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# Tacrolimus versus Cyclosporine after Hematopoietic Cell Transplantation for Acquired Aplastic Anemia

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## A B S T R A C T

Combinations of cyclosporine (CSP) with methotrexate (MTX) have been widely used for immunosuppression after allogeneic transplantation for acquired aplastic anemia. We compared outcomes with tacrolimus (TAC)+MTX versus CSP+MTX after transplantation from HLA-identical siblings (SIB) or unrelated donors (URD) in a retrospective cohort of 949 patients with severe aplastic anemia. Study endpoints included hematopoietic recovery, graft failure, acute graft-versus-host disease (GVHD), chronic GVHD, and mortality. TAC+MTX was used more frequently in older patients and, in recent years, in both SIB and URD groups. In multivariate analysis, TAC+MTX was associated with a lower risk of mortality in URD recipients and with slightly earlier absolute neutrophil count recovery in SIB recipients. Other outcomes did not differ statistically

Cyclosporine
Tacrolimus

between the 2 regimens. No firm conclusions were reached regarding the relative merits of TAC+MTX versus CSP+MTX after hematopoietic cell transplantation for acquired aplastic anemia. Prospective studies would be needed to determine whether the use of TAC+MTX is associated with lower risk of mortality in URD recipients with acquired aplastic anemia.

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## INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for patients with severe aplastic anemia (SAA), but graft failure and graft-versus-host disease (GVHD) have impeded its success [1-8]. Combinations of cyclosporine (CSP) or tacrolimus (TAC) with methotrexate (MTX) have been widely used for immunosuppression after allogeneic HCT [2,9-13]. CSP has been used preferentially after HCT for SAA [14] whereas TAC has been used preferentially after HCT for hematological malignancies, since 3 prospective randomized studies of bone marrow transplantation (BMT) showed lower risks of acute and chronic GVHD with TAC more than a decade ago [9-11].

Outcomes with TAC+MTX versus CSP+MTX after unrelated BMT for patients with SAA have been compared in only 1 Japanese study [15]. In a matched-pair retrospective study of 94 patients, the risk of mortality was lower with the use of TAC+MTX [15], but rates of acute and chronic GVHD did not differ statistically between the 2 prophylaxis regimens. These results have not been validated in larger cohorts with related or unrelated donors or evaluated in patients who received growth factor−mobilized peripheral blood cell transplantation (PBSCT). The purpose of the current study was to compare outcomes with TAC+MTX versus CSP+MTX after HCT for SAA using data collected by the Center for International Bone Marrow Transplant Research (CIBMTR). As observed in several studies mostly including patients with hematological malignancies [9-12,16], we anticipated that TAC+MTX would be associated with lower risks of acute and chronic GVHD after HCT for SAA.

## METHODS
### Patients

This retrospective study cohort included patients reported to the CIBMTR who had their first allogeneic BMT or PBSCT from HLA-identical siblings (SIB) or from unrelated donors (URD) for treatment of acquired SAA from January 2001 to December 2011. Patients who had GVHD prophylaxis other than CSP+MTX or TAC+MTX, those who received ex vivo T cell−depleted grafts, and those with congenital disorders were excluded, leaving 949 eligible patients in the cohort. CIBMTR observational studies using deidentified data comply with Health Insurance Portability and Accountability Act regulations and are conducted with a waiver of informed consent per the institutional review board of the Medical College of Wisconsin.

### Study Endpoints and Definitions

Study endpoints included hematopoietic recovery, secondary graft failure, grades II to IV acute GVHD, grades III and IV acute GVHD, limited or extensive chronic GVHD, and mortality. *Time to neutrophil* and *platelet recovery* were defined as the time from transplantation to the first of 3 consecutive days with an absolute neutrophil count (ANC) $\geq$ 500/mm$^3$ and platelet count $\geq$ 20 × 10$^9$/L unsupported by transfusion for 7 days, respectively. *Secondary graft failure* was defined as subsequent loss of ANC to < 500/mm$^3$ and < 5% donor chimerism after neutrophil recovery. Acute GVHD was graded according to consensus criteria [17]. Chronic GVHD was diagnosed by historical criteria [18]. HLA matching was defined as described previously [19].

### Statistical Analysis

Multivariate Cox regression models were constructed to evaluate hazard ratios (HR) for endpoints with TAC+MTX compared with CSP+MTX. Factors violating the proportional hazards assumption were adjusted through stratification. A stepwise procedure was used in developing models for each outcome, using a P value threshold of .05. All models were adjusted for graft type (BMT versus PBSCT) and year of transplantation. Center effect was also adjusted as a random effect to account for differences in practice at individual centers, including the choice and targeted blood concentrations of calcineurin inhibitors [20]. Analyses were performed separately in SIB and URD recipients. Interactions between the main variable (GVHD prophylaxis) and the adjusted covariates were tested at the significance level of .01. Proportions of causes of death were compared using Fisher's exact test.

## RESULTS
### Transplantation from an HLA-identical Donor

Patient characteristics are summarized in Table 1. SIB recipients who received TAC+MTX were older and more frequently of Caucasian race, had older donors, had more frequent treatment for SAA with antithymocyte globulin (ATG) before HCT, had HCT in more recent years with more frequent use of cyclophosphamide-based conditioning, ATG or alemtuzumab, and hematopoietic growth factors after HCT. In multivariate analysis (Figure 1A), TAC+MTX was associated only with earlier ANC recovery (HR, 1.47; 95% confidence interval, 1.04 to 2.08; P = .03). Other outcomes did not differ statistically between the 2 regimens. No statistically significant interactions were observed between the main variable and the adjusted covariates. The proportion of graft failure as a cause of death was higher with TAC+MTX than with CSP+MTX (overall P = .007; Table 2).

### Transplantation from an URD

URD recipients who received TAC+MTX were older and less frequently of Caucasian race, had younger donors, had HCT in more recent years with more frequent use of cyclophosphamide-based conditioning including total body irradiation with less frequent use of ATG or alemtuzumab, and more frequent use of PBSCT and hematopoietic growth factors after HCT (Table 1). In multivariate analysis (Figure 1B), TAC+MTX was associated with a lower risk of mortality (HR, .42; 95% confidence interval, .23 to .80; P = .008). Other outcomes did not differ statistically between the 2 regimens. No statistically significant interactions were observed between the main variable and the adjusted covariates. Causes of death were similar between the 2 GVHD prophylaxis regimens (overall P = .91) (Table 2). Because several studies showed inferior survival after PBSCT compared with after BMT for SAA [21-24], stratified analysis was also performed by graft type (Figure 2). Results for BMT were similar to results of the nonstratified analysis. Results for PBSCT showed no statistically significant differences for any outcome, but analytic power was limited in this subgroup.

## DISCUSSION

In the absence of a prospective, randomized comparison, this large international cohort study provides valuable information. Based on adjusted multivariate analyses, the use of TAC+MTX was unexpectedly associated with a lower risk of mortality among URD recipients and with slightly

**Table 1**
Patient Characteristics

| Characteristic | HLA-identical Sibling (SIB) | | | Unrelated Donor (URD) | | |
|---|---|---|---|---|---|---|
| | CSP+MTX (n = 569) | TAC+MTX (n = 62) | P* | CSP+MTX (n = 198) | TAC+MTX (n = 120) | P* |
| Patient age at transplantation, median (range), yr | 19 (<1-66) | 25 (2-70) | <.001 | 18 (<1-61) | 24 (2-68) | <.001 |
| Male patient | 343 (60) | 31 (50) | .12 | 107 (54) | 67 (56) | .76 |
| Patient race | | | .003 | | | .03 |
| Caucasian | 279 (49) | 42 (68) | | 136 (69) | 62 (52) | |
| African-American | 27 (5) | 4 (6) | | 4 (2) | 7 (6) | |
| Asian/Pacific Islander | 131 (23) | 2 (3) | | 36 (18) | 27 (23) | |
| Hispanic | 88 (15) | 11 (18) | | 11 (6) | 14 (12) | |
| Other | 38 (7) | 2 (3) | | 7 (4) | 5 (4) | |
| Missing | 6 (1) | 1 (2) | | 4 (2) | 5 (4) | |
| Donor age, median (range), yr | 19 (<1-72) | 23 (1-72) | .03 | 32 (19-61) | 29 (18-52) | .02 |
| Donor-recipient sex match | | | .07 | | | .82 |
| Male-male | 184 (32) | 18 (29) | | 68 (34) | 47 (39) | |
| Male-female | 129 (23) | 12 (19) | | 66 (33) | 37 (31) | |
| Female-male | 159 (28) | 13 (21) | | 35 (18) | 19 (16) | |
| Female-female | 97 (17) | 19 (31) | | 23 (12) | 16 (13) | |
| Missing | 0 | 0 | | 6 (3) | 1 (<1) | |
| HLA matching | | | NA | | | .97 |
| HLA-identical sibling | 569 (100) | 62 (100) | | 0 | 0 | |
| Unrelated well-matched | 0 | 0 | | 133 (67) | 81 (68) | |
| Unrelated partially-matched | 0 | 0 | | 45 (23) | 27 (23) | |
| Unrelated mismatched | 0 | 0 | | 15 (8) | 8 (7) | |
| Unrelated missing | 0 | 0 | | 5 (3) | 4 (3) | |
| Graft type | | | .10 | | | .008 |
| BM | 455 (80) | 44 (71) | | 173 (87) | 91 (76) | |
| Mobilized PBSC | 114 (20) | 18 (29) | | 25 (13) | 29 (24) | |
| Pretransplantation therapy | | | .03 | | | .66 |
| None | 317 (56) | 34 (55) | | 9 (5) | 9 (8) | |
| Any ATG | 91 (16) | 18 (29) | | 177 (89) | 107 (89) | |
| Any cyclosporine | 71 (12) | 3 (5) | | 7 (4) | 1 (1) | |
| Any others | 87 (15) | 6 (10) | | 4 (2) | 3 (3) | |
| Missing | 7 (1) | 2 (3) | | 2 (1) | 1 (<1) | |
| Time from SAA diagnosis to transplantation, median (range), mo | 3 (<1-347) | 3 (<1-500) | .98 | 13 (2-316) | 12 (2-298) | .90 |
| Year of transplantation | | | <.001 | | | .02 |
| 2001-2004 | 316 (56) | 15 (24) | | 75 (38) | 30 (25) | |
| 2005-2007 | 179 (31) | 20 (32) | | 74 (37) | 44 (37) | |
| 2008-2011 | 74 (13) | 27 (44) | | 49 (25) | 46 (38) | |
| Conditioning regimen | | | .03 | | | .01 |
| Fludarabine-included | 127 (22) | 11 (18) | | 89 (45) | 37 (31) | |
| Busulfan-included | 67 (12) | 1 (2) | | 4 (2) | 1 (1) | |
| CY ± ATG ± TBI | 309 (54) | 44 (71) | | 95 (48) | 66 (55) | |
| Others | 66 (12) | 6 (10) | | 10 (5) | 16 (13) | |
| Use of ATG/alemtuzumab in conditioning regimen or GVHD prophylaxis | | | .002† | | | <.001† |
| ATG rabbit | 106 (19) | 27 (44) | | 24 (12) | 14 (12) | |
| ATG horse | 135 (24) | 18 (29) | | 69 (35) | 31 (26) | |
| ATG unknown | 128 (23) | 7 (11) | | 82 (41) | 26 (22) | |
| Alemtuzumab | 6 (1) | 1 (2) | | 5 (3) | 10 (8) | |
| None | 194 (34) | 9 (15) | | 18 (9) | 39 (33) | |
| TBI dose in conditioning regimen | | | NA | | | <.001 |
| None | 560 (98) | 58 (94) | | 68 (34) | 15 (13) | |
| ≤800 cGy | 7 (1) | 4 (6) | | 121 (61) | 95 (79) | |
| >800 cGy | 2 (<1) | 0 | | 8 (4) | 10 (8) | |
| Dose unknown | 0 | 0 | | 1 (1) | 0 | |
| Use of growth factors after transplantation‡ | 224 (39) | 35 (56) | .009 | 58 (29) | 52 (43) | .01 |
| Median follow-up of survivors, (range), mo | 62 (3-145) | 54 (12-142) | .41 | 61 (3-144) | 61 (12-126) | .16 |

NA indicates not applicable; BM, bone marrow; TBI, total body irradiation.

Data presented are n (%), unless otherwise indicated.

\* Statistical tests used are chi-square test for independence for categorical variables and the Wilcoxon rank-sum test for continuous variables. Missing values in categorical variables were excluded from statistical tests.

† P value reflects testing ATG or alemtuzumab versus none.

‡ G-CSF or GM-CSF given in time frame of 1 day before transplantation to 7 days after transplantation.

earlier ANC recovery among SIB recipients. Contrary to our expectations, the results did not show a lower risk of acute or chronic GVHD with the use of TAC+MTX, and we found no statistically significant differences in the risk of other outcomes with the 2 prophylaxis regimens.

Although the number of SIB recipients treated with TAC+MTX was limited, the results showed no better outcomes with the use of TAC+MTX. Although the proportion of

deaths caused by graft failure was higher with TAC+MTX than with CSP+MTX, the overall risk of death did not show any statistically significant differences. HR indicated trends suggesting higher risks of acute and chronic GVHD with the use of TAC+MTX in SIB recipients. These results contrast with results from previous studies of patients, mostly with hematological malignancies, showing that the use of TAC was associated with lower risks of acute GVHD [9,11,16], chronic
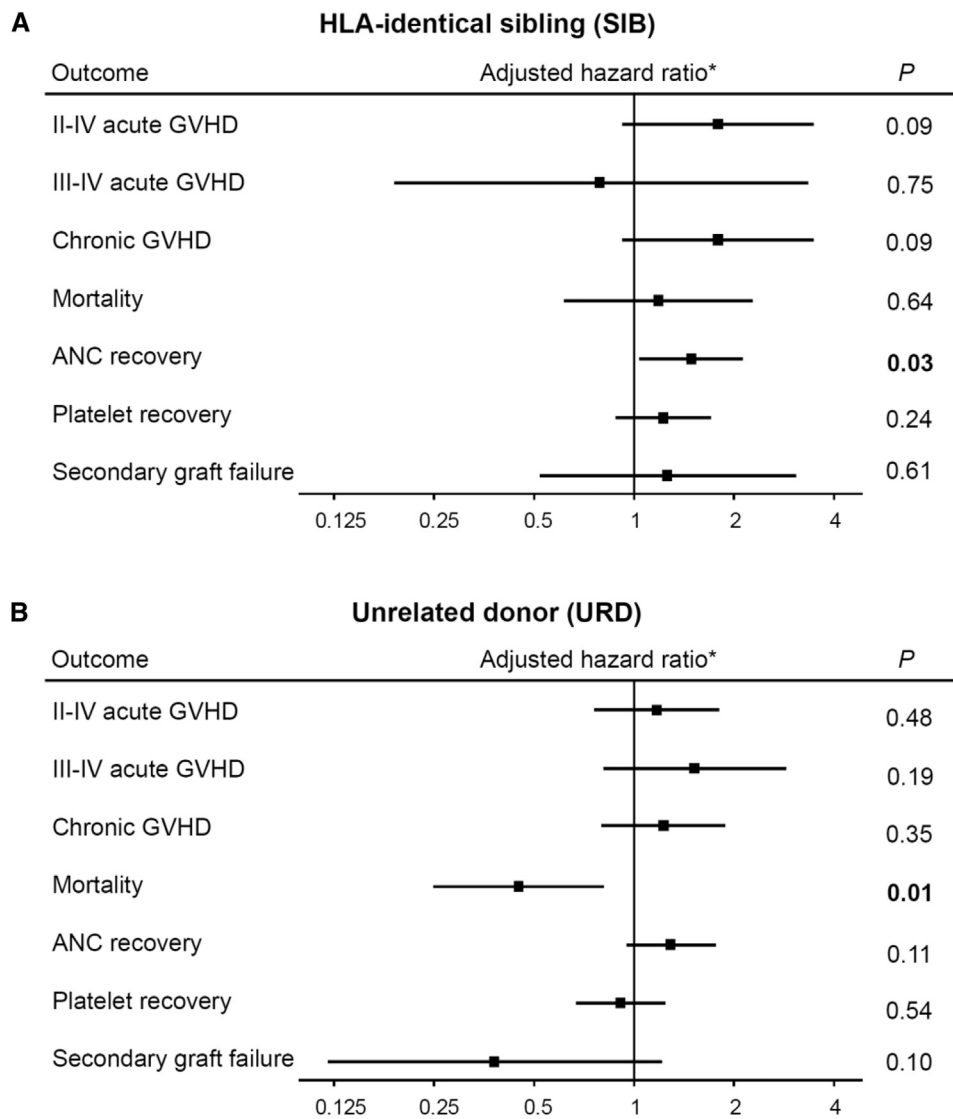
**A**

## HLA-identical sibling (SIB)



**B**

## Unrelated donor (URD)



**Figure 1.** Comparison of outcomes with TAC+MTX versus CSP+MTX. Hazard ratios with 95% confidence intervals are shown for TAC+MTX compared with CSP+MTX. (A) Transplantation from an HLA-identical sibling (SIB). (B) Transplantation from an unrelated donor (URD). *All models were adjusted for graft type, year of transplantation, and center effect. For grades II to IV GVHD in URD, results were adjusted for ABO matching, cytomegalovirus serology, HLA matching, pre-transplantation therapy, and donor-recipient gender combination. For grades III to IV GVHD in SIB, results were adjusted for ABO matching. For grades III to IV GVHD in URD, results were adjusted for donor age. For chronic GVHD in SIB, results were adjusted for patient age. For chronic GVHD in URD, results were adjusted for patient age, HLA matching, time from SAA diagnosis to transplantation, pretransplantation therapy, and total body irradiation dose in conditioning regimen. For mortality in SIB, results were adjusted for patient age, type of ATG or alemtuzumab in the conditioning regimen, or GVHD prophylaxis and cytomegalovirus serology. For mortality in URD, results were adjusted for patient age, performance score at transplantation, and HLA matching. For ANC recovery in SIB, results were adjusted for patient age and use of growth factors after transplantation. For ANC recovery in URD, results were adjusted for donor-recipient gender combination and use of growth factors after transplantation. For platelet recovery in SIB, results were adjusted for ABO matching, patient age, type of ATG or alemtuzumab in the conditioning regimen or GVHD prophylaxis, cytomegalovirus serology, time from SAA diagnosis to transplantation, and performance score at transplantation. For platelet recovery in URD, results were adjusted for performance score at transplantation.

**Table 2**
Causes of Death

| Cause of death, no. (%) | HLA-identical Sibling (SIB) | | Unrelated Donor (URD) | |
|---|---|---|---|---|
| | CSP+MTX | TAC+MTX | CSP+MTX | TAC+MTX |
| Total no. | 85 (100) | 15 (100) | 38 (100) | 17 (100) |
| Infection | 25 (29) | 2 (13) | 6 (16) | 2 (12) |
| Organ failure | 20 (24) | 2 (13) | 8 (21) | 4 (24) |
| GVHD | 16 (19) | 0 (0) | 10 (27) | 4 (24) |
| Graft failure | 8 (9) | 7 (47) | 4 (11) | 2 (12) |
| Idiopathic pneumonia | 5 (6) | 1 (7) | 5 (13) | 1 (6) |
| Secondary malignancy | 2 (2) | 1 (7) | 1 (3) | 0 (0) |
| Others | 9 (11) | 2 (13) | 4 (11) | 4 (24) |

Data presented are n (%), unless otherwise indicated.

GVHD [9,11,12], and mortality among SIB recipients in some studies [16] but not others (Table 3) [9,11,12]. The relative merits of TAC might differ according to the underlying disease because incidence rates of acute and chronic GVHD are much lower after HCT among patients with SAA compared with those with hematological malignancies.

Notably, the better survival with TAC+MTX for URD recipients was consistent with results from the previous matched-pair study [15], but these results should be interpreted with caution because the lower mortality was not explained by a lower risk of GVHD or by different causes of death with the use of TAC+MTX in either our study or the previous matched-pair study. Differences in the distribution
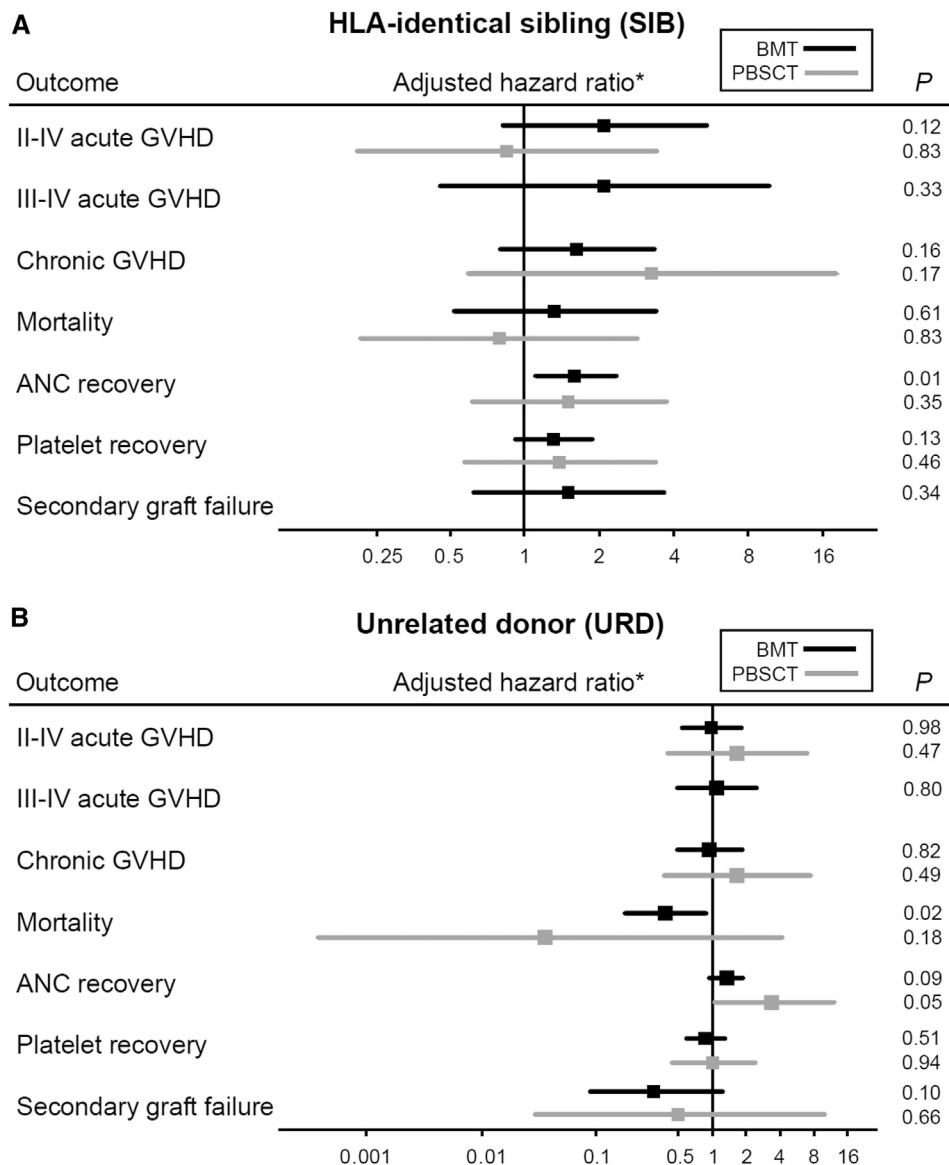
**Figure 2.** Comparison of outcomes with TAC+MTX versus CSP+MTX, stratified by donor and graft type. Hazard ratios with 95% confidence intervals are shown for TAC+MTX compared with CSP+MTX. (A) Transplantation from an HLA-identical sibling. (B) Transplantation from an unrelated donor. Some results for PBSCT were not available because of small numbers of events (grades III to IV acute GVHD and secondary graft failure in SIB; and grades III to IV acute GVHD in URD). *All models were adjusted for year of transplantation and center effect. For grades II to IV GVHD in URD, results were adjusted for ABO matching, cytomegalovirus serology, HLA matching, pretransplantation therapy, and donor-recipient gender combination. For grades III to IV GVHD in SIB, results were adjusted for ABO matching. For grades III to IV GVHD in URD, results were adjusted for donor age. For chronic GVHD in SIB, results were adjusted for patient age. For chronic GVHD in URD, results were adjusted for patient age, HLA matching, time from SAA diagnosis to transplantation, pretransplantation therapy, and total body irradiation dose in conditioning regimen. For mortality in SIB, results were adjusted for patient age, type of ATG or alemtuzumab in the conditioning regimen or GVHD prophylaxis, and cytomegalovirus serology. For mortality in URD, results were adjusted for patient age, performance score at transplantation and HLA matching. For ANC recovery in SIB, results were adjusted for patient age and use of growth factors after transplantation. For ANC recovery in URD, results were adjusted for donor-recipient gender combination and use of growth factors after transplantation. For platelet recovery in SIB, results were adjusted for ABO matching, patient age, type of ATG or alemtuzumab in the conditioning regimen or GVHD prophylaxis, cytomegalovirus serology, time from SAA diagnosis to transplantation, and performance score at transplantation. For platelet recovery in URD, results were adjusted for performance score at transplantation.

of unrecognized risk factors could account for the lower mortality associated with the use of TAC+MTX. A lower risk of mortality associated with TAC was reported in only 1 retrospective study of patients, mostly with hematological malignancies [12], whereas other studies showed no statistical differences in mortality between TAC and CSP among URD recipients (Table 3) [10,11,13,16].

This study has several limitations. First, although the center effect was adjusted in all models and was not statistically associated with any outcomes, CIBMTR did not collect data for blood concentrations of calcineurin inhibitors, the doses and schedules of MTX administration, or the doses and schedules of ATG or alemtuzumab at individual centers. Practice variations could have affected the results of this study. For example, omission of the day 11 methotrexate dose can increase the risk of acute GVHD [25]. Second, the choice between TAC and CSP might have been dictated by center-specific prognostic factors not captured by CIBMTR, which could have introduced some bias. Thus, the data do not support any firm conclusions regarding the relative

**Table 3**
Results of Tacrolimus Compared with Cyclosporine in Previous Studies

| Year | 1998 | 2000 | 2001 | | 2004 | | 2009 | 2011 | 2012 | | 2015 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Ratanatharathorn [9] | Nash [10] | Hiraoka [11] | | Yanada [12] | | Yagasaki [15] | Inamoto [13] | Jagasia [16] | | Current study | |
| Design | RCT | RCT | RCT | | Retro | | Retro | Retro | Retro | | Retro | |
| No. of patients | 329 | 180 | 136 | | 2712 | | 94 | 456 | 5561 | | 949 | |
| Disease | Any | Any | Any | | Any | | SAA | Malignancy | Malignancy | | SAA | |
| Donor | SIB | URD | SIB | URD | SIB | URD | URD | Both | SIB | URD | SIB | URD |
| Graft type | | | | | | | | | | | | |
| BM | 329 | 180 | 74 | 62 | 1507 | 777 | 94 | 0 | 806 | 1081 | 499 | 264 |
| PBSC | 0 | 0 | 0 | 0 | 428 | 0 | 0 | 456 | 2385 | 1289 | 132 | 54 |
| II-IV GVHD | ↓ | ↓ | ↓ | ↓ | ns | ↓ | ns | ns | ↓ | ↓ | ns | ns |
| III-IV GVHD | ns | ↓ | | | | | | ns | ↓ | ns | ns | ns |
| Chronic GVHD | ↓ | ns | ↓ | ↓ | ↓ | ns | ns | ns | | | ns | ns |
| Overall mortality | ↑ | ns | ns | ns | ns | ↓ | ↓ | ns | ↓ | ns | ns | ↓ |
| ANC recovery | ns | ns | ns | ns | | | ns | | | | ↑ | ns |
| Recurrent malignancy | ns | ns | ↑ | ns | ns | ns | | ns | | | | |

RCT indicates randomized controlled trial; Retro, retrospective analysis; ns, no statistical difference.

merits of TAC+MTX versus CSP+MTX after HCT for acquired SAA. Prospective studies would be needed to determine whether the use of TAC+MTX is associated with a lower risk of mortality in URD recipients with acquired aplastic anemia.

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