Sirolimus demonstrates activity in the primary therapy of acute graft-*versus*-host disease without systemic glucocorticoids

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ABSTRACT

Background
Advances in acute graft-*versus*-host disease therapy are needed.

Design and Methods
We examined the efficacy of sirolimus as primary therapy for acute graft-*versus*-host disease in 32 patients.

Results
Acute graft-*versus*-host disease involved the skin in 53% of cases, gastrointestinal tract in 66%, liver in 16%. The syndrome was overall grade 1 in 12% cases, grade 2 in 75%, and grade 3 in 13%. Sirolimus was targeted to achieve serum trough levels of 5-14 ng/mL. Sixteen (50%) patients achieved sustained, complete resolution of acute graft-*versus*-host disease with sirolimus alone. In contrast, 19 of 32 (59%) matched historical controls treated with standard 1 mg/kg steroids achieved complete response (P=0.47). With median follow-up time for surviving patients of 16 (range 6-26) months, one year overall survival was 56% (95% CI 38-74%). The cumulative incidence of relapse at one year was 37% (95% CI 23-60%), and mortality in remission was 20% (95% CI 10-42%). The cumulative incidence of chronic graft-*versus*-host disease was 55% (95% CI 39-79%). Thrombotic microangiopathy occurred in 3 cases (grade 1 n=1; grade 2 n=2), and responded to dose reduction of calcineurin inhibitor.

Conclusions
In this retrospective series, sirolimus demonstrates activity comparable to that of high-dose glucocorticoids in the primary therapy of acute graft-*versus*-host disease. Confirmation of this activity requires prospective clinical trials.

Key words: sirolimus, acute GVHD, glucocorticoids, primary therapy.

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Introduction

Prednisone at 1-2 mg/kg constitutes the present standard primary therapy for acute graft-*versus*-host disease (GVHD) following allogeneic hematopoietic cell transplantation (HCT). However, complete response to this therapy is achieved in 40-50% of cases.[1-4] Patients with glucocorticoid-refractory acute GVHD have limited response to available rescue therapies and have inferior survival compared to those with glucocorticoid-responsive disease.[5-7] In the therapy of acute and chronic GVHD, morbidity from glucocorticoid therapy is observed in HCT recipients.[8-12] The limited efficacy and associated toxicity of glucocorticoid therapy provide the rationale for novel approaches in the therapy of acute GVHD.

Previous reports of combined therapy with glucocorticoids and additional immunosuppressive agents were disappointing.[13,14] The combination of glucocorticoids and mycophenolate mofetil may offer the promise of improved GVHD control,[15] but this additional immunosuppression may enhance the risk of opportunistic infection and primary malignancy relapse after HCT. These and historical efforts have been based on the assumption that glucocorticoids constitute a necessary component of primary therapy for acute GVHD.

In a previous report, we suggested that sirolimus is active as sole primary therapy of acute GVHD.[16] This approach may allow the dual benefit of acute GVHD control and avoidance of systemic glucocorticoids. Given the antitumor activity of mTOR inhibitors demonstrated in related literature,[17-20] as well as evidence that its use as prophylaxis is associated with decreased lymphoma relapse post transplant,[21] sirolimus may be a particularly attractive therapy for acute GVHD in those HCT recipients with high risk for relapse after transplant. As further evidence of the activity of sirolimus in the primary therapy of acute GVHD, we report an expanded cohort of HCT recipients treated with sirolimus as primary therapy for acute GVHD with extended follow up.

Design and Methods

Through retrospective review, 32 HCT recipients were identified who were treated with sirolimus as primary therapy of acute GVHD; biopsy confirmation of acute GVHD was available in 31 of 32 cases. In older patients, primary glucocorticoid therapy was not given to avoid toxicity, and in patients with active malignancy, sirolimus was preferred for its dual activity as immunosuppressant and anti-cancer drug. All patients received tacrolimus in combination with methotrexate (MTX) or mycophenolate mofetil (MMF) as acute GVHD prophylaxis. The target serum level of tacrolimus was reduced to 3-7 ng/mL while receiving concomitant sirolimus to reduce the risk for thrombotic microangiopathy (TMA). Sirolimus was administered orally with a target serum level of 4-12 ng/mL by mass spectrometry or 5-14 ng/mL by the Architect assay (Abbott, Abbott Park, IL, USA). In the absence of ongoing acute GVHD, tacrolimus was tapered with empiric dose reductions.

Baseline characteristics were summarized with descriptive statistics. Established consensus criteria were utilized to score acute GVHD weekly from onset to sustained complete resolution or last follow up.[19] Complete response (CR) to sirolimus as primary therapy was defined as sustained complete resolution of acute GVHD manifestations for at least four weeks without the addition of systemic glucocorticoids or other systemic immunosuppressive agents. The association between complete response to sirolimus alone and acute GVHD characteristics, including organ involvement and severity, was examined using logistic regression analysis. Chronic GVHD was scored according to the proposed National Institutes of Health (NIH) consensus criteria.[20] Indication, initial dose, and duration of any glucocorticoid therapy was recorded and considered a failure of primary therapy with sirolimus. The cumulative incidence of disease relapse, non-relapse mortality, and cGVHD was estimated, accounting for competing risk.[22] All outcomes were assessed from the initiation date of sirolimus. Overall and relapse free survival were calculated by the Kaplan-Meier method; primary disease relapse or death were considered events in the estimation of relapse free survival. Survival was estimated from date of sirolimus initiation. The incidence of cytomegalovirus (CMV) reactivation, and TMA are reported; TMA was scored according to proposed CTN consensus definitions.[23] This study was approved as a retrospective review by the University of South Florida Institutional Review Board (IRB). While sirolimus was utilized as primary therapy of acute GVHD outside a prospective clinical trial, patients were adequately informed prior to therapy of the rationale for avoiding high-dose steroid therapy, of the potential risks associated with sirolimus, and of the monitoring required to achieve and sustain therapeutic sirolimus levels. Sirolimus was utilized in this setting with patients who had been adequately counseled on the anticipated risks, benefits and alternatives to this approach. All patients had signed an IRB-approved consent form indicating willingness to participate in long-term follow-up studies.

Results

Baseline characteristics of this series are summarized in Table 1. The cohort is notable for advanced age (median 60 years, range 28-73 years), and for high-risk malignancy, as 23 (72%) were not in remission at the time of HCT. Primary acute GVHD prophylaxis consisted of either tacrolimus plus methotrexate (n=29) or tacrolimus plus mycophenolate mofetil (n=3). Four patients with an HLA mismatched donor received additional thymoglobulin 7.5 mg/kg ending on day -1. Patients were treated with sirolimus as the primary therapy for acute GVHD at a median of 30 (range 15-106) days after HCT. Sirolimus was administered orally as a median loading dose of 6 mg (range 2 to 9 mg), followed by maintenance dosing to sustain the desired target therapeutic levels. Therapeutic sirolimus levels were achieved in all cases, including patients with gastrointestinal involvement. When used in prophylaxis of acute GVHD, mycophenolate mofetil was continued with the initiation of sirolimus; however, tacrolimus was reduced to target a range of 3-7 ng/mL.

Sixteen (50%) patients achieved complete response of acute GVHD following primary therapy with sirolimus without the addition of systemic glucocorticoids or any other systemic immunosuppressive agents (Table 2). Among these 16 patients who achieved complete resolution of acute GVHD with sirolimus alone, initial overall response (composite of partial and complete response) was achieved at a median of seven days (range 5-21 days) and complete response was achieved by a median of 14 days (range 5-28 days). In 2 of these cases, recurrent acute GVHD developed 7-12 weeks after initial complete response; resolution of recurrent acute GVHD was achieved in both with the addition of 0.2-0.5 mg/kg body

Table 1. Baseline characteristics of study sample and historical control.

	Sirolimus primary therapy cohort		Historical prednisone treated cohort	
Median age, years	60 (range 28 – 73)		51 (range 25 – 70)	
Median time to acute GVHD onset, days	30 (range 15 – 106)		20 (range 5 – 42)	
Condition	**Number**	**%**	**Number**	**%**
Diagnosis				
AML	14	44%	8	25%
MDS	6	19%	11	34%
MPD	4	13%	0	0%
ALL	3	9%	1	3%
MM	3	9%	2	6%
NHL	1	3%	3	9%
CEL	1	3%	0	0%
CML	0	0%	2	6%
SAA	0	0%	2	6%
CLL	0	0%	3	9%
Remission status				
In CR	9	28%	13	41%
Not in CR	23	72%	19	59%
Cell source				
PBSC	32	100%	32	100%
BM	0	0%	0	0%
Donor HLA matching				
HLA-matched sibling	7	22%	7	22%
HLA-matched unrelated	20	63%	20	63%
HLA-mismatched unrelated	5	16%	5	16%
Recipient/donor gender				
Female/female	5	16%	4	13%
Female/male	7	22%	9	28%
Male/female	5	16%	4	13%
Male/male	15	47%	15	47%
Conditioning regimen				
FLU/BU	26	81%	31	97%
FLU/MEL	3	9%	0	0%
Pento/BU/rituxan	2	6%	0	0%
FLU/BU/rituxan	1	3%	0	0%
Bu/Cy	0	0%	1	3%
Acute GVHD prophylaxis				
TAC/MTX	29	91%	29	91%
TAC/MMF	3	9%	3	9%
Donor/recipient CMV				
Neg/neg	9	28%	15	47%
Neg/pos	10	31%	14	44%
Pos/neg	4	13%	0	0%
Pos/pos	9	28%	3	9%
Overall acute GVHD grade at initiation of sirolimus			Overall acute GVHD grade at initiation of prednisone	
I	4	13%	4	13%
II	24	75%	24	75%
III	4	13%	4	13%
IV	0	0%	0	0%
acute GVHD onset organ stage				
Skin				
0	15	47%	15	47%
1	8	25%	8	25%
2	4	13%	4	13%
3	5	16%	5	16%
4	0	0%	0	0%
Any	17	53%	17	53%
GI				
0	11	34%	11	34%
1	18	56%	18	56%
2	3	9%	3	9%
3	0	0%	0	0%
4	0	0%	0	0%
Any	21	66%	21	66%
Liver				
0	27	84%	27	84%
1	4	13%	4	13%
2	1	3%	1	3%
3	0	0%	0	0%
4	0	0%	0	0%
Any	5	16%	5	16%

ALL: acute lymphoblastic leukemia; MM: multiple myeloma; AML: acute myelogenous leukemia; MPD: myeloproliferative disorder; NHL: non-Hodgkin's lymphoma; MDS: myelodysplastic syndrome; CEL: chronic eosinophilic leukemia; CML: chronic myelogenous leukemia; CR: complete remission; BM: bone marrow; PBSC: peripheral blood stem cells; Flu: fludarabine; Bu: busulfan; Mel: melphalan; Cy: cyclophosphamide; Pento: pentostatin; TAC: tacrolimus; MTX: methotrexate; MMF: mycophenolate mofetil; ATG: rabbit anti-thymocyte globulin; CMV: cytomegalovirus.

weight of prednisone. In the remaining 16 cases, systemic glucocorticoids were initiated at a median of nine days (range 2-28 days) after initiation of sirolimus with a prednisone-equivalent median dose of 0.5 mg/kg (range 0.2-1 mg/kg), and 12 achieved resolution of acute GVHD (Figure 1). Importantly, uniform criteria for initiation of systemic steroids after first-line sirolimus therapy were not employed. Among these cases, prednisone was started after initial sirolimus therapy for persistent acute GVHD manifestations of unchanged severity in 6 cases (median nine days from sirolimus initiation, range 2-19 days), grade progression in 6 cases (median nine days from sirolimus initiation, range 2-16 days), in the setting of partial response in 2 cases (6-7 days after sirolimus initiation), and in 2 cases for recurrent acute GVHD within four weeks after initial complete response to sirolimus. Four patients (12%) had persistent acute GVHD that was treated with mycophenolate mofetil. Of these 4 patients, one died following primary disease relapse, 2 died from non-relapse causes (sepsis, and refractory acute GVHD with sepsis), and one is alive following resolution of acute GVHD and without relapse. On logistic regression analysis, neither acute GVHD severity nor organ involvement were significantly associated with complete response to sirolimus.

To further qualify our results, we performed a retrospective comparison of complete response rate following

Table 2. Summary of individual patient outcomes.

Age	Disease	Remission at HCT	Acute GVHD prophylaxis	Overall onset grade	Skin/GI/liver stage	CR with sirolimus alone	Required steroids	Malignancy relapse	Death
28	ALL	No	TAC/MTX	II	2/0/1	Yes	No	No	No
56	MM	No	TAC/MTX	II	0/1/0	Yes	No	Yes	Yes
68	AML	No	TAC/MTX	II	0/1/0	Yes	No	Yes	Yes
52	MPD	No	TAC/MTX	II	3/1/0	Yes	Yes 0.5 mg/kg (recurrent 7 weeks after CR)	No	No
58	MPD	No	TAC/MTX	II	1/1/0	No	Yes 0.5 mg/kg (persistent)	No	No
34	NHL	No	TAC/MTX	II	0/1/0	No	Yes 1 mg/kg (persistent)	No	No
57	AML	Yes	TAC/MTX	II	3/0/0	No	Yes 1 mg/kg and MMF (persistent)	No	No
66	MDS	Yes	TAC/MMF	II	0/1/0	*	No	Yes	Yes
63	AML	No	TAC/MMF	II	0/1/0	Yes	No	Yes	Yes
67	AML	No	TAC/MMF	III	1/2/0	Yes	No	Yes	No
65	MDS	No	TAC/MTX	I	2/0/0	Yes	No	Yes	Yes
57	MM	No	TAC/MTX	II	2/1/0	Yes	No	No	No
64	MM	No	TAC/MTX	I	1/0/0	Yes	No	Yes	Yes
73	MDS	No	TAC/MTX	I	1/0/0	No	Yes 0.3 mg/kg (persistent)	No	Yes
65	AML	No	TAC/MTX	II	1/1/0	Yes	No	Yes	No
61	ALL	Yes	TAC/MTX	III	0/0/2	No	Yes 0.6 mg/kg (persistent)	No	No
35	AML	Yes	TAC/MTX	II	0/1/0	Yes	No	No	No
51	CEL	No	TAC/MTX	III	0/2/0	No	Yes 1 mg/kg, MMF, infliximab (persistent)	No	Yes
47	AML	No	TAC/MTX	II	0/1/0	No	Yes 0.5 mg/kg (persistent)	Yes	Yes
67	AML	No	TAC/MTX	II	3/0/0	No	Yes 1 mg/kg, MMF (persistent)	Yes	Yes
72	AML	Yes	TAC/MTX	II	0/1/0	No	Yes 1 mg/kg, MMF (persistent)	No	Yes
53	AML	No	TAC/MTX	II	3/0/0	Yes	No	Yes	No
33	ALL	Yes	TAC/MTX	II	0/1/1	No	Yes 0.5 mg/kg (persistent)	No	Yes
50	CMML	No	TAC/MTX	III	0/2/0	No	Yes 1 mg/kg (persistent)	No	No
53	MDS	No	TAC/MTX	II	0/0/1	No	Yes 0.4 mg/kg (persistent)	No	No
57	AML	Yes	TAC/MTX	II	0/0/1	Yes	No	No	No
54	AML	No	TAC/MTX	II	1/1/0	No	Yes 0.5 mg/kg (persistent)	No	Yes
63	MDS	No	TAC/MTX	II	0/1/0	Yes	No	No	No
62	AML	Yes	TAC/MTX	II	1/1/0	No	Yes 1 mg/kg (persistent)	Yes	Yes
64	MPD	No	TAC/MTX	II	3/1/0	Yes	Yes 0.2 mg/kg (recurrent 12 weeks after CR)	No	No
62	MDS	No	TAC/MTX	II	2/1/0	No	Yes 0.42 mg/kg (persistent)	Yes	Yes
66	AML	Yes	TAC/MTX	I	1/0/0	No	Yes 0.2 mg/kg (persistent)	No	Yes

**1 mg/kg of prednisone utilized at the onset of acute GVHD, but then rapidly tapered off after addition of sirolimus with total duration steroid treatment of nine days; maintained CR of acute GVHD with no further steroids. **ALL: acute lymphoblastic leukemia; MM: multiple myeloma; AML: acute myelogenous leukemia; MPD: myeloproliferative disorder; NHL: non-Hodgkin's lymphoma; MDS: myelodysplastic syndrome; CEL: chronic eosinophilic leukemia; CMML: chronic myelomonocytic leukemia.*

sirolimus primary therapy to complete response following standard primary glucocorticoid therapy in a historical matched cohort treated at our center. These control subjects all had biopsy-confirmed acute GVHD, and were identified by matching to cases at each of the following variables: acute GVHD organ involvement and severity, donor relation, HLA matching, stem cell source, and acute GVHD prophylaxis agents utilized. All matched control subjects were treated with 1 mg/kg of prednisone as primary therapy. Nineteen of these 32 subjects (59%) achieved complete remission, as compared to 16 of 32 (50%) of those treated with sirolimus primary therapy (Fisher's exact test, P=0.47). These retrospective comparative data suggest comparable complete response rates achieved with sirolimus primary therapy as compared with standard 1 mg/kg of prednisone.

The cumulative incidence of chronic GVHD was 55% (95% CI 39-79%), with maximal NIH criteria global chronic GVHD score of mild in 5, moderate in 9, and severe in 3 patients, respectively. With a median follow up for living patients of 16 months (6-26 months), one year overall survival was 56% (95% CI 38–74%) (Figure 2), and one year relapse free survival was 37% (95% CI 19-55%). Causes of death include: relapse (n=9), sepsis (n=3), veno-

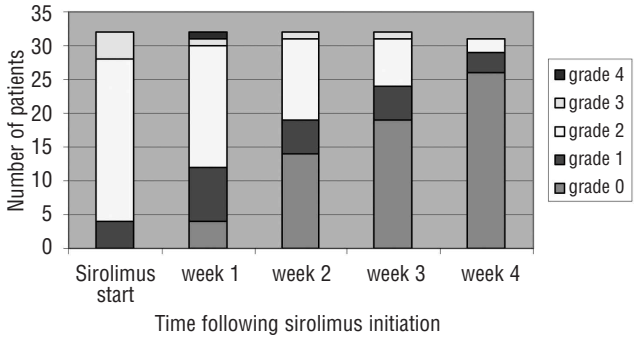

Figure 1. Weekly overall acute GVHD grade following initiation of sirolimus as primary therapy.

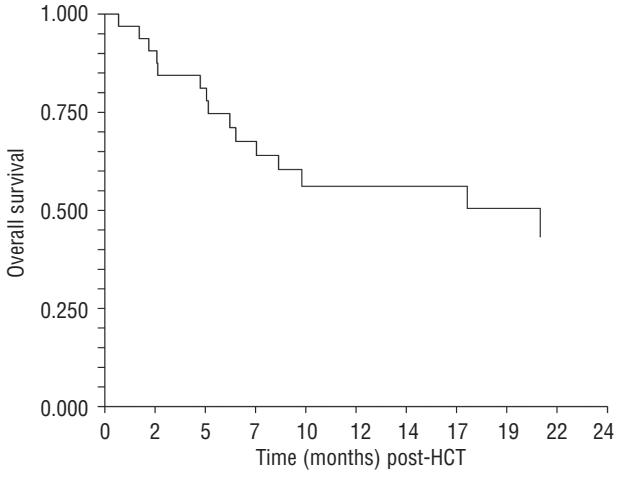

Figure 2. Overall survival from date of sirolimus initiation.

occlusive disease and CMV pneumonitis (n=1), cardiomyopathy (n=1), and chronic GVHD (n=1). The one year cumulative incidence of relapse was 37% (95% CI 23-60%), and the one year cumulative incidence of non-relapse mortality was 20% (95% CI 10-42%). None of the 16 patients with complete response to sirolimus died in remission, compared to 4 of 12 (33%) of those with complete response to sirolimus plus systemic glucocorticoids, and 2 of 4 (50%) of those with persistent acute GVHD. By time of last follow up, no patients in this series had successfully discontinued all immune suppression.

TMA occurred in 3 cases; per CTN consensus criteria, this was grade 1 in one case, and grade 2 in 2 cases. TMA resolved with dose reduction of tacrolimus in all cases. In one case, all immunosuppression was withdrawn due to primary disease relapse. CMV infection or reactivation differed according to donor/recipient serostatus: 0/9 for negative/negative; 4/10 for negative/positive; 1/4 for positive/negative; and 4/9 for positive/positive.

Discussion

High-dose glucocorticoid therapy induces complete resolution in a minority of cases, and imposes a well characterized burden of early and late complications. Given this limited efficacy and marked toxicity, advances in primary therapy of acute GVHD are needed. We have previously reported early experience of sirolimus as a sole primary therapy of acute GVHD in a series of 10 patients deemed high risk for steroid toxicity and primary malignancy relapse.[16] In this report, we have examined the activity of sirolimus in a larger cohort including the original 10, and with extended follow up. These more mature data demonstrate the efficacy of sirolimus alone in the induction of sustained complete remission of acute GVHD in 50% of cases. Complete responses were observed across diverse organ involvement and acute GVHD severity. Importantly, these patients achieved the major therapeutic goal of acute GVHD resolution, while being spared the toxicity of systemic glucocorticoids. An additional 38% (total 88%) achieved complete resolution of acute GVHD with the addition of glucocorticoid doses which were mainly less than 1 mg/kg.

The low non-relapse mortality observed is encouraging in this group of older adults who mainly received unrelated donor and mismatched unrelated donor allografts. This was particularly striking in those who achieved complete remission of aGVHD with sirolimus alone. The efficacy in aGVHD with this approach was also balanced by a favorable toxicity profile. Sirolimus was safely administered with tacrolimus with an overall low incidence of TMA, which was successfully managed with dose reduction or discontinuation of tacrolimus. This evidence further complements the durable efficacy of sirolimus in the primary therapy of acute GVHD.

These are encouraging results. However, the study has several limitations. First, patients were treated according to the physician's discretion, introducing selection bias. This likely had a significant impact on the distribution of acute GVHD severity among the included patients. Also, uniform criteria for utilization of systemic glucocorticoids after first-line sirolimus therapy were not employed. Accordingly, patients received steroids for a variety of indications, including persistent but stable manifestations, progressive severity, recurrent manifestations after initial complete response, and in the setting of partial response. As those with stable manifestations and partial response may have ultimately experienced complete response with sirolimus alone if additional time were allowed, the true failure rate or requirement for systemic glucocorticoids after primary sirolimus therapy is not clear from these data.

Additionally, while we did not detect significant differences in complete response rate according to organ involvement and acute GVHD severity, these analyses are necessarily limited by small numbers. In particular, the cohort does not include grade 4 aGVHD. The absence of this severity of acute GVHD in our series precludes any conclusion on the activity of sirolimus in primary therapy of grade 4 acute GVHD. While complete response rate would be anticipated to be less in grade 4 disease, this limited efficacy remains the unfortunate reality of available immune suppressive therapeutic agents. Another major concern is the potentially limited efficacy of sirolimus in advanced gastrointestinal tract (GI) involvement given the exclusively oral formulation of the drug. While we have observed therapeutic serum levels of sirolimus and clinical response in cases with gastrointestinal tract involvement,

this effect may be undermined in the setting of vomiting and diarrhea of greater severity. Given this limitation, oral sirolimus may not be an effective primary intervention in an acute GVHD syndrome manifesting large volume diarrhea. While the data reported here are encouraging, these limitations would be best addressed through a prospective clinical trial of sirolimus as primary therapy for acute acute graft-*versus*-host disease.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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