**Title: Comparison of HLA-matched sibling and unrelated donor transplantation in adult patients with acquired severe aplastic anemia**

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**Running title:** Comparable outcomes of MSD-SCT and URD-SCT for SAA

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**ABSTRACT**

The recent improvements in the outcomes of severe aplastic anemia (SAA) patients who received allogeneic stem cell transplantation (SCT) from unrelated donors (URD) suggest the possibility of its alternative first-line treatment. To address this issue, results of adult SAA patients receiving allogeneic SCT were compared between the following three donor-type groups: 8/8–matched sibling (MSD; n=153), 8/8 well-matched unrelated (WM-URD; n=72), and 6–7/8 partially-matched unrelated (PM-URD; n=33). Proportion of patients experiencing immunosuppressive treatment failure~~s~~ was significantly higher in the URD groups than in the MSD group (*P* < 0.01). The incidences of graft failure and transplant-related mortality, and graft-versus-host disease-free, failure-free survival rates of the three groups (MSD, WM-URD, and PM-URD) were 14.6%, 0%, and 0% (*P* < 0.01); 6.1%, 10.3%, and 21.7% (*P* = 0.03); and 76.7%, 55.5% and 51.5% (*P* < 0.01), respectively. The overall survival (OS) rate of the MSD group (93.9%) was higher than that of the PM-URD (78.3%; *P* < 0.01) group, but not to that of the WM-URD (86.2%; *P* = 0.18) group. Our study showed comparable OS between the MSD group and WM-URD group, which suggest that the URD-SCT can be used as a first-line treatment for adult SAA patients with WM-URD.

**Keywords;** allogeneic stem cell transplantation; severe aplastic anemia; matched sibling donor; unrelated donor

**INTRODUCTION**

Severe aplastic anemia (SAA) is a rare disease characterized by pancytopenia in the peripheral blood (PB) followed by bone marrow (BM) hypoplasia due to an immune-mediated destruction of hematopoietic precursors [[1](#_ENREF_1)]. ~~Patients with a severe form of the disease (severe aplastic anemia [SAA]) are significantly at higher risk of death due to its severe complications, such as fatal infection and/or hemorrhage, if they do not receive optimal therapeutic interventions.~~ According to several guidelines, allogeneic stem cell transplantation (SCT) from human leukocyte antigen (HLA)-matched sibling donors (MSD-SCT) and immunosuppressive treatment (IST) have been considered as a first-line treatment for younger (≤ 40–50 years old) and older (> 40–50 years old) adult SAA patients, respectively [[2](#_ENREF_2), [3](#_ENREF_3)]. Allogeneic SCT from HLA-matched unrelated donors (URD-SCT) has been considered as a second-line treatment option for patients who experienced IST failures, according to previous studies showing relatively poorer outcomes compared to that of MSD-SCT [[4-6](#_ENREF_4)]. However, although patients who received IST as a first-line treatment can achieve long-term overall survival (OS) of 80–90%, a significant proportion of those patients suffer from a high treatment failure rate, including lack of response with transfusion-dependency, disease relapse, and clonal evolution [[7](#_ENREF_7)]. ~~Additionally, because of a frequently observed partial response after IST, achieving complete recovery of the quality of life seems to be difficult, followed by restrictions to daily activities due to subnormal hemoglobin and/or platelet counts or increased risk of infections due to subnormal neutrophil count and long-standing cyclosporin (CsA) exposure [~~[~~8~~](#_ENREF_8)~~].~~

Over the last two decades, high-resolution HLA typing with more optimized transplant-related techniques and better supportive care have improved the outcomes of URD-SCT for pediatric and adult SAA patients [[9](#_ENREF_9), [10](#_ENREF_10)]. Recent studies showed that the outcomes of children and adolescent patients who received URD-SCT as a first-line treatment were not significantly different to those of patients who received MSD-SCT [[11](#_ENREF_11), [12](#_ENREF_12)]. Reflecting these results, an updated guideline recommends that URD-SCT may be considered as a first-line treatment for pediatric patients without suitable MSD [[3](#_ENREF_3), [13](#_ENREF_13)]. However, comparative studies regarding the outcomes of adult SAA patients who received MSD-SCT and URD-SCT are rare, except the two recently published retrospective studies [[14](#_ENREF_14), [15](#_ENREF_15)]. To address this issue, major long-term outcomes of consecutive adult SAA patients who received MSD-SCT and URD-SCT at our institution were comparatively analyzed, including propensity score matching sub-cohort analysis.

**PATIENTS AND METHODS**

**Patients and treatment strategies**

We analyzed the outcomes of 257 consecutive adult (≥ 18 years old) SAA patients who received MSD-SCT or URD-SCT between March 2002 to May 2018 at the Seoul St. Mary’s Hospital, Seoul, Korea. According to conventional therapeutic schemes [[2](#_ENREF_2), [3](#_ENREF_3)], younger (≤ 40–50 years old) patients with appropriate MSD received MSD-SCT as a first-line treatment. Patients who were not considered as candidates of MSD-SCT received IST, consisting of horse or rabbit anti-thymocyte globulin (ATG) plus cyclosporin (CsA), as a first-line treatment. However, patients who immediately required treatment, per physicians’ discretion, received URD-SCT as a first-line treatment [[7](#_ENREF_7)]. On the contrary, patients experiencing IST failures received URD-SCT as a second-line treatment. In searching for the appropriate MSD (8 of 8 allele-matched) and/or URD (≥ 6 of 8 allele-matched) by screening for HLA–A, HLA–B, HLA–C, and HLA–DRB1 alleles, the high-resolution (DNA sequencing) molecular typing method was performed. ~~All patients were ≤ 65 years old with adequate organ function and performance status at the time of transplantation.~~ This study was approved by the institutional review board of the Seoul St. Mary’s Hospital. In addition, informed consent was obtained from all patients.

**Transplant-related procedures**

Patients received a conditioning of fludarabine (Flu, 30 mg/m2 intravenously [IV] for 6 days) and cyclophosphamide (Cy, 50 mg/kg IV for 2 days) plus rabbit ATG (Thymoglobulin®, 2.5 mg/kg IV for 4 days) for MSD-SCT or fractionated total body irradiation (TBI, 400–800 cGy) plus Cy (50–60 mg/kg IV for 2 days) for URD-SCT. If potential candidates for MSD-SCT experienced severe infection with/without significant co-morbidities, they received a conditioning of total nodal irradiation (750 cGy for 1 day) plus rabbit ATG (1.25 mg IV for 3 days or 2.5 mg IV for 2 days). Since August 2009, low-dose rabbit ATG (1.25 mg/kg IV for 2 days) has been administered to patients who received URD-SCT from HLA-mismatched donor and/or PB stem cells [[16](#_ENREF_16)]. Thereafter, the protocol was amended so that all patients, who have received URD-SCT since December 2016, received rabbit ATG (2.5 mg/kg for 2 days). Although we have requested BM harvest to all potential donors, the choice of BM and PB stem cells were determined according to their preferences. ~~After the infusion of BM stem cells or granulocyte-colony stimulating factor-mobilized PB stem cells, the prophylaxis for graft-versus-host disease (GVHD) was as follows: short-course methotrexate (10 mg/m~~~~2~~ ~~for MSD-SCT or 5 mg/m~~~~2~~ ~~for URD-SCT at day 1, 3, 6, and 11) plus CsA (target through level of 150–300 ng/mL) for MSD-SCT or FK506 (target through level of 10–15 ng/mL) for URD-SCT.~~ Other detailed transplant-related procedures, including supportive care strategies, were described in our previous reports [[16](#_ENREF_16), [17](#_ENREF_17)].

**Definitions**

The diagnosis of the disease and categorization of the severity were performed according to the criteria proposed by Camitta et al [[18](#_ENREF_18)]. Patients’ pre-transplant comorbidities were assessed according to the Hematopoietic Cell Transplantation-Specific Comorbidity index [[19](#_ENREF_19)]. Neutrophil and platelet engraftment were defined as an absolute neutrophil (ANC) count ≥ 0.5 × 109/L for at least 3 consecutive days and a platelet count ≥ 20 × 109/L for at least 7 consecutive days without transfusion support. Primary and secondary graft failure (GF) were characterized by a failure of neutrophil engraftment at days 28 with either irreversible ANC < 0.5 × 109/L or platelet count < 20 × 109/L, with and without evidence of previous donor engraftment, respectively. Post-transplant complications ~~of acute GVHD and chronic GVHD, grade ≥ 3 infectious complications, sinusoidal obstruction syndrome, and hemorrhagic cystitis~~ were evaluated according to the previous published criteria [[20](#_ENREF_20)]. We defined a composite end-point of GVHD-free, failure-free survival (GFFS) based on the following: being alive without experiencing grade III-IV acute GVHD, chronic GVHD requiring systemic therapy, and primary or secondary GF [[17](#_ENREF_17), [21](#_ENREF_21)]. In our current study, allogeneic SCT as a first-line treatment indicates transplantation without previously receiving IST, including horse or rabbit ATG plus CsA and CsA monotherapy.

**Statistical analysis**

This study aimed to compare the major outcomes, including GF incidence, transplant-related mortality (TRM) incidence, GFFS rate, and OS rate, of adult SAA patients who received allogeneic SCT from the following donor-type groups: MSD (the MSD group), well-matched URD (8/8 allele-matched; the WM-URD group), and partially-matched URD (6–7/8 allele-matched; the PM-URD group). All time-dependent parameters were measured from the first day of stem cell infusion. Continuous and categorical variable were described by median with ranges and count with relative frequency, respectively. Comparisons between the baseline and transplant-related characteristics according to donor-type groups were performed by using the independent two-sample t-test, the χ2 test, and Fisher’s exact test. GFFS and OS rates were calculated using Kaplan–Meier estimates and compared using the log-rank test. The neutrophil and platelet engraftment, primary and secondary GF, acute GVHD and chronic GVHD, and TRM were described as the cumulative incidence estimate and compared using the Grey’s test. The prognostic significance of covariates was determined using the Cox proportional hazards model for GFFS and OS, and the proportional hazards model for the sub-distribution of a competing risk for acute and chronic GVHD, primary and secondary GF, and TRM. Furthermore, we compared the major outcomes between the MSD and the URD (WM-URD + PM-URD) groups for the propensity score-matching sub-cohort of patients receiving allogeneic SCT as a first-line treatment. ~~considering the limited number of patients of the URD group.~~ The propensity score-matching sub-cohort was established by propensity score calculated by using a logistic regression model [[22](#_ENREF_22)], for each individual patient, fitted for a donor-type group according to the following variables: age, interval from diagnosis to transplant, and stem cell source, which significantly affected transplant-related outcomes in a previous study [[23](#_ENREF_23)]. Subsequently, one-to-three matched groups were created by nearest neighbor matching without replacement. Factors were considered significant if they had an associated *P* < 0.05 as determined by the likelihood ratio test, using two-tailed significance testing. Data were analyzed in December 2018 using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Baseline and transplant-related characteristics**

The median age of our patients was 34 (range, 15–64) years at transplantation, with 167 (64.7%) aged ≤ 40 years. At the transplantation, 133 (51.6%) patients experienced failures for one or more courses of IST, with the proportions significantly higher in the WM-URD (*P* < 0.01) and the PM-URD (*P* < 0.01) groups compared to that of the MSD group, which contributed to relatively higher proportions of patients who had longer (> 12 months) interval from diagnosis to transplantation (*P* < 0.01 and *P* = 0.02, respectively) and heavily (> 100 units) transfusion history (*P* = 0.01 and *P* = 0.05, respectively) of the WM-URD and the PM-URD groups compared to that of the MSD group. With the discriminable transplantation processes according to donor-type groups, the MSD group had relatively higher proportions of patients who were older (> 40 years) (*P* < 0.01 in both), using BM stem cells (*P* = 0.01 and *P* = 0.09, respectively), and using ABO blood type-matched donors (*P* = 0.01 and *P* < 0.01, respectively) compared to those of the WM-URD and PM-URD groups. More detailed baseline and transplant-related characteristics according to donor-type groups are described in Table 1. Infused CD34+ and CD3+ cell doses of patients who received BM and PB stem cells were 3.01 × 106/kg (range, 0.25–14.37) and 4.92 × 106/kg (range, 1.81–17.03), and 38.79 × 106/kg (range, 1.70–463.68) and 329.64 × 106/kg (range, 1.34–1234.70), respectively.

**Engraftment**

Except two (0.8%) patients who died of infectious complication at day 7 (in the PM-URD group) and cerebrovascular event at day 10 (in the MSD group), all patients achieved neutrophil engraftment at a median 12 (range, 5–26) days. Excluding three (1.2%) patients who did not experience platelet count nadir (in the MSD group), 230 (95.0%) patients achieved platelet engraftment at a median 17 (range, 7–433) days. More detailed incidences of neutrophil and platelet engraftments are described in Table 2.

**GVHD and other post-transplant complications**

At a median 29 (range, 9–162) days, 68 (26.4%) patients experienced grades II-IV acute GVHD, including grade II in 53 (20.5%), grade III in 10 (3.9%), and grade IV in 5 (1.9%) patients. Grades II-IV acute GVHD incidences of the MSD, the WM-URD, and the PM-URD groups were 8.5% (95% CI, 4.8–13.6), 36.1% (95% CI, 25.1–47.2), and 57.6% (95% CI, 38.6–72.6) at day 100, respectively (*P* < 0.01). At a median 7.3 (range, 0.9–131.9) months, 57 (22.1%) patients developed mild-to-severe chronic GVHD, including mild in 23 (8.9%), moderate in 21 (8.1%), severe in 15 (5.8%) patients. Mild-to-severe chronic GVHD incidences of the MSD, the WM-URD, and the PM-URD groups were 8.6% (95% CI, 4.8–13.8), 43.4% (95% CI, 31.6–54.6), and 36.6% (95% CI, 20.3–53.0) at 6 years, respectively (*P* < 0.01). More detailed incidences of acute ~~(including grades III-IV)~~ ~~GVHD~~ and chronic ~~(including moderate-to-severe and severe)~~ GVHD according to donor-type groups are presented in Table 2.

At a median 2.1 (range, 0.2–114.4) months, 86 (33.3%) patients experienced grade ≥ 3 infectious complications. Grade ≥ 3 infectious complications incidences of the MSD, the WM-URD, and the PM-URD groups were 26.1% (95% CI, 19.3–33.5), 35.2% (95% CI, 24.2–46.4), and 57.6% (95% CI, 38.6–72.6) at 6 years, respectively (*P* < 0.01). There were no significant differences of other post-transplant complications incidences according to donor-type groups (*P* > 0.10). More detailed post-transplant complications incidences according to donor-type groups are described in Table 3.

**Graft failure and transplant-related mortality**

Although primary GF was not observed in any patient, 23 (8.9%) patients (only in the MSD group) experienced secondary GF at a median 14.1 (range, 0.9–97.2) months. Secondary GF incidences of the MSD, the WM-URD, and the PM-URD groups were 14.6% (95% CI, 9.3–20.9), 0%, and 0% at 6 years, respectively (*P* < 0.01). The secondary GF incidence of the MSD group was significantly higher compared to that of the WM-URD (*P* < 0.01) and the PM-URD (*P* < 0.01) groups (Fig. 1A). ~~Of those who experienced secondary GF, 19 (86.4%) patients received second allogeneic SCT, followed by achieving sustained engraftment without mortality. Three (13.6%) who only received supportive care patients remained alive at the last follow-up.~~

At a median 2.1 (range, 0.2–9) months, 23 (8.9%) patients died without experiencing GF due to the following causes: acute GVHD in 8 (3.1%), infectious complications in 8 (3.1%), secondary malignancies in 4 (1.6%), chronic GVHD in 2 (0.8%), and cerebrovascular hemorrhage in one (0.4%). TRM incidences of the MSD, the WM-URD, and the PM-URD groups were 6.1% (95% CI, 3.0–10.8), 10.3% (95% CI, 4.4–19.0), and 21.7% (95% CI, 9.4–37.4) at 6 years, respectively (*P* = 0.03). The TRM incidence of the PM-URD group was significantly higher than that of the MSD group (*P* = 0.01). There were no significant differences of TRM incidences between the MSD and the WM-URD groups (*P* = 0.21), and the WM-URD and the PM-URD groups (*P* = 0.19) (Fig. 1B). Other baseline and transplant-related characteristics did not affect the TRM incidence (*P* > 0.20).

**GFFS and OS**

With a median survivor’s follow-up duration of 79.1 (range, 6.1–177.6) months, 175 (67.8%) patients were alive without experiencing GF and grades III-IV acute GVHD, and chronic GVHD requiring systemic therapy. The GFFS rates of the MSD, the WM-URD, and the PM-URD groups were 76.7% (95% CI, 63.2–80.2), 55.5% (95% CI, 41.3–67.5), and 51.5% (95% CI, 33.5–66.9) at 6 years, respectively (*P* < 0.01). The GFFS rate of the MSD group was significantly higher compared to that of the WM-URD (*P* < 0.01) and the PM-URD (*P* < 0.01) groups. There was no significant difference of the GFFS rates between the WM-URD and the PM-URD groups (*P* = 0.22) (Fig. 1C). Patients’ age (≤ 40 years vs. > 40 years; 76.8% vs. 64.3% at 6 years, *P* = 0.06) and preceding IST history (yes vs. no; 61.3% vs. 76.7% at 6 years, *P* = 0.01) were also potential candidates affecting GFFS rate. However, donor-type group (WM-URD vs. MSD; hazard ratio [HR] 1.78, 95% CI 1.02–3.13, *P* = 0.04 and PM-URD vs. MSD; HR 2.44, 95% CI 1.25–4.76, *P* < 0.01) was the only significant factor affecting GFFS rate in multivariate analysis (*P* < 0.01) (Table 4).

At the time of analysis, 234 (90.7%) patients were alive. The OS rates of the MSD, the WM-URD, and PM-URD groups were 93.9% (95% CI, 88.6–96.8), 86.2% (95% CI, 72.9–93.3), and 78.3% (95% CI, 59.6–89.0) at 6 years, respectively (*P* = 0.02). The OS rate of the MSD group was significantly higher than that of the PM-URD (*P* < 0.01), but not to that of the WM-URD (*P* = 0.18) group (Fig. 1D). There was no significant difference in OS rates between the WM-URD and the PM-URD groups (*P* = 0.18). Heavily transfusion history (≤ 100 units vs. > 100 units; 97.7% vs. 89.3%, *P* = 0.09) was another potential candidate affecting OS rate. However, donor-type group (WM-URD vs. MSD, HR 1.69, 95% CI 0.65–4.40; *P* = 0.28 and PM-URD vs. MSD; HR 3.27, 95% CI 1.21–8.85; *P* = 0.02) was only significant factor affecting OS rate in multivariate analysis (*P* = 0.04) (Table 4).

**Subgroup analysis for the propensity-score matching cohort of patients receiving** **allogeneic stem cell transplant as a first-line treatment**

We compared the major post-transplant outcomes between the MSD and the URD groups for the propensity score matching cohort of patients who received allogeneic SCT as a first-line treatment (one-to-three matching; 54 and 18 patients of the MSD and URD groups, respectively). The patients’ baseline and transplant-related characteristics were not significantly different between the MSD and the URD groups, except significantly higher proportion of patients who had male sex (*P* = 0.03), long interval from diagnosis to transplant (P < 0.01), and used PB stem cells (*P* < 0.01) in the URD group (Table S1). Grades II–IV acute (5.6% vs. 50.0% at day 100; *P* < 0.01) and grades III–IV acute GVHD (0% vs. 16.7% at day 100; *P* < 0.01), and mild-to-severe chronic (12.0% vs. 38.7% at 6 years; *P* < 0.01), moderate-to-severe chronic (19% vs. 22.2% at 6 years; *P* < 0.01) and severe chronic (0% vs. 16.7% at 6 years; *P* < 0.01) GVHD incidences were significantly higher in the URD group compared to those of the MSD group. There were no significant differences of GF incidence (15.9% vs. 0%; *P* = 0.06), TRM incidence (3.7% vs. 11.8% at 6 years; *P* = 0.25), GFFS rate (78.5% vs. 66.7% at 6 years; *P* = 0.21), and OS rate (96.3% vs. 88.9% at 6 years; *P* = 0.24) between the MDS and the URD groups. (Fig. 2).

**DISCUSSION**

In our current study, which compared the long-term outcomes of adult SAA patients who received allogeneic SCT according to donor-type groups, there was no significant difference of the OS rates between the MSD and the WM-URD groups. However, the OS rate of the PM-URD group was significantly lower compared to that of the MSD group, although it was acceptable to be used in the clinical practice. These results suggest the possibility of URD-SCT, especially using WM-URD, as a first-line treatment option for adult SAA patients, at least in terms of OS rate. Nevertheless, there are several considerations that should be taken with caution.

The most evident limitation of this study is the unbalanced distribution of the clinical and transplant-related characteristics of the donor-type groups, mainly due to our therapeutic scheme. ~~According to our therapeutic scheme, the proportion of older (> 40 years) patients was significantly higher in the MSD group compared to that of URD groups. Conversely, the proportions of those who had longer interval from diagnosis to transplant (> 12 months) and heavily transfusion history (> 100 units) were significantly higher in the URD groups, since most patients in the URD groups experienced previous IST failures, compared to that of the MSD group. Additionally, PB stem cells were more frequently used in the URD groups due to donors’ preferences than in the MSD group.~~ The unequally distributed characteristics might suggest that most of the results from our current study can be depreciated. However, most of ~~these factors were associated with poor post-transplant outcomes,~~ unequally distributed factors which are associated with poor post-transplant outcomes [[23-26](#_ENREF_23)], except a significantly higher proportion of patients having older age (> 40 years), were more frequently observed in the MSD group than in the URD groups. ~~It might more negatively attribute post-transplant outcomes of the URD groups than the MSD group.~~ Consequently, an unbalanced distribution of the clinical and transplant-related characteristics of the donor-type groups cannot significantly affect our major conclusion of at least not inferior ~~the comparable~~ OS rate of the WM-URD group compared to that of ~~between~~ the MSD ~~and the WM-URD~~ group~~s~~. ~~Certainly, this observed limitation of this study should be validated by further well-designed prospective cohorts with well-balanced groups.~~

A substantially high secondary GF incidence only in the MSD group may be an additional limitation in our study. The GF incidences of the previously published studies using Flu-based conditioning were low (from 0% to 13.9%) [[27-29](#_ENREF_27)], supporting the hypothesis that a high secondary GF incidence of the MSD group was not only due to the low intensity of conditioning regimen. When we compared the clinical and transplant-related characteristics of the current study and other previous studies’ cohorts, the proportion of patients who had heavily transfusion history was relatively higher in our cohort (77.1%) than that in the previous studies’ cohort. Consequently, it suggests that a Flu-based conditioning may be insufficient to overcome the possible occurrence of GF in these high-risk patients of the MSD-SCT group. In contrast, despite the fact that a substantial proportion of patients in the URD groups had a heavily transfusion history and/or 1–2 allele mismatched donor, secondary GF was not observed in any of them. Previous studies investigating the factors affecting GF incidence for SAA patients who received allogeneic SCT showed that irradiation-based conditioning might facilitate sustained engraftment [[30](#_ENREF_30), [31](#_ENREF_31)]. Therefore, a very low GF incidence of the URD groups may be due to the potent immunosuppression of the TBI-based conditioning sufficient to overcome a possible GF occurrence in high-risk patients of the URD groups [[32](#_ENREF_32)]. ~~Furthermore, w~~Whether this limitation of Flu-based conditioning can be solved by the intensification of conditioning in high risk patients should be investigated by further studies.

Yagasaki et al. analyzed the outcomes of children and adolescent SAA patients who received allogeneic SCT, which showed no significant difference of OS rates between the MSD and the URD groups (100% vs. 93.8% at 10 years; *P* = 0.25) [[11](#_ENREF_11)]. Dufour et al. also showed comparable OS rates of pediatric SAA patients who received allogeneic SCT as a first-line treatment between the MSD and the URD groups (91% vs. 96% at 2 years; *P* = 0.30) [[12](#_ENREF_12)]. These above-mentioned studies suggest an extending role of URD-SCT as a considerable first-line treatment option for children and adolescent ~~SAA~~ patients, which have changed the treatment scheme for these patients [[3](#_ENREF_3)]. ~~However, comparative studies that analyzed the outcomes of adult SAA patients who received MSD-SCT and URD-SCT are insufficient.~~ Regarding adult SAA patients, only two recently published retrospective studies by Vaht et al. and Zhang et al. compared the OS rates of patients who received MSD-SCT and URD-SCT, which provided results similar to that of the current study (90.6% vs 83.3% at 5 years; *P* = 0.41 and 89.3% vs. 82.0% at 5 years; *P* = 0.40, respectively) [[14](#_ENREF_14), [15](#_ENREF_15)]. However, because these studies analyzed an extremely small sample of patients who received or who did not receive heterogeneous transplant strategy, they had substantial difficulty in drawing confirmatory results. Our study showed insignificantly different OS rates between the MSD and WM-URD groups in a sufficient number of adult SAA patients, along with the clinically acceptable outcomes of the PM-URD group. This supports a considerable role of URD-SCT as a first-line treatment option in adult SAA patients. Furthermore, our additional propensity score matching sub-cohort analysis showing a comparable OS rate of patients who received MSD-SCT and URD-SCT as a first-line treatment makes our results more evident, although a very limited number of patients of this cohort result in a difficulty in drawing conclusive results.

The incidences of acute and chronic GVHD of the URD groups were significantly higher than those of the MSD group. Additionally, we showed the GFFS was significantly higher in the MSD group than that of the URD groups. Considering relatively high morbidity and mortality of patients experiencing acute and chronic GVHD [[33](#_ENREF_33), [34](#_ENREF_34)], these results should be a major consideration when performing URD-SCT as a first-line treatment for adult SAA patients. Therefore, all possible efforts to ameliorate the incidences of acute and chronic GVHD for patients to achieve long-term survival with an adequate quality of life are essential. Our recently published report for adult SAA patients who received URD-SCT using PM-URD or PB stem cells may provide with a possible solution for this issue [[16](#_ENREF_16)]. It showed significantly lower acute grade II–IV and chronic GVHD incidences (31.2% vs. 61.5% at day 100; *P* < 0.01 and 21.9% vs. 65.4% at 3 years; *P* < 0.01, respectively) in patients who received low-dose ATG (2.5 mg/kg) compared to patients who did not receive low-dose ATG. Furthermore, emerging prophylactic approaches of various action mechanisms, including T-cell depletion, functional inhibition of donor T-cell activation, inhibition of signals mediated by extracellular mediators, and B-cell depletion [[35](#_ENREF_35)], with an improved understanding of GVHD pathophysiology will lead us to overcome this challenging area of allogeneic SCT. Consequently, these may support the extended role of URD-SCT in SAA patients as a first-line treatment in the near future.

In conclusion, our current study showed that OS rates between the MSD and the WM-URD groups of adult SAA patients who received allogeneic SCT, along with the clinically acceptable outcomes of PM-URD group were not significantly different, which suggests the possibility for the role of URD-SCT as a first-line treatment option. The strength of our study is this is a unique comparative analysis including only adult SAA patients who received allogeneic SCT between the MSD and the URD groups. However, this is a retrospective study with an unbalanced distribution of clinical and transplant-related characteristics of the donor-type groups, although it is an unavoidable feature of a real-world description. In addition, only a limited number of patients received allogeneic SCT as a first-line treatment, especially in both WM-URD and PM-URD groups. Therefore, our results should be interpreted with caution. Until more clinical evidences by future well-designed prospective studies are available, URD-SCT as the first-line treatment for SAA should be recommended in younger patients (<40 years old). ~~Therefore, future well-designed prospective studies are warranted to confirm our results.~~

Supplementary information is available at Bone marrow transplantation’s website

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**FIGURE LEGEND**

Fig. 1 (**a)** Graft failure incidence, (**b)** transplant-related mortality incidence, (**c)** GFFS rate, and (**d)** OS rate according to donor-type groups.

Fig. 2 (**a)** Graft failure incidence, (**b)** transplant-related mortality incidence, (**c)** GFFS rate, and (**d)** OS rate according to donor-type groups for the propensity-score matching cohort of patients receiving SCT as a first-line treatment.