8-24-2021

Transitioning tacrolimus to sirolimus in allogeneic hematopoietic cell transplantation

Linda Arrabi
Henry Ford Health, larrabi1@hfhs.org

Anna Jan

Chitra Hosing

Denái R. Milton

Jason Yeh

Recommended Citation

Arrabi L, Jan A, Hosing C, Milton DR, and Yeh J. Transitioning tacrolimus to sirolimus in allogeneic hematopoietic cell transplantation. Eur J Haematol 2021.

Received: 23 March 2021 | Revised: 20 August 2021 | Accepted: 23 August 2021

DOI: 10.1111/ejh.13701

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Transitioning tacrolimus to sirolimus in allogeneic hematopoietic cell transplantation

Linda Arrabi[1] | Anna Jan[2] | Chitra Hosing[3] | Denái R. Milton[4] | Jason Yeh[2]

[1]Department of Pharmacy, Henry Ford Health System, Detroit, MI, USA

[2]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3]Division of Cancer Medicine, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence
Linda Arrabi, Department of Pharmacy, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, USA.
Email: larrabi1@hfhs.org

Abstract

Objectives: Calcineurin inhibitor (CNI) use for acute graft-versus-host disease (aGVHD) prophylaxis in allogeneic hematopoietic cell transplantation (allo-HCT) recipients has been associated with toxicities. Toxicities may be managed by converting CNI to sirolimus as often done in solid organ transplantation. This study aimed to characterize allo-HCT patients who completely transitioned from tacrolimus to sirolimus and evaluate the incidence of aGVHD within 100 days post-transition, overall survival (OS), and incidence of relapse.

Methods: Safety and efficacy data were collected at baseline and at day 30 and 90 post-transition from tacrolimus to sirolimus and at one-year post-HCT.

Results: Most patients who transitioned had acute leukemia, received a matched unrelated donor allo-HCT, and transitioned due to nephrotoxicity or neurotoxicity. The resolution rate was 83% and 48% in the nephrotoxicity group, 78% and 61% in the neurotoxicity group, 33% and 33% in the group that developed both nephrotoxicity and transplant-associated thrombotic microangiopathy at 30 and 90 days of assessments, respectively. Patients who transitioned before day 55 post-allo-HCT were more likely to develop new or worsening aGVHD. The one-year OS and relapse rates were 37% and 20%, respectively.

Conclusions: The conversion from tacrolimus to sirolimus demonstrates promising resolution of acute toxicities; however, overall mortality remains high.

KEYWORDS

graft-versus-host disease, sirolimus, stem cell transplantation, tacrolimus

1 | INTRODUCTION

Acute graft-versus-host disease (aGVHD) is the second leading cause of death in patients receiving allogeneic hematopoietic stem cell transplant (allo-HCT).[1] It often occurs after allo-HCT within the first 100 days and is a reaction of donor immune cells against host tissues that include the skin, liver, and gastrointestinal tract (GI).[2,3] Numerous risk factors have been recognized to be associated with increased incidence or severity of aGVHD, such as age, histocompatibility antigen disparity between the hematopoietic cell donor and recipient, source of allogeneic hematopoietic cells, and intensity of conditioning regimen.[4]

Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, have long been the standard of care for organ rejection prophylaxis in solid organ transplantation and GVHD prophylaxis in allo-HCT.[1,5] However, CNIs are not devoid of risks. Long-term toxicities, such as nephrotoxicity, neurotoxicity, and transplant-associated thrombotic microangiopathy (TA-TMA), can limit the use of tacrolimus.[5,6]

One strategy to manage these side effects is to convert the CNIs to sirolimus.

Development of the mammalian target of rapamycin inhibitors, such as sirolimus, could offer an alternative to CNIs to reduce or eliminate CNI toxicities. The mammalian target of rapamycin inhibitors exert their immunosuppressive effect through a separate mechanism and exhibit a different adverse effect profile than CNIs.[7,8] They inhibit the activation and proliferation of T-lymphocytes which blocks growth factor-induced transduction signals that mediate cellular division in response to alloantigens.[8] Sirolimus has been used in the prevention and treatment of GVHD after allo-HCT.[9] Its safety and efficacy have been compared in several trials to tacrolimus and were found to provide similar GVHD-free survival.[10,11]

Multiple randomized trials showed improved renal function with the conversion from tacrolimus to sirolimus in solid organ transplant recipients.[12,13] Significant improvement in neurotoxicity, secondary to CNI use, was witnessed in liver transplant patients after the conversion from tacrolimus to sirolimus.[8,14] There have not been any studies evaluating the safety and efficacy of this transition strategy in allo-HCT patients.

The primary objective of this study was to characterize the allo-HCT population who transitioned from tacrolimus to sirolimus due to toxicity or treatment failure. The secondary objectives of the study were to evaluate the incidence of new or worsening aGVHD within 100 days post-transition from tacrolimus to sirolimus and to evaluate overall survival (OS) and cumulative incidence of relapse at one-year post-HCT.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This non-interventional retrospective cohort study was conducted at The University of Texas MD Anderson Cancer Center. It included all patients aged 18 years or older who received an allo-HCT and were completely transitioned from tacrolimus to sirolimus from January 1, 2014, to December 31, 2018. Patients were excluded if they were previously on aGVHD prophylaxis not containing tacrolimus or if they developed refractory aGVHD that was treated with concomitant tacrolimus and sirolimus. This retrospective chart review was approved by the Institutional Review Board.

2.2 | Data collection and assessment

Patient demographics, pertinent medical history, disease characteristics, donor and stem cell source, conditioning regimen, immunosuppressive therapy, laboratory values, GVHD, and adverse effects were collected using the electronic medical record utilized at the institution. Data were collected at baseline to characterize allo-HCT patients who fit the inclusion criteria, at day 30 and 90 post-transition from tacrolimus to sirolimus, and at one-year post-HCT. The resolution of nephrotoxicity assessment was based on previous solid organ transplant trials which defined resolution of nephrotoxicity as glomerular filtration rate improvement of 5 ml/min or greater at time of assessment. Cockcroft gault calculation was used to estimate glomerular filtration rate.[12,13] TA-TMA diagnosis and resolution was determined by the Overall Thrombotic Microangiopathy Grouping which assessed the presence of normal coagulation assay, presence of schistocytes, increase in lactate dehydrogenase, thrombocytopenia, decreased hemoglobin, decreased haptoglobin, and negative Coombs' test.[6] Neurotoxicity was diagnosed and assessed by the provider based on physical and neurologic examination and ruling out other causes of neurotoxicity, such as infection, preexisting conditions, medications. Neurotoxicity resolution was determined based on clinical assessment and documentation in the medical records.

2.3 | Statistical analysis

Patient demographics, disease characteristics, toxicities, and allo-HCT outcomes were summarized for all patients by aGVHD group (ie, those with incidence of new or worsening aGVHD within 100 days vs. those without). Categorical measures were summarized by frequencies and percentages and evaluated by Fisher's exact test or its generalization. Continuous measures were summarized by medians and ranges (minimum and maximum) and assessed by Wilcoxon rank-sum test. Associations between incidence of aGVHD and measures of interest (eg, days post-allo-HCT and tacrolimus level) were determined using logistic regression models. OS was computed two ways: (i) from allo-HCT date to date of last known vital sign and (ii) from 90 days after the start of sirolimus treatment (landmark). Patients alive at their last follow-up date were administratively censored. OS was estimated using the Kaplan-Meier method. One-year OS rates (landmark) were compared by aGVHD group using the log-rank test. To determine the association between OS (allo-HCT) and incidence of developing aGVHD, aGVHD was included in a Cox proportional hazards regression model as a time-dependent covariate. Cumulative incidence of relapse was computed from allo-HCT date to date of relapse and determined using the competing risks method, where the competing risk included was death and patients who did not relapse and were still alive at their last follow-up date were censored.

3 | RESULTS

3.1 | Patient demographics

A total of 56 consecutive patients (median age 57.5 years; range 23-72) met the inclusion criteria. The patients' baseline characteristics, transplant data, and initial GVHD prophylaxis regimens are summarized in table 1. Most patients who transitioned had acute leukemia and received an allo-HCT from a matched unrelated donor (52%),

TABLE 1 Baseline characteristics of all patients

Characteristics	Total (N = 56)
Age	
Median (range), years	57.5 (23-72)
<65 y (%)	46 (82)
≥65 y (%)	10 (18)
Sex	
Male (%)	29 (52)
Female (%)	27 (48)
HCT-Comorbidity Index	
<3 (%)	26 (46)
≥3 (%)	30 (54)
Disease State	
Acute myeloid leukemia/Myelodysplastic syndrome (%)	29 (52)
Acute lymphocytic leukemia (%)	8 (14)
Myeloproliferative disease (%)	8 (14)
Lymphoma (%)	5 (9)
Chronic myeloid leukemia (%)	3 (5)
Multiple myeloma (%)	2 (4)
Chronic lymphocytic leukemia (%)	1 (2)
Type of Transplant	
Matched unrelated donor (%)	29 (52)
Haploidentical donor (%)	16 (29)
Matched related donor (%)	11 (20)
Conditioning Regimen	
Busulfan based (%)	36 (64)
Melphalan based (%)	16 (29)
Other (%)	4 (7)
GVHD Prophylaxis Regimen	
Tacrolimus/Methotrexate (%)	24 (43)
Tacrolimus/cyclophosphamide/mycophenolate mofetil (%)	17 (30)
Tacrolimus/cyclophosphamide (%)	14 (25)
Tacrolimus/mycophenolate mofetil (%)	1 (2)
Day post-HCT of transition	
Median (range), days	50.5 (6-98)

a busulfan-based conditioning regimen (64%), and a post-transplant cyclophosphamide-based GVHD prophylaxis regimen (55%).

3.2 | GVHD prophylaxis during transition

All patients received tacrolimus as part of their aGVHD prophylaxis regimen. In 11 patients, tacrolimus was stopped the same day sirolimus was started. In 21 patients, tacrolimus was stopped at least 1 day before starting sirolimus. The remaining 24 patients started sirolimus while still receiving tacrolimus; the median time of overlap was 6.5 days (range 1-90).

Out of the 18 patients who received mycophenolate mofetil (MMF) as part of the aGVHD prophylaxis regimen, 14 of 18 (77.8%) patients were still on MMF at the time of conversion from tacrolimus to sirolimus, while 4 of 18 (22.2%) patients were off MMF at time of conversion. A total of 30 (53.6%) patients were bridged with corticosteroids during transition, defined as receiving corticosteroids for at least 1 day; seven patients were in the aGVHD group and 23 were in the non-aGVHD group. The median time of corticosteroid bridging was 4 days (range 1-78).

3.3 | Complications leading to transition

The reasons for transition from tacrolimus to sirolimus-based regimen were mainly nephrotoxicity, neurotoxicity, or TA-TMA and are summarized in table 2. The most common reason for transition was nephrotoxicity. There were 23 (41%) patients that transitioned from tacrolimus to sirolimus due to nephrotoxicity alone, 18 (32%) patients were transitioned secondary to neurotoxicity, and three (5%) patients developed TA-TMA. There were three (5%) patients who transitioned due to developing both nephrotoxicity and neurotoxicity and 3 (5%) transitioned due to concomitant nephrotoxicity and TA-TMA while on tacrolimus. Lastly, 6 (11%) patients were transitioned from tacrolimus to sirolimus due to therapeutic failure of tacrolimus, such as persistent subtherapeutic levels despite dose increases and aGVHD development while on tacrolimus.

Sirolimus is often adjusted to maintain a serum trough concentration of 3-12 ng/mL. At our institution, the target trough of sirolimus is 5-10 ng/mL. The median time for sirolimus levels to reach therapeutic level ≥5 ng/mL after transition was 7 days (range 0-41). The median tacrolimus level prior to transitioning to sirolimus was 5.6 ng/mL (range 2.3-16.4) in all 56 patients. The group which did not develop aGVHD had a median tacrolimus level of 6.1 ng/mL prior to transitioning to sirolimus which was higher than the median level of 4.7 ng/mL in the group of patients that developed aGVHD.

3.4 | Resolutions of complications after transition

Resolutions of complications after transition are summarized in table 2 for the 50 patients who transitioned due to toxicities. In patients that transitioned from tacrolimus to sirolimus due to nephrotoxicity alone, 19 out of 23 (83%) patients had resolution of nephrotoxicity 30 days after transition. When nephrotoxicity was assessed 90 days after transition, resolution of nephrotoxicity was sustained for 11 (48%) patients, while 4 (17%) had died and three (13%) were lost to follow-up. Of the 18 patients who transitioned due to neurotoxicity alone, 14 (78%) experienced resolution at 30 days after transition, two (11%) died before the assessment, and one (6%) was lost to follow-up. At the 90-day assessment, 11 of 18 patients (61%) had sustained resolution of neurotoxicity and seven (39%) died

TABLE 2 Resolution of complications

		Day 30 assessment				Day 90 assessment			
Complication	Total (N = 50)	Resolution	Death	No resolution	LFU	Resolution	Death	No resolution	LFU
Nephro	23	19	0	4	0	11	4	5	3
Neuro	18	14	1	2	1	11	7	0	0
TA-TMA	3	2	0	1	0	2	0	1	0
Nephro and neuro	3	2[†]	1	0	0	1	2	0	0
Nephro and TA-TMA	3	0	0	3	0	1[‡]	2	0	0

Abbreviations: LFU, lost to follow-up; Nephro, nephrotoxicity; Neuro, neurotoxicity; TA-TMA, transplant-associated thrombotic microangiopathy.

[†]1 patient had resolution of nephrotoxicity only.

[‡]Resolution of nephrotoxicity only.

TABLE 3 Incidence of new or worsening aGVHD within 100 days post-transition

aGVHD	Total (N = 14)	Organs affected
Grade I-II (%)	10 (71)	Lower GI, Upper GI, Skin, and Liver
Grade III-IV (%)	4 (29)	Skin and Lower GI

before the assessment. From the three patients that developed TA-TMA alone, resolution occurred in two (67%) patients at both day 30 and day 90 assessments. Three patients were transitioned to sirolimus due to developing both nephrotoxicity and neurotoxicity. Of those, one (33%) patient had resolution of both complications at day 30 and 90 assessments and one (33%) had only nephrotoxicity resolution at 30 and died prior to the day 90 assessment.

3.5 | Incidence of aGVHD within 100 days post-transition

Fourteen (25%) patients developed new or worsening aGVHD within 100 days post-transition (table 3). Five of the 14 patients had GVHD at the time of transition. The majority of the aGVHD incidences were grades I-II in the lower and upper GI, liver, and skin. Grade III-IV aGVHD affecting the lower GI and skin occurred in four patients. Patients who transitioned before day 55 post-allo-HCT were more likely to develop new or worsening aGVHD (odds ratio [95% CI]: 6.00 [1.19, 30.15]; $P = .030$). We performed a subgroup analysis described in Table 4 that compares the baseline characteristics between the patients that did not develop aGVHD and the patients that developed new or worsening aGVHD within 100 days post-transition. The analysis was aimed to identify risk factors for developing aGVHD post-transition.

3.6 | Survival and relapse

Thirty-nine of the 56 (70%) patients died during the study; 71% in the aGVHD group and 69% in the non-aGVHD group. The most common primary cause of death was GVHD (acute and chronic; 15/39 [38%] patients), followed by recurrent or persistent disease (13/39 [33%] patients) and viral or bacterial infection (6/39 [15%] patients). Five (13%) patients died from other known or unknown causes. OS rates at one year and final assessment were 37% and 15%, respectively (Figure 1). Patients who developed aGVHD post-transition experienced similar risk of death compared with those who did not develop aGVHD. Figure 2 presents landmark OS by aGVHD group. The one-year OS rates for the aGVHD patients was 29% compared with 67% for the non-aGVHD patients ($P = .051$).

Fifteen of the 56 (27%) patients relapsed during the study, 14% in the aGVHD group and 31% in the non-aGVHD group. The cumulative incidence of relapse at one year was 20% and at final assessment was 30% for all patients.

4 | DISCUSSION

While there has been literature evaluating the transition from tacrolimus to sirolimus in solid organ transplant, this is the first known study evaluating the efficacy and safety of the transition in allo-HCT patients.

4.1 | Resolution

The 50 patients who transitioned from tacrolimus to sirolimus due to nephrotoxicity, neurotoxicity, and TA-TMA were included in the resolution assessment. Most patients were transitioned after developing nephrotoxicity, which was resolved in 83% (19/23) of patients by 30 days after transition. Eleven of the 19 patients sustained resolution of nephrotoxicity at the 90-day assessment. When compared to an open-label trial evaluating the conversion in renal allograft recipients, resolution in the intention to treat group was 38.2% and 33.6% at 12 months and 24 months, respectively.[13] Thirty- and 90-day assessments were not reported.

The second most common reason for transition was neurotoxicity. Seventy-eight percent of these patients experienced resolution

TABLE 4 Baseline characteristics by incidence of aGVHD post-transition

Characteristics	Non-aGVHD N = 42	aGVHD N = 14	*P*-value
Age			
Median (range), years	57.5 (25-72)	57.5 (23-64)	.92
<65 y (%)	32 (76)	14 (100)	.052
≥65 y (%)	10 (24)	0	
HCT-Comorbidity Index			
<3 (%)	22 (52)	4 (29)	.22
≥3 (%)	20 (48)	10 (71)	
Disease State			
Acute myeloid leukemia/myelodysplastic syndrome (%)	24 (57)	5 (36)	.16
Acute lymphocytic leukemia (%)	6 (14)	2 (14)	
Myeloproliferative disease (%)	5 (12)	3 (21)	
Lymphoma (%)	3 (7)	2 (14)	
Chronic myeloid leukemia (%)	3 (7)	0	
Multiple myeloma (%)	0	2 (14)	
Chronic lymphocytic leukemia (%)	1 (2)	0	
Type of Transplant			
Matched unrelated donor (%)	24 (57)	5 (36)	.053
Haploidentical donor (%)	13 (31)	3 (21)	
Matched related donor (%)	5 (12)	6 (43)	
Conditioning Regimen			
Busulfan based (%)	28 (67)	8 (57)	.28
Melphalan based (%)	10 (24)	6 (43)	
Other (%)	4 (10)	0	
GVHD Prophylaxis Regimen			
Tacrolimus/methotrexate (%)	19 (45)	5 (36)	.39
Tacrolimus/cyclophosphamide/mycophenolate mofetil (%)	14 (33)	3 (21)	
Tacrolimus/cyclophosphamide (%)	8 (19)	6 (43)	
Tacrolimus/mycophenolate mofetil (%)	1 (2)	0	
Day Post-HCT of Transition			
Median (range), days	55.0 (13-98)	36.0 (6-79)	.033
Tacrolimus Level Prior to Transition			
Median (range), ng/ml	6.1 (2.3-16.4)	4.7 (2.4-11.0)	.17
aGVHD vs. non-aGVHD Odds Ratio (95% CI)	0.84 (0.67, 1.04)		.11

at the 30 day assessment. Thirty-nine percent of patients with neurotoxicity died prior to day 90 assessment. Overall, the conversion from tacrolimus to sirolimus demonstrated promising resolution of nephrotoxicity and neurotoxicity at the 30 and 90 days of follow-up. Only three patients transitioned from tacrolimus to sirolimus due to TA-TMA alone. All three patients received treatment with eculizumab, a humanized monoclonal antibody, which has demonstrated clinical efficacy for TA-TMA.[15] Two patients had resolution at 30- and 90-day assessment. With this small subset, it is difficult to evaluate the efficacy of transition from tacrolimus to sirolimus for TA-TMA resolution; however, we have reported our experience with TA-TMA previously.[15]

4.2 | GVHD rate

In our study, 25% (14/56) of patients developed new or worsening aGVHD post-transition, thus this transition may be a reasonable option for patients that develop complications from CNIs. The rate of aGVHD post-transition from tacrolimus to sirolimus has not been well reported in previous studies. Therefore, a direct comparison of these rates cannot be made. Currently in the literature, the reported cumulative incidence of Grade II-IV aGVHD is 26%-56%, and the reported cumulative incidence of Grade III-IV aGVHD is 7%-21%.[16] Out of 14 patients that developed new or worsening aGVHD post-transition, three (21%) developed aGVHD at time of transition. Some

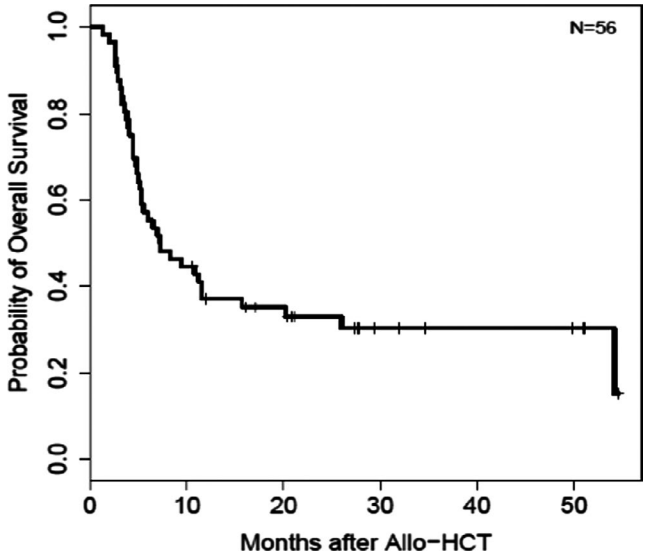

FIGURE 1 Kaplan-Meier estimates of overall survival

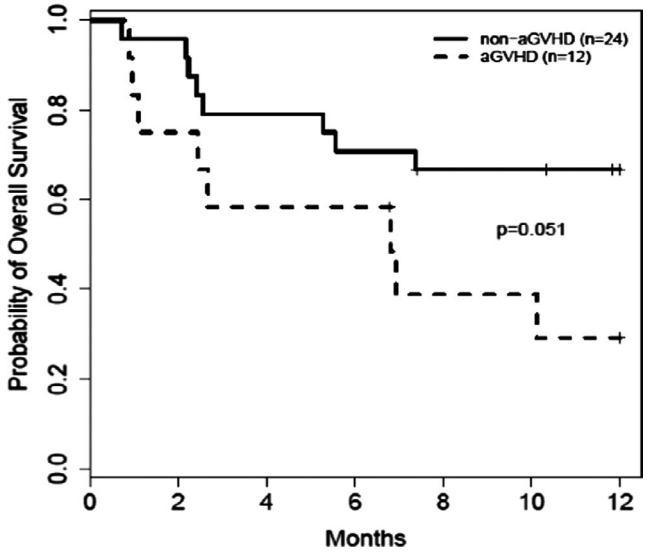

FIGURE 2 Kaplan-Meier estimates of overall survival by aGVHD group (landmark)

studies have indicated that the incidence of early-onset Grade III-IV aGVHD was associated with a higher risk of developing late aGVHD. This may have explained the persistent aGVHD witnessed in these three patients.[17]

4.3 | Risk factors

Patients in this study who transitioned earlier from tacrolimus to sirolimus were significantly more likely to develop new or worsening aGVHD. It is important to note that a safe date of transition is indeterminant. Patients in both the aGVHD and non-aGVHD groups were transitioned during a wide range of days after receiving allo-HCT. Patients who transitioned before day 55 post-allo-HCT experienced increased odds of developing aGVHD (odds ratio [95% CI]: 6.00 [1.19, 30.15]; $P = .030$). Therefore, it may be reasonable to delay transition after day 55 post-allo-HCT if the risk of transition delay does not outweigh the benefit of an earlier transition. The level of tacrolimus prior to transition was not statistically different between groups. Additionally, the median time needed for sirolimus to reach therapeutic level of ≥5 ng/mL was 7 days in both the non-aGVHD and aGVHD groups. Therefore, it is unlikely the level of sirolimus affected the rate of aGVHD in our patient population.

4.4 | Survival and relapse

The one-year OS rate was 37% for all patients in our study, lower than what was documented in the literature. Most patients, whose primary cause of death was aGVHD, experienced aGVHD prior to transition. Studies have shown that developing aGVHD decreases OS.[16] This could be considered an additional risk factor that increases the mortality rate and decreases OS in patients that have transitioned from tacrolimus to sirolimus. The literature noted the in-hospital mortality rate during the transplant admission was increased in patients developing nephrotoxicity, 37% in non-dialysis-requiring renal failure and 84% in patients requiring dialysis.[18-20] Another trial evaluated the long-term outcomes from CNI-induced neurotoxicity in allo-HCT patients, and the mortality rate was as high as 80% at a median of 33 days (2-594) after neurotoxicity development.

Our results demonstrate worse survival outcomes compared to the one-year survival rate of 78% reported in the general population of matched related and matched unrelated allo-HCT.[21] Since our patients developed serious complications during HCT that led to a change in immunosuppression, one could assume that these comorbidities negatively impacted overall survival. A literature review reported the estimated survival rate after developing grade three and four aGVHD was 0%-43%.[22] Therefore, our reported survival rate in patients that developed new or worsening aGVHD, 29%, fits within the range of what is documented in the literature. When patients who developed aGVHD post-transition were compared to patients who did not, our study showed a trend toward survival benefit in the landmark analysis. Although the conversion from tacrolimus to sirolimus demonstrated promising resolution of acute CNI-induced toxicities, the overall mortality rate still remains high. Caution should be considered when transitioning patients who have experienced aGVHD prior to transition or when transitioning patients before day 55 after allo-HCT.

The cumulative incidence of relapse for all patients in our study was 30%, which is consistent with what has been reported in the literature, 20%-60% of patients.[23] Sirolimus inhibits tumor growth by halting tumor cell proliferation, inducing tumor cell apoptosis, and suppressing tumor angiogenesis and through the same mechanism can also block cancer cell proliferation.[24] Some studies demonstrated that the use of sirolimus for GVHD prophylaxis in patients with lymphoma may lead to decreased incidence of disease progression and improved survival after allo-HCT.[25]

4.5 | Limitations

There are several limitations to our study. This was a retrospective study with inherent biases and no control arm. It is also possible that eligible patients were missed due to the retrospective nature of the study. Due to the infrequency of this transition, conducting a prospective study would have been challenging. The rate of aGVHD post-transition could have been affected by concomitant steroid use. Corticosteroids were used intermittently as part of aGVHD treatment or to aid in aGVHD prophylaxis during transition from CNI to sirolimus. Corticosteroids use during transition could have skewed the efficacy of the transition, and therefore the rate of GVHD. Other data on how aGVHD was treated and managed in the 14 patients who developed new or worsening GVHD were not collected. Different GVHD treatment strategies could have been confounding factors affecting the cumulative incidence of rate and OS among the patients. Even though this is the only study to date evaluating the safety and efficacy of this transition strategy in allo-HCT patients, the sample size was not large enough to detect more risk factors for developing aGVHD post-transition, besides time of transition. Assessments for neurotoxicity were not objective and were based on provider clinical assessment which could vary from provider to provider. Some patients who transitioned due to nephrotoxicity were receiving other nephrotoxic drugs. Nephrotoxicity resolution could have been overestimated in patients receiving nephrotoxins such as radiocontrast or antimicrobials and in patients infected with BK virus.

5 | CONCLUSION

Conversion from tacrolimus to sirolimus demonstrated promising resolution of acute toxicities, such as nephrotoxicity and neurotoxicity. This approach seems to be feasible with a low risk of developing aGVHD. However, providers need to be cautious with transitioning patients' earlier post-HCT since these patients may be at a higher risk of developing new or worsening aGVHD with subsequent increased risk of mortality. Caution should also be exercised in patients who have an aGVHD diagnosis prior to the transition. Additional data from larger studies and prospective data collection are needed to confirm these results.

ACKNOWLEDGEMENTS

The authors declare that the study has not received any funding

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from author.

ORCID

Jason Yeh https://orcid.org/0000-0002-7422-8951

REFERENCES

1. Goker H, Haznedaroglu IC, Chao NJ. Acute graft-vs-host disease: pathobiology and management. *Exp Hematol*. 2001;29(3):259-277.
2. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute graft versus host disease: a comprehensive review. *Anticancer Res*. 2017;37(4):1547-1555.
3. Pasquini MC, Wang Z, Horowitz MM, Gale RP. Report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders. *Clin Transpl*. 2010;2010:87-105.
4. Ram R, Storb R. Pharmacologic prophylaxis regimens for acute graft-versus-host disease: past, present and future. *Leuk Lymphoma*. 2013;54(8):1591-1601.
5. Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without…. *J Immunol*. 2013;191(12):5785-5791.
6. Rosenthal J. Hematopoietic cell transplantation-associated thrombotic microangiopathy: a review of pathophysiology, diagnosis, and treatment. *J Blood Med*. 2016;7:181.
7. El-Agroudy AE, Alarrayed SM, Al-Ghareeb SM, Farid E, Alhelow H, Abdulla S. Efficacy and safety of early tacrolimus conversion to sirolimus after kidney transplantation: long-term results of a prospective randomized study. *Indian J Nephrol*. 2017;27(1):28.
8. Augustine JJ, Bodziak KA, Hricik DE. Use of sirolimus in solid organ transplantation. *Drugs*. 2007;67(3):369-391.
9. Abboud R, Choi J, Ruminski P, et al. Insights into the role of the JAK/STAT signaling pathway in graft-versus-host disease. *Ther Adv Hematol*. 2020;11:2040620720914489.
10. Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 children's oncology group/pediatric blood and marrow transplant consortium trial. *Blood*. 2014;123(13):2017-2025.
11. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014;124(8):1372-1377.
12. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation*. 2009;87(2):233-242.
13. Tedesco-Silva H, Peddi VR, Sánchez-Fructuoso A, et al. Open-label, randomized study of transition from tacrolimus to sirolimus immunosuppression in renal allograft recipients. *Transplant Direct*. 2016;2(4):e69.
14. Morard I, Dumortier J, Spahr L, et al. Conversion to sirolimus-based immunosuppression in maintenance liver transplantation patients. *Liver Transpl*. 2007;13(5):658-664.
15. Jan AS, Hosing C, Aung F, Yeh J. Approaching treatment of transplant-associated thrombotic Microangiopathy from two directions with Eculizumab and transitioning from Tacrolimus to Sirolimus. *Transfusion*. 2019;59(11):3519-3524.
16. Lazaryan A, Weisdorf DJ, DeFor T, et al. Risk factors for acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation with umbilical cord blood and matched sibling donors. *Biol Blood Marrow Transplant*. 2016;22(1):134-140.
17. Omer AK, Weisdorf DJ, Lazaryan A, et al. Late acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(5):879-883.
18. Zager RA. Acute renal failure syndromes after bone marrow transplantation. *Adv Nephrol Necker Hosp*. 1997;27:263-280.
19. Zager RA, O'Quigley J, Zager BK, et al. Acute renal failure following bone marrow transplantation: a retrospective study of 272 patients. *Am J Kidney Dis*. 1989;13(3):210-216.
20. Zager RA. Acute renal failure in the setting of bone marrow transplatation. *Kidney Int*. 1994;46(5):1443-1458.
21. Bohannon LM, Page KM, Ren Y, et al. Decreased mortality after the first year of allogeneic hematopoietic stem cell transplant in

recipients of umbilical cord blood vs. matched related or matched unrelated donors. *Blood*. 2019;134(Supplement_1):4613.
22. Jamani K, Russell JA, Daly A, et al. Prognosis of grade 3–4 acute GVHD continues to be dismal. *Bone Marrow Transplant*. 2013;48(10):1359-1361.
23. Duncan CN, Majhail NS, Brazauskas R, et al. Long-term survival and late effects among one-year survivors of second allogeneic hematopoietic cell transplantation for relapsed acute leukemia and myelodysplastic syndromes. *Biol Blood Marrow Transplant*. 2015;21(1):151-158.
24. Egidi MF, Cowan PA, Naseer A, Gaber AO. Conversion to sirolimus in solid organ transplantation: a single-center experience. *Transplant Proc*. 2003;35(3):S131-S137. Elsevier.
25. Law BK. Rapamycin: an anti-cancer immunosuppressant? *Crit Rev Oncol Hematol*. 2005;56(1):47-60.

How to cite this article: Arrabi L, Jan A, Hosing C, Milton DR, Yeh J. Transitioning tacrolimus to sirolimus in allogeneic hematopoietic cell transplantation. *Eur J Haematol*. 2021;00:1–8. https://doi.org/10.1111/ejh.13701