternative approaches. One of the most extensively studied has been the combination of sirolimus (SIR) and calcineurin inhibitors (including cyclosporine and tacrolimus). An initial study found that a regimen of SIR, tacrolimus (TAC), and MTX was associated with low incidence of grade III-IV acute GVHD.[12] In contrast, two additional studies of SIR administered with MTX and a calcineurin inhibitor reported greater acute GVHD and serious toxicity.[13] Additional single center phase II trials and retrospective analyses have reported encouraging outcomes utilizing SIR/TAC.[14-17] Importantly, differences in included patients, transplantation characteristics, and intensity and duration of immune suppression exposure between these trials may have impacted the observed results. We recently reported results of a randomized clinical trial (*Clinicaltrials.gov identifier:00803010*) indicating that SIR/TAC resulted in significantly less grade II-IV acute and moderate-severe chronic GHVD compared to MTX/TAC.[18] Of note, this study investigated whether prolonged (one year post-HCT) administration of SIR would decrease risk for chronic GVHD. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) phase III randomized trial 0402 recently reported reduced grade III-IV acute GVHD but greater incidence of chronic GVHD in patients receiving SIR/TAC compared to MTX/TAC.[19]Across multiple studies, SIR/TAC appears to confer several benefits, i.e. reduction in severity of mucositis,[20] improvement in time to engraftment, reduction in GVHD, as well as increased risks, i.e. hepatic veno-occlusive disease,[21] and thrombotic microangiopathy.[22]

While these clinical results suggest competing risks and benefits associated with SIR/TAC, data on patient-reported quality of life (QOL) are needed. Significantly greater improvement in QOL after HCT among patients treated with SIR/TAC would provide further justification for its use over other regimens. While we previously reported QOL outcomes through Day 90 in our phase II trial,[18] we are not

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aware of other published QOL data from patients treated with SIR/TAC. Although patients randomized to the SIR/TAC arm reported worse pre-HCT QOL compared to patients in the MTX/TAC arm, at 30 and 90 days post-HCT, there were differences in QOL between study arms.[18] The current study builds on our previous work by describing QOL outcomes through Day 360. It was hypothesized that patients in the SIR/TAC arm would show greater improvements in QOL over time compared to patients in the MTX/TAC arm.

Methods

Patients

Patients were recruited as part of a randomized phase II study comparing sirolimus and tacrolimus (SIR/TAC) to methotrexate and tacrolimus (MTX/TAC) for prevention of GVHD. The study was approved by the University of South Florida Institutional Review Board. Study methodology has been described previously.[18] All patients provided written informed consent.

Table 1. Sociodemographic and clinical characteristics of the sample.

	MTX/TAC (n=34)	SIR/TAC (n=37)	P
Age: median (range)	49 (23-69)	49 (25-68)	0.19
Gender: n., % male	21 (62%)	28 (76%)	0.31
Ethnicity: n., % non-Hispanic	25 (74%)	33 (89%)	0.16
Race: n., % Caucasian	31 (91%)	34 (94%)	0.95
Marital status: n., % married	28 (82%)	30 (81%)	1.00
Education: n., % college grad	15 (44%)	20 (56%)	0.47
Annual household income: n., % $40,000 or greater	18 (67%)	19 (66%)	1.00
Diagnosis: n. (%)			0.10
Acute lymphoblastic leukemia	9 (26%)	5 (14%)	
Acute myelogenous leukemia	8 (24%)	15 (41%)	
Chronic lymphocytic leukemia	3 (9%)	3 (8%)	
Chronic myelogenous leukemia	0 (0%)	2 (5%)	
Myelodysplastic syndrome	7 (21%)	2 (5%)	
Multiple myeloma	2 (6%)	6 (16%)	
Myeloproliferative neoplasm	2 (6%)	0 (0%)	
Non-Hodgkin lymphoma	3 (9%)	4 (11%)	
Donor: n. (%)			0.92
Matched sibling donor	17 (50%)	17 (46%)	
Matched unrelated donor	17 (50%)	20 (54%)	
Conditioning regimen: n. (%)			0.26
Flu/Bu	28 (82%)	26 (70%)	
Pento/Bu	4 (12%)	4 (11%)	
Flu/Mel	2 (6%)	7 (19%)	
Maximum aGVHD grade: n. (%)			<0.01
0	2 (6%)	11 (30%)	
1	2 (6%)	10 (27%)	
2	27 (79%)	11 (30%)	
3	3 (9%)	4 (11%)	
4	0 (0%)	1 (3%)	
Maximum cGVHD grade: n. (%)			<0.01
0	9 (26%)	17 (46%)	
1	1 (3%)	10 (27%)	
2	10 (29%)	5 (14%)	
3	8 (24%)	1 (3%)	

Maximum grade of cGHVD not reported for 10 patients due to death. SIR: sirolimus; TAC: tacrolimus; MTX: methotrexate; Flu: fludarabine; Bu: busulfan; pento: pentostatin; Mel: melphalan; aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease; college grad: college graduate.

Study design

Briefly, all patients received peripheral blood mobilized grafts from sibling or unrelated donors matched at HLA-A, B, C, and DRB1 by high resolution typing. Randomization was stratified for age (i.e. >50 *vs.* <50 years) and donor source (i.e. sibling *vs.* unrelated). TAC was administered from Day -3 at 0.02 mg/kg/day and was then transitioned to oral formulation before hospital discharge. Serum TAC target was 5-15 ng/mL in the MTX arm and 3-7 ng/mL in the SIR arm. Patients without evidence of acute GVHD and not on systemic glucocorticoids were eligible for TAC taper at Day 50 following HCT. SIR was administered as a 9 mg oral loading dose on Day -1, followed by maintenance to target 5-14 ng/mL through at least one year post-HCT. MTX was administered on Day +1 at 15 mg/m^2, then 10 mg/m^2 on Days 3, 6 and 11. Beyond these requirements, the taper schedule for TAC, SIR, systemic glucocorticoids, and other immune suppressive agents was directed by physician judgment.

Data collection and evaluation

Self-reported socio-demographic characteristics were assessed prior to transplant. Clinical characteristics were collected prospectively as standard data elements in the parent clinical trial. QOL was assessed prior to transplant and at Days 30, 90, 180, 270 and 360 with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT).[23] The FACT-BMT is a 47-item measure with reliability and validity in HCT patients.[23,24] It yields a total score as well as subscales assessing physical well-being (PWB), functional well-being (FWB), social/family well-being (SWB), emotional well-being (EWB), and BMT-specific concerns (BMTS). A Trial Outcome Index (TOI) is calculated by summing the PWB, FWB, and BMTS subscales. TOI was selected as the QOL outcome of interest due to its sensitivity to GVHD.[7,25] Higher scores indicate better QOL. As in previous research,[26,27] a difference of 5-9 points on the TOI was considered clinically meaningful.

Statistical analysis plan

The initial analysis plan was to conduct random effects models to examine change in QOL by study arm over the six QOL assessment points (i.e. baseline, Days 30, 90, 180, 270, 360). Random effects models are a special application of regression analysis used to estimate trajectories in QOL. Random effects models were selected because they allow for analysis of multiple within-person assessment points using all available data. Results yield intercepts and beta weights similar to standard regression models. Because groups did not display equivalent QOL at baseline,[18] the analysis plan was revised to examine the trajectory of QOL over the five post-HCT assessment points (i.e. Days 30, 90, 180, 270, and 360), controlling for pre-HCT QOL. Consequently, the results presented here examine the effect of study arm on post-HCT change in QOL independent of base-line QOL.

Results

Participants

Seventy-four patients were randomized 1:1 to SIR/TAC *versus* MTX/TAC. Three participants did not provide enough QOL data to calculate trajectories, resulting in 71 participants who contributed data to the current analyses. Socio-demographic and clinical characteristics of the sample are displayed in Table 1.

QOL by study arm

BMT-TOI scores were normally distributed; no outliers

were evident. Analyses examining the effects of study arm on post-HCT change in TOI are shown in Table 2 and Figure 1. Results indicate that TOI increased significantly over time in both study arms (P<0.01). There was also a significant effect of study arm over time indicating that the SIR/TAC arm showed smaller improvements in TOI than the MTX/TAC arm (P=0.02). Study arm significantly predicted TOI at Day 360 such that scores in the SIR/TAC group were a mean of 7.17 points lower than the MTX/TAC group (P=0.03).

To explore the contribution of potential clinical differences between study arms on changes in TOI scores (i.e. acute GVHD, chronic GVHD, HGB), *post hoc* analyses were conducted including these variables as controls. These variables were selected because they were measured potential clinical confounds of group differences in QOL, even though the SIR group demonstrated lower incidence of acute and chronic GVHD[18] and GVHD is associated with worse QOL.[7,25] Results are shown in Table 3. Similar to the previous analyses, results indicated that TOI increased significantly over time in both study arms (P<0.001). Significant differences in study arms at Day 360 and over time persisted; the SIR/TAC group demonstrated less improvement in TOI over time when controlling for potential clinical cofounds (P<0.01) and reported TOI scores 9.54 points lower at Day 360 (P<0.01).

To explore the effects of study arm on specific domains of QOL, *post hoc* analyses were conducted examining the subscales that comprise TOI (i.e. PWB, FWB, BMTS) as outcomes. Study arm was a significant predictor of PWB at Day 360 (P=0.02) and across time (P=0.02) controlling for base-line PWB, such that the SIR/TAC arm reported worse physical well-being at Day 360 and across time. The effects of study arm and study arm by time on FWB were non-significant (P>0.05), controlling for base-line FWB. Similarly, the effects of study arm and study arm by time on BMTS were non-significant, controlling for base-line BMTS (P>0.05). Additional post hoc analyses were conducted to explore the effects of study arm on the seven items comprising the PWB subscale. Controlling for base-line responses to these items, a significant difference between study arms at Day 360 was found on item 1 (i.e. "I have a lack of energy"), with the SIR/TAC arm endorsing greater symptom severity (P<0.01). Significant differ-

Table 2. Changes in FACT-BMT Trial Outcome Index (TOI) by study arm.

Predictor	Regression coefficient (SE)	*t*	Interpretation
Intercept	38.82 (7.53)	5.16**	TOI at Day 360 adjusted for other predictors in the model was significantly different from 0 irrespective of study arm.
Time	0.04 (0.01)	6.41**	TOI significantly improved over time irrespective of study arm
Pre-HCT TOI	0.52 (0.10)	5.17**	Pre-HCT TOI significantly predicted change in TOI after HCT
Study arm	-7.17 (3.37)	-2.13*	At Day 360, average TOI scores in the TAC/MTX group were significantly higher than SIR/TAC
Study arm by time	-.02 (0.01)	-2.27*	The TAC/MTX group showed significantly greater improvement in TOI over time than SIR/TAC

*Results of random effects (i.e. regression-based) models are shown. MTX/TAC group membership was coded as 0 in analyses, while SIR/TAC group membership was coded as 1. Time is measured in days from Day 360. HCT: hematopoietic cell transplant. Regression coefficients indicate the magnitude of relationship between the predictor variable and TOI after adjusting for other variables in the model. For example, the intercept indicates the overall mean TOI score across both groups at Day 360 after apportioning out the effects due to time, pre-HCT TOI, study arm, and study arm by time. As another example, the regression coefficient for study arm indicates that the mean TOI score in the SIR/TAC group at Day 360 was 7.17 points lower than that of the MTX/TAC group after adjusting for the other variables in the model. *P<0.05; **P<0.01.*

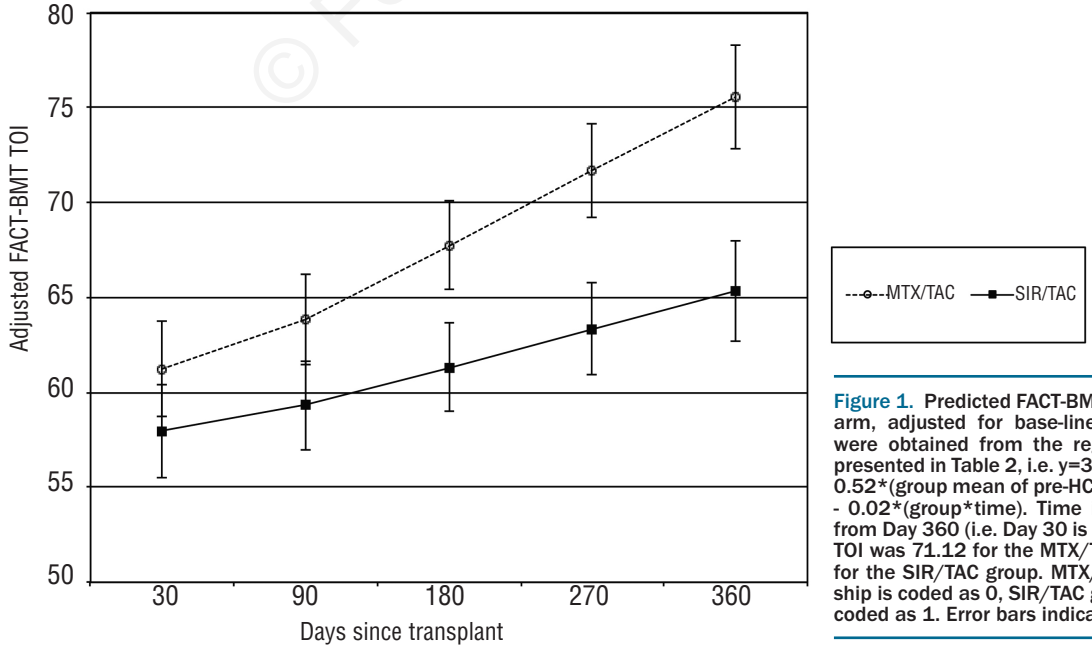

Figure 1. Predicted FACT-BMT TOI scores by study arm, adjusted for base-line TOI scores. Values were obtained from the regression coefficients presented in Table 2, i.e. y=38.82 + 0.04*(time) + 0.52*(group mean of pre-HCT TOI) – 7.17*(group) - 0.02*(group*time). Time is measured in days from Day 360 (i.e. Day 30 is -330). Mean pre-HCT TOI was 71.12 for the MTX/TAC group and 65.22 for the SIR/TAC group. MTX/TAC group membership is coded as 0, SIR/TAC group membership is coded as 1. Error bars indicate standard errors.

ences between study arms over time were observed on item 1 (P<0.01) and item 2 (i.e. "I have nausea") (P=0.01), with the SIR/TAC arm reporting less improvement in these symptoms over time. Study arm differences on these items remained significant when controlling for acute GVHD, chronic GVHD, and HGB (P<0.01).

Discussion

The present study examined QOL outcomes in a randomized clinical trial of SIR/TAC compared to MTX/TAC for the prevention of GVHD. Patients randomized to the SIR/TAC arm received SIR for at least one year post-HCT, while patients randomized to the MTX/TAC arm received MTX on Days +1, 3, 6, and 11. In both arms, TAC taper was started on Day 50 for patients who were free of acute GVHD and off systemic glucocorticoid therapy. Contrary to our hypothesis, the SIR/TAC arm demonstrated less improvement in QOL in the year post-HCT. By one year post-HCT, adjusted FACT-BMT TOI scores in the SIR/TAC arm were 7 points lower than the MTX/TAC arm. To put this finding into context, a difference of 5-9 points on the TOI is considered clinically meaningful in other cancer populations.[26,27] Thus, results from the current study suggest that administration of SIR as opposed to MTX for prevention of GVHD is associated with clinically significant, inferior recovery of QOL.

Reduced QOL associated with SIR is not explained by differences in base-line QOL, anemia, or severity of GVHD. Although the SIR/TAC arm also reported worse pre-HCT QOL, base-line differences were controlled in all statistical analyses, indicating that findings were not due to better initial QOL. Analyses controlling for HGB did not attenuate the relationship between study arm and QOL, indicating that anemia did not significantly contribute to study arm differences. QOL differences were also not attributable to differences in acute or chronic GVHD. Patients treated with SIR/TAC demonstrated a significantly lower incidence of grade II-IV acute GVHD and severe chronic GVHD than patients treated with MTX/TAC.[18] Based on these findings and the robust association between severity of chronic GVHD and reduced QOL,[7,25,28] it would be expected that reduced severity of chronic GVHD in the SIR/TAC arm would be associated with better, not worse, QOL. Analyses controlling for the effects of GVHD (Table 3) show that more severe chronic GVHD was associated with worse QOL at Day 360 and less improvement in QOL over time. Controlling for acute and chronic GVHD strengthened the relationship between study arm and QOL. These findings indicate that reductions in QOL associated with SIR were strong enough to overcome any beneficial effects of SIR on QOL due to reduced GVHD severity.

Reduced QOL associated with SIR is also not explained by potential differences in immunosuppressive medication usage between study arms. There was no difference in the proportion of living patients treated with prednisone, systemic glucocorticoids, or budesonide between study arms.[18] The incidence of TAC discontinuation by 30 months also did not differ between study arms.[18] Fewer patients in the SIR/TAC arm were treated with beclomethasone for acute GVHD to week 14, which suggests that reduced QOL in the SIR/TAC arm was not due to potential beclomethasone-associated side-effects.[18] Infrequent and heterogeneous use of second-line immune suppressive agents (i.e. those used beyond initial trial-mandated prophylaxis and steroid therapy to treat established acute and chronic GVHD) such as mycophenolate mofetil, infliximab, rituximab, and extra-corporeal photopheresis (ECP), precluded statistical comparisons for these agents across study groups. However, severity of acute and chronic GVHD can be considered a proxy for the extent of required immunosuppressive therapy. As noted

Table 3. Changes in FACT-BMT Trial Outcome Index (TOI) by study arm controlling for potential clinical confounds.

Parameter	Regression coefficient (SE)	*t*	Interpretation
Intercept	47.04 (8.31)	5.66**	TOI at Day 360 adjusted for other predictors in the model was significantly different from 0 irrespective of study arm
Time	0.06 (0.01)	4.98**	TOI significantly improved over time irrespective of study arm
Pre-HCT TOI	0.50 (0.10)	5.14**	Pre-HCT TOI significantly predicted change in TOI after HCT
aGVHD	-3.05 (1.77)	-1.72	aGVHD did not significantly predict TOI at Day 360
aGVHD by time	-.01 (0.01)	-1.59	aGVHD did not significantly predict change in TOI over time
cGVHD	-4.22 (1.51)	-2.79**	cGVHD significantly predicted TOI at Day 360
cGVHD by time	-0.04 (0.01)	-3.02**	cGVHD significantly predicted change in TOI over time
HGB	2.08 (1.42)	1.46	HGB did not significantly predict TOI at Day 360
HGB by time	0.00 (0.01)	0.14	HGB did not significantly predict change in TOI over time
Study arm	-9.54 (3.62)	-2.71**	At Day 360, average TOI scores in the TAC/MTX group were significantly higher than SIR/TAC
Study arm by time	-0.03 (0.01)	-2.96**	The TAC/MTX group showed significantly more improvement in TOI over time than SIR/TAC

*Results of random effects (i.e. regression-based) models are shown. Intercept indicates TOI scores across both study arms at Day 360 after apportioning out the effects due to other variables in the model. aGVHD indicates the effect of maximum grade of acute GVHD by Day 360. cGVHD indicates the effect of maximum grade of chronic GHVD by Day 360. HGB indicates the effect of hemoglobin level by Day 360. Study arm indicates difference in TOI by study arm at Day 360. MTX/TAC group membership was coded as 0 in analyses, while SIR/TAC group membership was coded as 1. Time is measured in days from Day 360. All regression coefficients are adjusted for the other variables in the model. For example, the regression coefficient for cGHVD indicates that an increase in severity of chronic GHVD by one stage resulted in a decrease in TOI of 4.22 points at 360 days after adjusting for other variables in the model. HCT: hematopoietic cell transplant. *P<0.05, **P<0.01.*

above, controlling for acute and chronic GVHD resulted in stronger associations between study arm and QOL, indicating that immunosuppressive therapy was likely not the cause of study arm differences in QOL.

Exploratory *post hoc* analyses indicated that QOL differences were due at least in part to more severe fatigue and nausea in the SIR/TAC arm. These findings are consistent with previous reports of fatigue and nausea as side-effects of SIR.[29-31] Notably, no statistically significant study arm differences in QOL were evident at Day 30 and 90. QOL instead began to diverge after 90 days when patients in the MTX/TAC arm were no longer being treated with MTX but patients in the SIR/TAC arm were still receiving SIR. Although the current protocol mandated SIR use through one year, while previous studies have discontinued SIR at earlier time points (commonly aiming to discontinue by 180 days post-HCT).[12-16] our findings suggest that QOL differences may be relevant to both regimens. Unfortunately, no QOL data have been reported from these other trials that have utilized SIR/TAC for GVHD prophylaxis.

Despite inferior recovery in QOL found in the current study, SIR/TAC is associated with a variety of clinical benefits including reduced severity of acute and chronic GVHD, shorter time to engraftment, and reduced severity of mucositis.[14,15,18,20] Consequently, we believe that the benefits of SIR/TAC outweigh reductions in QOL. However, our data support the need for greater attention to QOL in SIR-treated patients. Patients treated with SIR may benefit from proactive management of fatigue and nausea to increase QOL. Several studies have shown that moderate exercise (i.e. 75-80% of maximal heart rate) is associated with decreased fatigue and improved QOL among HCT patients.[32-36] Inpatient, home-based, and outpatient rehabilitation programs have all shown beneficial effects. Incorporation of exercise and behavioral methods for improving QOL into the treatment program could offset the inferior QOL recovery observed in patients treated with SIR/TAC, and should be explored further.

The current study is characterized by several strengths, including a randomized design and assessment of QOL at uniform times from transplant with a well-validated measure. Nevertheless, study limitations should be noted: the sample of 71 participants was relatively small and QOL was not equivalent between study arms at baseline. Although base-line QOL differences were controlled in analyses, there may have been one or more unmeasured variables that differed between arms and contributed to changes in QOL over time. It may also be possible that participants in the MTX/TAC study arm had unusually high QOL. FACT-BMT TOI scores in the MTX/TAC group were slightly higher than those reported previously in allogeneic HCT recipients,[7] although they were within a standard deviation. Also, we cannot determine whether inferior QOL is the result of intentionally prolonged administration of SIR itself, or if similar results would be observed with prolonged administration of other immune suppressive agents. In addition, patients' overall perception of their QOL results from an integration of multiple factors after transplant (e.g. ongoing or resolved graft *vs.* host disease, multiple immune suppressive agents, other medications, anemia, various organ dysfunction, diminished cardiopulmonary fitness, sleep disturbance, changes in mood, changes in relationships, ability, and personal and professional roles, etc.). While we have controlled for several relevant factors in the reported analyses, it is not possible to definitively implicate sirolimus alone in the observed results.

In summary, findings from the current study indicate that prolonged administration of SIR after HCT is associated with inferior QOL through one year post-HCT, despite reduction in significant chronic GVHD. This finding highlights a disparity between clinician and patient perception of benefit, and suggests the importance of inclusion of patient-reported outcomes in GVHD prevention trials. These data should be factored into counseling of prospective HCT patients who will be treated with this regimen, and post-HCT exercise and behavioral interventions to improve QOL should be explored in this setting to improve recovery in QOL.

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Authorship and Disclosures

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