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Abatacept is effective as GVHD prophylaxis in unrelated donor stem cell transplantation for children with severe sickle cell disease

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Key Points

- Strategies to minimize GVHD are essential if URD SCT is to be considered with curative intent in SCD.
- Abatacept-inclusive GVHD prophylaxis protects against transplant complications that contribute to morbidity/mortality after URD SCT in SCD.

We report results of a phase 1 multicenter stem cell transplantation (SCT) trial from HLA-matched (n = 7) or one-antigen-mismatched (n = 7) unrelated donors (URD) using bone marrow or cord blood as stem cell source, following reduced-intensity conditioning (RIC) in severe sickle cell disease (SCD). Conditioning included distal alemtuzumab, fludarabine, and melphalan (matched donors), with thiotepea (mismatched donors). Abatacept, a selective inhibitor of T cell costimulation, was added to tacrolimus and methotrexate as graft-versus-host disease (GVHD) prophylaxis to offset GVHD risks, and was administered for longer duration in bone marrow recipients than in cord blood recipients because of increased incidence of chronic GVHD with bone marrow. Median age at transplant was 13 years (range, 7-21 years). The incidence of grades II to IV and grades III to IV acute GVHD at day +100 was 28.6% and 7%, respectively. One-year incidence of chronic GVHD was 57% and mild/limited in all but 1 patient who received abatacept for a longer duration. Only 1 patient developed reversible posterior encephalopathy syndrome and recovered. With a median follow-up of 1.6 years (range, 1-5.5 years), the 2-year overall and disease-free survival was 100% and 92.9%, respectively. The encouraging results from the phase 1 portion of this RIC SCT trial, despite risk factors such as older age, URD, and HLA-mismatch, support further evaluation of URD SCT in clinical trial settings. The phase 2 portion of the trial is in progress. This trial was registered at www.clinicaltrials.gov as NCT03128996.

Introduction

Allogeneic stem cell transplantation (SCT) from HLA-matched sibling donors has excellent disease-free survival (DFS) of >90% in children with sickle cell disease (SCD) but is limited by donor unavailability in >80% of eligible patients.¹ Unrelated donors (URD) are potential alternate donor sources. Patients of African origin have a 19% chance of finding fully (8/8) HLA-matched, but a 57% chance of finding minimally mismatched (7/8), URD in donor registries.² However, SCT from URD bone marrow has been associated with high risks of acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) and consequent mortality in the first URD SCT trial for SCD performed following reduced-intensity conditioning (RIC) designed to offset high-dose chemotherapy-related organ toxicities. The 2-year overall survival (OS) was 79% (95% confidence interval [95% CI], 59%-90%) suggesting caution for this approach.³ aGVHD also complicated unrelated cord blood transplantation with RIC.^{4,5} Further, graft-versus-host disease (GVHD) risks rise exponentially with recipient age >12 years irrespective of donor source.^{3,6,7} African Americans, encompassing most SCD patients, have a higher risk of GVHD.⁸⁻¹⁰ GVHD prophylaxis or treatment with corticosteroids also increase hypertension-related complications such as posterior reversible encephalopathy syndrome (PRES) and

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Study protocol synopsis and individual participant data (after deidentification) that underlies the result reported in this article will be made available on request to the

corresponding author, Alexander Ngwube (e-mail: angwube@phoenixchildrens.com), after the publication of this manuscript.

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Table 1. Patient characteristics and outcomes

Patient	Age, y/sex	Indication	Stem cell source/HLA match	Number of abatacept doses received	Myeloid chimerism at last evaluation, %	aGVHD/cGVHD (cGVHD NIH grade)	Follow up, y	Organ toxicity/ outcome	Systemic immune suppression (time withdrawn)	Performance score pre/at last follow up
1	10/F	Stroke	Bone marrow/A antigen	4*	95	0/limited (mild)	5.5	SJS/resolved	Off (1 y, 9 mo)	100/100
2	13/F	VOE	Bone marrow/DRB1 antigen	4*	100	Gr 1/extensive (severe)	4.8	PRES/resolved	On	100/70
3	21/M	Stroke	Bone marrow/none	8	95	0/limited (mild)	4.5	Pancreatic insufficiency/ongoing	Off (1 y)	100/100
4	18/F	VOE	Bone marrow/C allele	8	100	0/limited (mild)	3.3	None	Off (1 y, 1 mo)	80/100
5	19/M	VOE, ACS	Bone marrow/A allele	8	100	Gr 2/0	2.9	AKI/resolved	Off (1 y, 1 mo)	90/100
6	7/M	ACS	Bone marrow/none	8	96	0/limited (mild)	2.1	None	Off (1 y, 5 mo)	90/100
7	18/F	VOE, ACS	Bone marrow/A antigen	8	100	Gr 2/extensive (severe)	1.6	Peripheral neuropathy/resolved	On	90/80
8	16/F	VOE, RBC antibodies	Bone marrow/none	8	96	0/limited (mild)	1.5	None	Off (1 y)	100/100
9	9/M	VOE, ACS	Cord blood/DRB1	4	100	Gr2/0	1.5	Transient red cell aplasia, AKI, cholelithiasis/resolved	Off (1 y, 6 mo)	90/90
10	8/F	Stroke	Bone marrow/B allele	8	100	Gr 4/limited (mild)	1.5	None	On	80/90
11	13/F	Stroke	Bone marrow/none	4	0	NE	GR	None	NE	90/90
12	21/M	Stroke	Bone marrow/none	8	100	0/0	1.4	None	Off (1 y)	100/100
13	2/M	ACS	Cord blood/B antigen	4	100	0/0	1	AKI/resolved	Off (1 y)	100/100
14	7/M	Stroke	Bone marrow/A antigen	8	100	0/0	1	None	Off (1 y)	70/90

ACS, acute chest syndrome; AKI, acute kidney injury; F, female; Gr, grade; GR, graft rejection; M, male; NE, not evaluable; NIH, National Institutes of Health; RBC, red blood cell; SJS, Stevens-Johnson syndrome; VOE, vaso-occlusive episodes.

*The first 2 patients were treated on an earlier version of the protocol and received 4 doses of abatacept. Abatacept administration was extended to 8 doses in bone marrow transplants subsequently.

cerebral hemorrhage, complications that SCD patients are highly susceptible for at baseline.^{3,11} Thus, it is critically important to prevent GVHD and limit complications to successfully expand this curative therapy in SCD patients.

Abatacept is a fusion protein that selectively inhibits T-cell costimulation by binding to CD80/CD86 on antigen-presenting cells and blocking CD28-mediated signaling.¹² A first-in-human trial of abatacept prophylaxis after SCT for malignant disorders safely protected against aGVHD, earning the agent a breakthrough designation for this indication from the US Food and Drug Administration and provided background for this approach.¹³ In the phase 2 portion of the trial, grade 3 to 4 aGVHD decreased to 2.3% following URD SCT when short-term abatacept was administered until day +28 in 4 doses, but no benefit was noted on cGVHD following HLA-mismatched SCT compared with controls¹⁴. We report the results of the phase 1 portion of a trial (NCT03128996) of URD SCT in recipients \leq 21 years with severe

SCD using the RIC previously reported, followed by tacrolimus, methotrexate, or mycophenolate (in cord blood recipients), and abatacept as GVHD prophylaxis.⁵ The primary end points were engraftment, OS, and DFS at 1 year. Secondary end points included the kinetics of engraftment, nature and severity of GVHD, disease symptoms, organ toxicities, infections, and immune reconstitution for 2 years.

Methods

The institutional review board at each participating institution approved the protocol. Between August 2016 and June 2018, 14 SCD patients, age 7 to 21 years (median, 13 years), with stroke ($n = 6$), ≥ 3 severe vaso-occlusive pain crises per year ($n = 6$), or ≥ 2 acute chest syndrome episodes per year ($n = 5$) underwent URD SCT at 5 participating centers after consent. Seven received 8/8 HLA-matched (-A, -B, -C, and -DRB1) bone marrow, 5 received 7/8 matched bone marrow, and 2 received 5/6 matched (-A, -B,

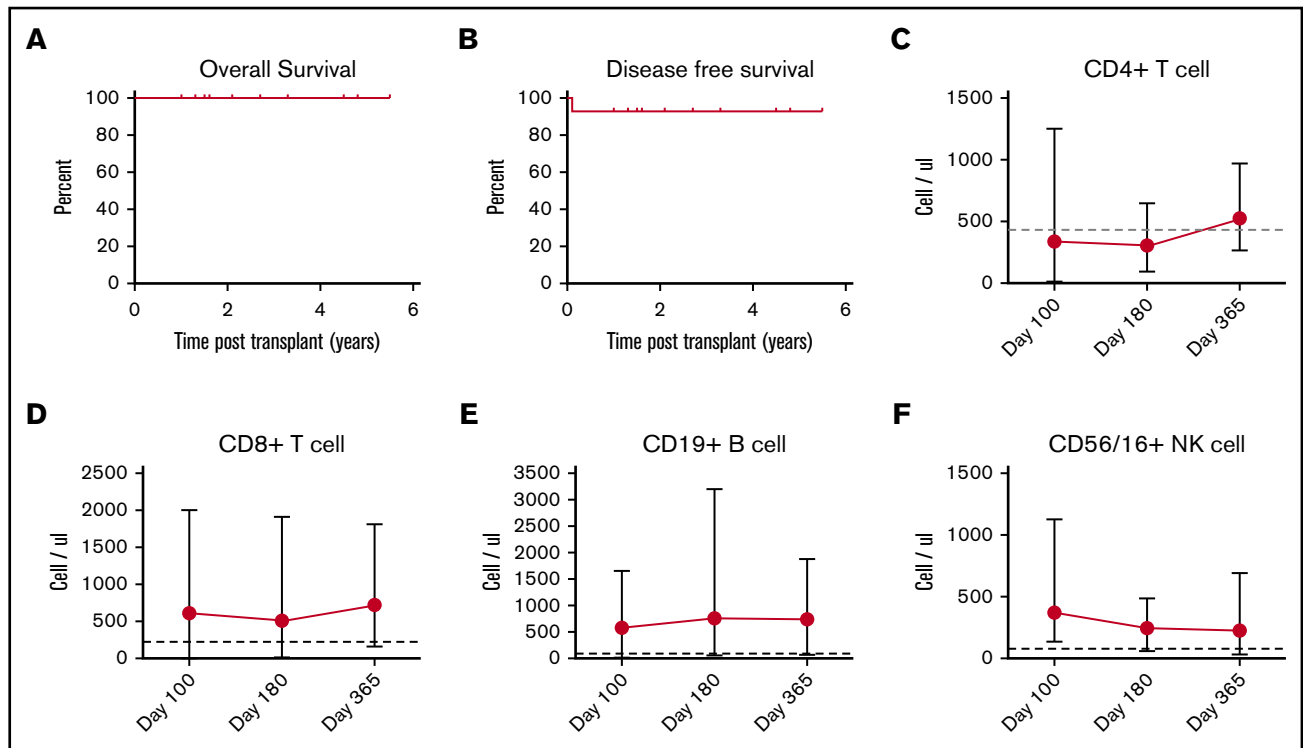


Figure 1. Probability of survival and serial immune reconstitution. (A) Five-year OS, 100%. (B) Five-year DFS, 92.9%. Dots depict a censored event. Recovery of CD4+ T cells (C), CD8+ T cells (D), CD19+ B cells (E), and CD16/56+ NK cells (F) presented as absolute numbers on days +100, +180, and +365. Cut offs for normal values are indicated with horizontal dashed lines.

and -DRB1) cord blood (Table 1). Hemoglobin S was <30% prior to conditioning in all patients. RIC included hydroxyurea (days -50 to -21), distal alemtuzumab (days -22 to -19), fludarabine (days -8 to -4), and melphalan (day -3) as previously described.³ Thiotepa (8 mg/kg) on day -4 was added to the regimen for mismatched bone marrow and cord blood products.⁵ GVHD prophylaxis included tacrolimus and short-course methotrexate (bone marrow) or mycophenolate mofetil (cord blood) as previously described.³ Abatacept (10 mg/kg) was administered intravenously on days -1, +5, +14, +28, +100, +180, +270, and +365. Cord blood transplants reported in this study received abatacept until day +28 (4 doses). After April 2019, as a result of aGVHD risks we reported with unrelated cord blood in the first few months post-SCT but lower cGVHD risks, the protocol was changed so that abatacept doses are continued only until day +100 in cord blood transplants.^{5,15,16} Abatacept dosing was extended in bone marrow transplant recipients as an amendment after the first 2 patients, to evaluate the possible benefit of extended use on cGVHD, a complication to which this population is highly susceptible (Table 1). The interval between doses with the extended use was based on the assumption that proliferation of alloreactive T cells in damaging numbers would have a lag period after wash-out of a previous dose, and balancing the interval between doses would be advantageous for immune reconstitution. Supportive care included hypertension control, seizure prophylaxis, and hemoglobin/platelet count maintenance.³ GVHD was graded according to previously published criteria.¹⁷ The probability of OS and DFS was estimated from

the time of transplantation using Kaplan-Meier product-limit estimates.

Results and discussion

Patient demographics, transplantation details, and outcomes are summarized in Table 1. All patients had risk factors for transplant-related morbidity and/or mortality on the basis of age ($n = 10$), URD source, and HLA-mismatch ($n = 7$).¹⁸⁻²¹ The median number of total nucleated and CD34+ cells per kilogram of body weight was 3.0×10^8 (range, 0.75×10^8 to 5.5×10^8) and 3.36×10^6 (range, 0.19×10^6 to 4.5×10^6), respectively. At a median follow up of 1.6 years (range, 1-5.5 years), 13 of 14 recipients had stable donor engraftment. One patient with cytomegalovirus (CMV) reactivation had secondary graft rejection on day +30. This patient subsequently rejected another URD graft following myeloablative conditioning and received a haploidentical transplant with donor engraftment at early follow-up. The 2-year probability of OS and DFS was 100% and 92.9%, respectively (Figure 1A-B). The median time to neutrophil and platelet ($>50 \times 10^3/\mu\text{L}$) engraftment was 14 days (range, 10-24 days) and 19.5 days (range, 16-39 days), respectively. All engrafted patients had >95% donor chimerism at their last evaluation. No patient had SCD manifestations such as vaso-occlusive episodes, acute chest syndrome, or central nervous system events or radiologic progression in the follow-up period post-SCT.

The incidence of grade II to IV aGVHD at day +100 was 28.6%. Three patients developed grade 2 aGVHD involving the skin, and

Table 2. Etiology and timing of infections posttransplant

Infection type	Infections recorded		
	0-100 d posttransplant	101-180 d posttransplant	181-365 d posttransplant
Bacterial	<i>Pantoea</i> (1)	<i>Klebsiella</i> (1)	
	<i>Acinetobacter</i> (1)	<i>Staphylococcus</i> (1)	
	<i>Staphylococcus</i> (1)		
	<i>Salmonella</i> (1)*		
	<i>Clostridium</i> (1)		
Fungal	<i>Candida</i> (1)	<i>Fusarium</i> (1)	
Viral	CMV	Adenovirus (1)	Influenza (2)
	Reactivation (7)	Parainfluenza (2)	Parainfluenza (1)
	BK virus (1)	EBV reactivation (2)	
	Adenovirus (1)	Influenza (1)	
		CMV reactivation (2)	

The numbers in parentheses indicate number of patients with the infection.

*Except for *Salmonella* enteritis, the other bacterial infections were bacteremias diagnosed by blood culture.

were treated with topical therapy. One developed grade 4 GVHD of the gut, and required systemic therapy until resolution. All patients continued GVHD prophylaxis as dictated by the trial. Seven patients developed localized skin rash or oral plaques in the first year that responded to topical therapy. Systemic immune suppression wean was commenced 9 to 12 months post-SCT successfully per protocol. Only 1 of 9 patients who received URD bone marrow and abatacept doses beyond day +100 developed extensive cGVHD affecting the lung; that patient continues systemic immune suppression. One patient developed PRES that was self-limiting, in contrast to 34% reported previously with URD SCT.³

The sharp decrease in complications is attributed to changes in GVHD prophylaxis (tacrolimus weaned 9-12 months post-SCT, deletion of corticosteroid prophylaxis, and addition of abatacept). GVHD prophylaxis was modified on the basis of advantages provided by abatacept's mechanism of action and low toxicity in primate models and subsequent clinical trials in malignant disorders.^{12,14} The continued risk of cGVHD in the first 2 participants in this trial prompted an amendment to extend costimulation blockade with abatacept to 1 year post-transplant in SCD patients receiving bone marrow products, though discontinued on day +100 following cord blood transplants. Another trial is exploring the benefits of intermediate-duration abatacept on the risk of GVHD in SCD SCT.²² If successful, this strategy of GVHD prophylaxis avoids exposure to chemotherapy-based prophylaxis such as high dose post-SCT cyclophosphamide.²³

Abatacept did not hinder donor engraftment. T-cell subsets gradually recovered after day +100 to the normal range by 1 year (Figure 1C-F). The pace of immune reconstitution was robust after 6 months despite the use of abatacept. Asymptomatic CMV reactivation, noted in 8 patients prior to day +180, responded to antiviral therapy and was concomitant with graft rejection in 1 patient. Thus, susceptible patients (recipient seropositive) were at high-risk for early CMV reactivation during the most severe period of immune incompetence and could

benefit from prophylaxis if at risk.²⁴ EBV replication noted in 1 patient was asymptomatic and treated with 2 doses of rituximab. One was treated with 2 doses of rituximab, and the other received no treatment. EBV replication subsided in both without symptoms. Additional infections in single patients included adenovirus viremia, BK viremia, influenza, *Salmonella* enteritis, line infection with *Fusarium*, and methicillin-resistant *Staphylococcus aureus* (Table 2); all responded to treatment. The low GVHD incidence that successfully allowed taper of systemic immune suppression (Table 1) likely enhanced immune reconstitution and recovery from infectious complications. Though infection risks seemed to abate after the initial few months post-SCT, continued monitoring is prudent until immune suppression is discontinued.

The most frequent organ toxicity noted was renal dysfunction (n = 3), which resolved with weaning calcineurin inhibitors. One patient developed pure red aplasia that was treated with immunoglobulin, bortezomib, and prednisolone, with resolution. One patient required cholecystectomy for cholelithiasis. No patient had SCD-related symptoms post-SCT.

Our preliminary results suggest that this RIC regimen combined with abatacept-inclusive GVHD prophylaxis protects against transplant complications that contribute to morbidity/mortality after URD SCT. These results support further study of URD SCT in clinical trial settings. Phase 2 trials of URD SCT, adding abatacept to standard GVHD prophylaxis are underway. Safely expanding the donor pool so SCD patients can benefit from curative intervention with minimal treatment-related morbidity remains a goal for hematology and transplant teams.

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Authorship

Contribution: A.N., N.S., and S.S. designed the trial, analyzed the data, and drafted the manuscript; and all authors enrolled patients, collected data, critically reviewed, and approved the final manuscript.

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and has a consultancy with bluebird bio. The remaining authors declare no competing financial interests.

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References

1. Krishnamurti L, Abel S, Maiers M, Flesch S. Availability of unrelated donors for hematopoietic stem cell transplantation for hemoglobinopathies. *Bone Marrow Transplant.* 2003;31(7):547-550.
2. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014;371(4):339-348.
3. Shenoy S, Eapen M, Panepinto JA, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. *Blood.* 2016;128(21):2561-2567.
4. Kamani NR, Walters MC, Carter S, et al. Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). *Biol Blood Marrow Transplant.* 2012;18(8):1265-1272.
5. Abraham A, Cluster A, Jacobsohn D, et al. Unrelated umbilical cord blood transplantation for sickle cell disease following reduced-intensity conditioning: results of a phase I trial. *Biol Blood Marrow Transplant.* 2017;23(9):1587-1592.
6. Cappelli B, Volt F, Tozatto-Maio K, et al; Eurocord, the Cellular Therapy and Immunobiology Working Party (CTIWP) and the Paediatric Diseases Working Party (PDWP) of the EBMT. Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease. *Haematologica.* 2019;104(12):e543-e546.
7. King AA, Kamani N, Bunin N, et al. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. *Am J Hematol.* 2015;90(12):1093-1098.
8. Majhail NS, Nayyar S, Santibañez ME, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. *Bone Marrow Transplant.* 2012;47(11):1385-1390.
9. Morishima Y, Kawase T, Malkki M, et al; International Histocompatibility Working Group in Hematopoietic Cell Transplantation. Significance of ethnicity in the risk of acute graft-versus-host disease and leukemia relapse after unrelated donor hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2013;19(8):1197-1203.
10. Eckrich MJ, Ahn KW, Champlin RE, et al. Effect of race on outcomes after allogeneic hematopoietic cell transplantation for severe aplastic anemia. *Am J Hematol.* 2014;89(2):125-129.
11. Gaziev J, Marziali S, Paciaroni K, et al. Posterior reversible encephalopathy syndrome after hematopoietic cell transplantation in children with hemoglobinopathies. *Biol Blood Marrow Transplant.* 2017;23(9):1531-1540.
12. Watkins BK, Tkachev V, Furlan SN, et al. CD28 blockade controls T cell activation to prevent graft-versus-host disease in primates. *J Clin Invest.* 2018;128(9):3991-4007.
13. Tiwari D, Horan J, Langston A, et al. A first-in-disease trial of in vivo costimulation blockade for acute GvHD prevention: the addition of abatacept to standard GvHD prophylaxis controls early CD4+ T cell proliferation and is associated with low rates of severe acute GvHD. *Blood.* 2012;120(21):741.
14. Watkins B, Qayed M, Bratrude B, et al. T cell costimulation blockade with abatacept nearly eliminates early severe acute graft versus host disease after HLA-mismatched (7/8 HLA matched) unrelated donor transplant, with a favorable impact on disease-free and overall survival [abstract]. *Blood.* 2017;130(suppl 1). Abstract 212.
15. Ruggeri A, Eapen M, Scaravadou A, et al; New York Blood Center. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. *Biol Blood Marrow Transplant.* 2011;17(9):1375-1382.
16. Locatelli F, Kabbara N, Ruggeri A, et al; Eurocord and European Blood and Marrow Transplantation (EBMT) group. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood.* 2013;122(6):1072-1078.
17. Blood and Marrow Transplant Clinical Trials Network. Technical manual of procedures. https://web.emmes.com/study/bmt2/public/MOP/BMT_CTNTechnicalMOPv3.pdf. Assessed November 2019.
18. Jacobsohn DA, Arora M, Klein JP, et al. Risk factors associated with increased nonrelapse mortality and with poor overall survival in children with chronic graft-versus-host disease. *Blood.* 2011;118(16):4472-4479.
19. Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood.* 2012;119(1):296-307.
20. Shouval R, Fein JA, Labopin M, et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. *Lancet Haematol.* 2019;6(11):e573-e584.
21. Eapen M, Brazauskas R, Walters MC, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. *Lancet Haematol.* 2019;6(11):e585-e596.

22. Chaudhury S, Laskowski J, Rangarajan HG, et al. Abatacept for GVHD prophylaxis after hematopoietic stem cell transplantation (HCT) for pediatric sickle cell disease (SCD): a sickle transplant alliance for research (STAR) trial. *Biol Blood Marrow Transplant*. 2018;24(3):S91.
23. Bolaños-Meade J, Cooke KR, Gamper CJ, et al. Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial. *Lancet Haematol*. 2019;6(4):e183-e193.
24. Robin C, Thiebaut A, Alain S, et al. Letermovir for secondary prophylaxis of cytomegalovirus infection and disease after allogeneic hematopoietic cell transplantation: results from the French compassionate program. *Biol Blood Marrow Transplant*. 2020;26(5):978-984.